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Correlation between tumor to liver SUV ratio and molecular subtypes of invasive breast carcinoma in PET CT

Nada Adel Awad El Kiki*, Fatma Salah Eldeen Mohamed, Amal Amin Abu ElMaati and Nermeen Nasry Keriakos

Abstract

Background: Breast cancer is known to be one of the most cancer affecting women around the globe and the second most common cancer in general. In third worlds countries, breast cancer is the most cause of cancer death. Early diagnosis and accurate follow-up of these patients affect the management. There are multiple prognostic factors most important one is the immunohistochemical molecular markers in the specimens including human epidermal growth factor, progesterone, and estrogen receptors (HER2, PR, ER). In breast cancer, the HER2 positive molecular subtype is associated with a bad prognosis and aggressive histological features, yet while following neoadjuvant chemotherapy, it achieves an increased pathological complete response rate. 18F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG PET) has proved to be an effective and accurate imaging technique for lymph node and distant metastasis assessment, tumor staging, restaging of recurrence, treatment response, and follow-up. In breast cancer, tumor molecular subtype, tumor size, proliferation index, and histological grade correlated with 18F-fluoro-2-deoxy-D-glucose (FDG) uptake. This study evaluates the possible correlation between tumor to liver and tumor to spleen (standardized uptake value) SUV max ratio and the four different molecular subtypes in patients with pathologically proven primary breast cancer.

Results: Tumor to liver and tumor to spleen SUV max ratio (TLR, TSR) was a significant parameter for HER2 molecular subtype identification (*P* value = 0.0005 and 0.014 respectively) and luminal A molecular subtype identification (*P* value = 0.016 and 0.037 respectively). The specificity, sensitivity, and area under the receiver operating-characteristic curve (AUC) of TLR parameters for HER2-positive subtype identification were 89.4%, 83.3%, and 0.89, respectively. The specificity, sensitivity, and AUC of the TSR parameter for HER2-positive subtype identification were 57.9%, 100%, and 0.83, respectively.

Conclusions: TLR and TSR appeared to be valuable for HER2- and luminal A molecular subtype detection. thus, 18F-FDG PET/CT could be a beneficial tool for prediction of tumor biological characteristics that help in management of breast cancer patients.

Keywords: Fluoro-deoxy-glucose uptake (FDG uptake), Positron emission tomography/computed tomography (PET/CT), HER2, Luminal A, Breast cancer, TLR, TSR

Background

Breast cancer is known to be one of the most cancer affecting women around the globe and the second most common cancer in general. In third worlds countries, breast cancer is the most cause of cancer death [1].

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Management of breast carcinoma includes Surgery, radiation, and chemotherapy in various combinations, depending on tumor size and site, TNM staging, and the molecular subtype [2].

Molecular subtype classification of the breast carcinoma based on immunohistochemistry including the estrogen, progesterone, and human epidermal growth factor receptors (ER, PR, HER2) is now widely used. According to the expression of these receptors, luminal A, luminal B, HER2 positive, and triple-negative are the accepted molecular subtypes [3].

In breast cancer, the HER2 positive molecular subtype is affiliated with bad prognosis and aggressive histological features, yet while following neoadjuvant chemotherapy. Hence, accurate molecular subtype diagnosis is necessary for the development of individualized, and rational treatments [4].

Positron emission tomography (PET) can detect abnormal metabolic activity, and 18F-2-deoxy-D-glucose (FDG) PET provides tumor-related quantitative and qualitative metabolic data that may help in the prognosis, diagnosis, and follow-up. Furthermore, PET, and computed tomography (PET/CT) combined, has benefits over CT alone, as this combined system allows us to assess the functional information and morphological data, and it also has benefits over PET alone, because pathological areas of tracer uptake are accurately localized, and the image acquisition time is reduced [5].

PET/CT can detect the primary breast tumor, and the ability depends on tumor size and histology. It can detect up to 68% of the small tumor (less than 2 cm) and the accuracy increases up to 98% in larger tumor size (2–5 cm). It also has high sensitivity in detection of the axillary and internal mammary lymph nodes reaching up to 94% and 92% respectively. It also has advantage over the conventional imaging modalities such as chest films, bone scanning, and abdominal ultrasound as it can detect metastasis at different sites and organs during a single examination [6].

In breast cancer, tumor molecular subtype, tumor size, proliferation index, and histological grade were correlated with 18F-fluoro-2-deoxy-D-glucose (FDG) uptake. Nevertheless, few studies have analyzed the diagnostic performance of F-18FDG-PET/CT-based predictions of molecular subtype [7].

The aim of this study is to evaluate the possible correlation between tumor to liver and tumor to spleen SUV max ratio (TLR, TSR) and the four different molecular subtypes in patients with pathologically proven primary breast cancer.

Methods

Patients

This study is retrospective study included 25 female patients with pathologically proven primary breast cancer underwent ^{18}F-FDG PET/CT imaging at the radiology department of Ain Shams University Hospitals from the time interval between August 2019 and June 2021. Data were collected after having patients' written informed consent following rules of ethical committee. we excluded patients who received chemotherapy/radiotherapy, underwent surgical tumoral intervention, post-splenectomy status or unavailable histo-pathological reports.

18FDG PET/CT imaging

Patients' preparation

- Patients were required to fast for at least 5 h.
- Avoid severe physical activities 1 day before F-18 FDG-PET/CT acquisition.
- Blood glucose levels before scanning should be less than 200 mg/dL.
- Diabetic patients should take their regular dose of the anti-diabetic drugs with breakfast before the scan by 6 h.
- Before injection of the 18F-FDG, the patient should seat in a quiet and dimly lit room.

PET/CT examination

At our university, we used a reliable hybrid PET/CT scanner [(GE discovery IQ 5 rings) and enhanced helical CT (optima 540 16-slice)]. Patients were positioned supine on the table. Single-phase contrast material–enhanced helical CT using a standardized protocol [28–30 mAs; 120 kV; slice thickness 5 mm] was conducted after injection of 125 mL of a low osmolarity iodinated contrast medium (Optiray 350) at a rate of 4 mL/s by using a power injector. A whole-body CT examination including neck, chest, abdomen, and pelvis scanning was performed. The related PET imaging instantly followed over the same body parts without repositioning the patient on the table. In the three-dimensional acquisition mode, six to seven-bed positions were planned for scanning the entire patient within 5–7 min of acquisition per each bed position. PET images were performed with shallow breathing. Attenuation was corrected using the CT images, and the images were reconstructed.

Image interpretation

Image data were interpreted by two nuclear medicine radiologists using a workstation with fusion software

GE workstation (Advantage window 4.7) which provided multi-planar reformatted images and displayed PET images, CT images, and PET/CT fusion images. Contrast-enhanced CT images were interpreted to detect any enhancing lesions and bone window was used to evaluate any bony pathologies. For semi-quantitative analysis, estimating the maximum standardized uptake value of the IBC (tumor SUV max) on axial images by drawing a region-of-interest (ROI) that contained as much of the tumor area that showed the most intense area of F-18FDG accumulation and it was recorded automatically by the workstation if multifocal disease was present, the ROI was placed over the largest visible tumor for calculation of the SUVmax value. In addition, the liver SUVmax was calculated by drawing a circular ROI 3.0 cm in diameter over the relatively homogenous intense slice of the right lobe of normal liver parenchyma on PET images, avoiding the partial volume effect (PVE) caused by adjacent organs on the margins of the liver. The SUVmax of the spleen was measured also by drawing circular ROI of 3.0 cm diameter over the relatively homogenous intense slice of the normal spleen parenchyma. TLR and TSR were calculated as ratios of the tumor SUV max to the liver and spleen SUVs max, respectively. The inter-reader agreement between the two nuclear radiologists was calculated for the semi-quantitative data. To assess the metabolic nodal stage, any axillary lymph node showing higher uptake than the mediastinal blood pool on PET/CT images was considered as positive; also, we reported quantitative data such as the size and SUV max of the lymph node. Any abnormal focal increased tracer uptake associated with suspicious CT features at any part of the body was considered as positive for distant metastasis.

Histopathological and immuno-histo-chemistry analysis

Tumor histology parameters were evaluated from the core needle biopsy samples taken from the breast tumor or malignant axillary lymph nodes. We obtained the histopathological findings, including the histological type, histological grade, ER and PR receptor status, HER2neu and proliferation index of the primary tumor by reviewing the pathology reports. According to the ER, PR, and HER2 status, IBCs were categorized into four molecular subtypes as follows:

1. luminal A (ER-positive and/or PR-positive, HER2 negative),
2. luminal B (ER-positive and/or PR-positive, HER2 positive),
3. HER2-positive (ER-negative, PR-negative, and HER2 positive),
4. triple-negative (ER-negative, PR-negative, and HER2 negative).

Statistical analysis

In this study, we used SPSS (Statistical package for social science) program version 23 for data analysis. Quantitative data were introduced as median and range to illustrate the studied sample. Qualitative data were introduced as count and percentage. Also, we used the Chi-square statistic to test relationships between categorical variables, and One-Way ANOVA test to compare parametric quantitative data between more than two groups.

An ideal cut-off value established on maximal sensitivity and specificity was determined to detect HER2/Neu molecular subtype, using the highest area under the receiver operating characteristic (ROC) curve. We identified significance as a P value of less than 0.05 and high significance as a P value less than 0.01 (Figs. 1, 2 and 3).

Results

Patient and tumor characteristics

A total of 25 patients were included, their demographic factors and tumor characteristics are reviewed in Table 1.

The 25 IBCs were categorized according to their molecular subtype as follows: luminal A, 11 (44%); luminal B, 5 (20%); HER2-positive, 6 (24%); and triple-negative, 3 (12%). The maximal tumor diameters ranged from 10 to 60 mm, with a median of 36 mm.

The inter-reader agreement was done for each quantitative data including the liver, spleen and tumor SUV max and the lymph node activity and the results were not significant as seen in Table 2.

Molecular subtypes and the tumor characteristics and PET findings

Twenty-one cases (84%) of the primary breast tumors were invasive ductal carcinoma (8 cases were luminal A, 4 cases were luminal B, 3 cases were triple negative and 6 were HER2 positive molecular subtype) and only four cases (16%) were invasive lobular carcinoma (3 of them was luminal A and one was luminal B subtype).

Most of luminal A positive molecular subtype cases were associated with grade II tumor (8 cases 72%), positive for axillary lymph nodes metastasis (9 cases 81.8%) and negative for distant metastasis (6 cases 54.5%).

Patients with HER2 positive molecular subtype were associated with axillary lymph node metastasis and high tumoral grade (II and III) yet 2 cases only (33.3%) showed distant metastasis.

HER2 positive molecular subtype showed higher liver SUV max value with mean $2.27 \pm$ SD 0.7 than luminal A

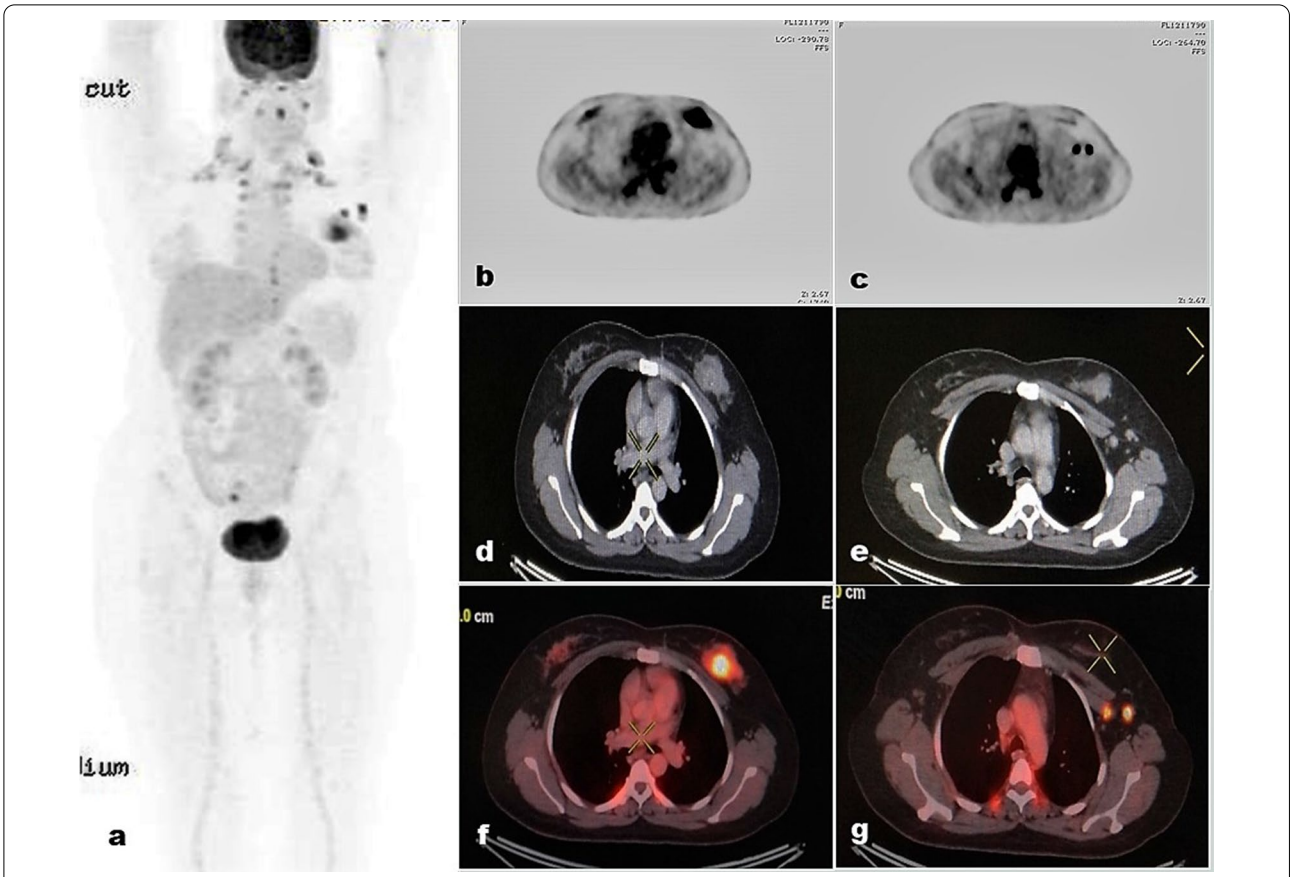

Fig. 1 43 years old patient with recently diagnosed left sided HER2 positive breast carcinoma. TLR = 3.2 and TSR = 3. **a** Maximum intensity projection. **b** and **c** Trans axial PET images corresponding axial CT cut in **d** and **e** shows left breast retro-areolar heterogenous enhancing soft tissue mass lesion with foci of calcifications. It measures about 5.5 × 3.5 cm associated with enlarged suspicious looking two left axillary lymph nodes. The largest measures about 1 × 1.1 cm. **f** fused PET/CT axial cut shows left breast retro areolar FDG avid lesion displaying SUVmax ~ 9.3. **g** fused PET/CT axial cut show two FDG avid axillary lymph node displaying SUVmax ~ 11.14

positive molecular subtype with mean 2.08 ± SD 0.73 as seen in Table 3.

HER2 positive molecular sub type also showed higher spleen SUV max value with mean 2.27 ± SD 0.82 than luminal A positive molecular subtype with mean 1.78 ± SD 0.54 as seen in Table 3.

Relation between tumor SUV max, TLR and TSR and the molecular subtype

Significant statistical relation was found between tumor SUV max and luminal A and HER2 positive molecular subtype ($P = 0.027$, 0.003) respectively. We also found significant statistical relation between TLR and TSR max ratio and luminal A molecular subtype ($P = 0.016$, 0.037) respectively also between them and HER2 molecular subtype ($P = 0.005$, 0.014) respectively as illustrated in Table 4 and Figs. 4 and 5.

The specificity and sensitivity of the TLR for identification of the HER2-positive subtype were 89.47% and 83.33%, respectively, when applying a cut-off value of more than 3.12. The AUC for identification of the HER2-positive subtype was 0.89, as illustrated in Fig. 6.

The specificity and sensitivity of the TSR for identification of the HER2-positive subtype were 57.89% and 100%, respectively, when applying a cut-off value of more than 2.43. The AUC for identification of the HER2-positive subtype was 0.84, as illustrated in Fig. 7.

The specificity and sensitivity of the TLR for identification of the luminal A subtype were 85.71% and 72.73%, respectively, when applying a cut-off value of less than 2.17. The AUC for identification of the luminal A subtype was 0.78, as illustrated in Fig. 8.

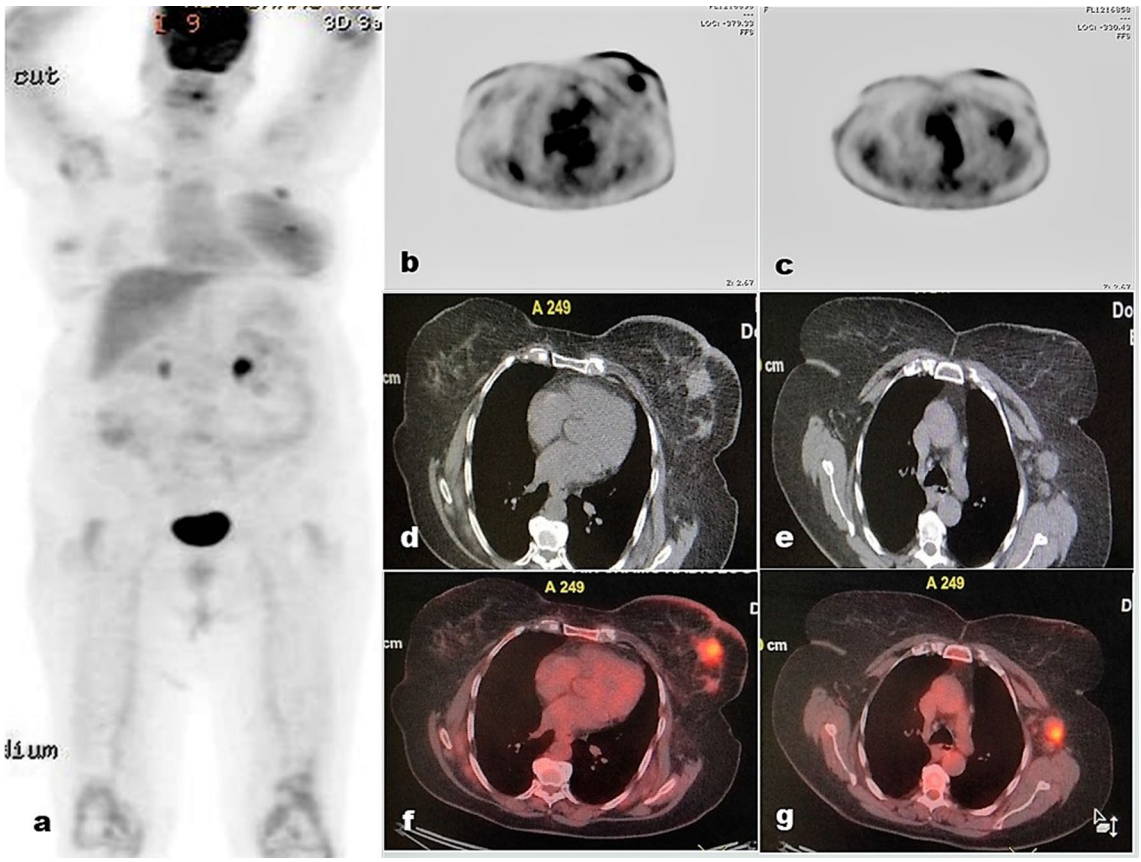

Fig. 2 60 years old patient with recently diagnosed left sided HER2 positive breast carcinoma. TLR = 2 and TSR = 2.2 **a** Maximum intensity projection. **b** and **c** Trans axial PET images corresponding axial CT cut in **d** and **e** shows left breast retro-areolar isodense soft tissue mass lesion associated with skin thickening. It measures about 5 × 4 cm associated with enlarged suspicious looking left axillary lymph node. It measures about 2 × 1.7 cm. **f** fused PET/CT axial cut shows left breast retro-areolar FDG avid lesion displaying SUVmax ~ 4.7. **g** fused PET/CT axial cut show FDG avid axillary lymph node displaying SUVmax ~ 4.8

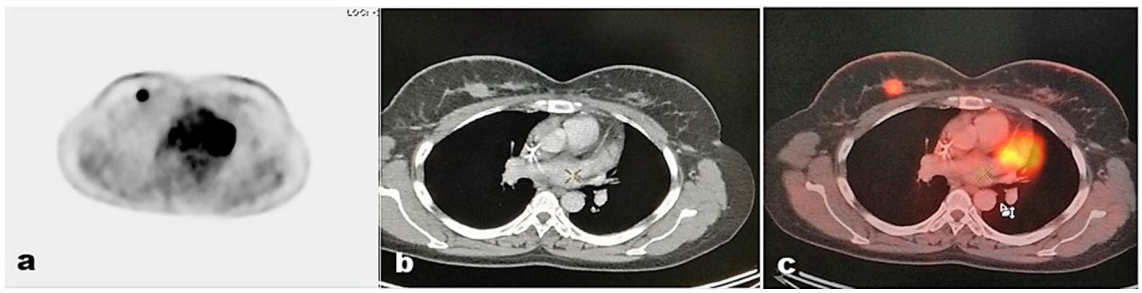

Fig. 3 35 years old patient with recently diagnosed right sided luminal A breast carcinoma. TLR = 2.17, TSR = 2.7. **a** Trans axial PET image with corresponding CT axial cut in **b** showing a speculated isodense enhancing soft tissue mass at the upper quadrant of the right breast. It measures about 5.2 × 2.5 cm. **b** Fused PET/CT axial cut shows that the lesion is FDG avid displaying SUV_{max} ~ 4.35

The specificity and sensitivity of the TSR for identification of the luminal A subtype were 92.86% and 63.64%, respectively, when applying a cut-off value of less than 1.6. The AUC for identification of the luminal A subtype was 0.75.

Table 1 Patient demographic Factors and tumor characteristics

Characteristic	Number (%)
Age mean, range	53.36 (29–79)
Size median, range	36 (10–60)
Location	
Right	10 (40.0%)
Left	11 (44.0%)
Bilateral	4 (16.0%)
Histopathology	
Invasive ductal	21 (84.0%)
Invasive lobular	4 (16.0%)
Grade	
I	1 (4.0%)
II	15 (60.0%)
III	9 (36.0%)
Immuno-histo-chemistry	
Luminal A	11 (44%)
Luminal B	5 (20%)
Tripple negative	3 (12%)
HER2/Neu	6 (24%)

Correlation between TLR and TSR and other PET/CT findings

TLR and TSR were significantly positively correlated with the number of breast lesions ($r=0.419$ and 0.507, $P=0.037$ and 0.10 respectively) and the axillary LN activity ($r=0.447$ and 0.461, $P=0.041$ respectively) and significantly negatively correlated with the size of the axillary lymph nodes ($r=-0.5$ and -0.4, $P=0.025$ and 0.028 respectively) as seen in Table5 and Figs. 9 and 10.

Discussion

18FDG PET/CT is a non-invasive imaging modality that evaluates the metabolic activity of tissues and their anatomical details [8].

SUVmax is a semi-quantitative method that reflects the intensity of the 18FDG uptake which is related to the metabolic activity of the cells estimating their behaviour that helps in the diagnosis, staging, and follow-up of various tumors [9].

When compared to primary breast tumors with lower 18F-FDG uptake, tumors with high 18F-FDG uptake had a poor prognosis [10, 11].

Patients with HER2-positive and triple-negative subtype tumors have a higher rate of distant metastasis, local recurrence, and mortality than tumors with luminal A and B subtype-positive tumors [12].

In the literature, multiple studies have reviewed 18F-FDG uptake in patients with breast tumors and related it to histopathological grade, tumor size, and hormone receptor expression as prognostic factors [13–15].

Kajáry et al. reported that aggressive tumors (HER2/Neu positive and triple-negative subtype tumors) have high uptake levels of 18F-FDG and higher SUVmax values; as a result, 18F-FDG PET imaging may be useful in predicting disease prognosis [16].

In our study, we used the TLR and TSR as well as the tumor SUVmax. Patients with viable malignant tumors have a higher mean SUV in the liver and spleen as they are organs with increased reticuloendothelial system activity [17].

TLR would provide a proper overview of the tumor metabolic activity and a more accurate diagnostic implementation than SUVmax. Using the TLR obviously remove the SUV limitation such as possible inaccuracies regarding scanner calibration, injected dose, and patient weight index (either actual body weight, lean body mass, or body surface area) [18–20].

TLR has been used in multiple new studies to predict axillary lymph node metastasis, evaluate prognosis, and treatment response in locally advanced breast carcinoma [21].

In our study, the mean TLR and TSR had statistically significant relation with the molecular subtype of the breast tumor with P value $=0.018$ and 0.061, it was found to be high among the HER2/Neu positive

Table 2 Inter reader agreement

	Observer 1			Observer 2			Difference			Test value	*P* value
	Mean	SD	SE	Mean	SD	SE	Mean	SD	SE		
Liver SUV	2.08	0.63	0.22	2.15	0.48	0.17	0.07	0.31	0.11	0.672	0.523
Spleen SUV	1.79	0.65	0.23	1.85	0.50	0.18	0.06	0.39	0.14	0.435	0.677
Tumor SUV	5.95	2.76	0.98	3.56	2.85	1.01	− 2.39	4.91	1.74	− 1.260	0.208
LN activity	5.54	3.16	1.12	5.29	2.82	1.00	− 0.25	3.63	1.28	− 0.196	0.850

Table 3 Molecular subtypes, tumor characteristics and PET findings

	Luminal A	Luminal B	Triple negative	HER2/Neu
Number of the patients	11 (44%)	5 (20%)	3 (12%)	6 (24%)
Age	52.09 ± 14.88	51.60 ± 13.54	53.33 ± 6.66	57.17 ± 10.80
	Range: 29–79	Range: 29–63	Range: 46–59	Range: 43–75
Histological type of the carcinoma	Invasive ductal: 8 (72.7%)	Invasive ductal: 4 (80%)	Invasive ductal: 3 (100%)	Invasive ductal: 6 (100%)
	Invasive lobular: 3 (27.3%)	Invasive lobular: 1 (20%)	Invasive lobular: 0 (0%)	Invasive lobular: 0 (0%)
Grade	I: 0 (0%)	I: 1 (20%)	I: 0 (0%)	I: 0 (0%)
	II: 8 (72.7%)	II: 2 (40%)	II: 2 (66.7%)	II: 3 (50%)
	III: 3 (27.3%)	III: 2 (40%)	III: 1 (33.3%)	III: 3 (50%)
LN	Positive: 9 (81.8%)	Positive: 3 (60%)	Positive: 2 (66.7%)	Positive: 6 (100%)
	Negative: 2 (18.2%)	Negative: 2 (40%)	Negative: 1 (33.3%)	Negative: 0 (0%)
Metastasis	Positive: 5 (45.5%)	Positive: 0 (0%)	Positive: 2 (66.7%)	Positive: 2 (33.3%)
	Negative: 6 (54.5%)	Negative: 5 (100%)	Negative: 1 (33.3%)	Negative: 4 (66.7%)
Ki67	33.27 ± 18.14	27.4 ± 8.88	30 ± 7	34.17 ± 9.33
	Range: 20–85	Range: 12–35	Range: 25–38	Range: 25–50
Liver SUVmax	2.08 ± 0.73	2.06 ± 0.40	1.67 ± 0.15	2.27 ± 0.70
	Range: 1.2–3.8	Range: 1.5–2.5	Range: 1.5–1.8	Range: 1.3–2.9
Spleen SUVmax	1.78 ± 0.54	1.92 ± 0.66	1.47 ± 0.15	2.27 ± 0.82
	Range: 1–1.3	Range: 1.1–2.9	Range: 1.3–1.6	Range: 1.2–3.1

Table 4 Four molecular subtypes and tumor SUV max, TLR and TSR SUV max ratios

	Tumor SUV max	*P* value	TLR SUVmax ratio	*P* value	TSR SUVmax ratio	*P* value
Luminal A	2.13 (1.6–4.6)	**0.027**	1.4 (1–2.7)	**0.016**	1.55 (1.12–2.87)	**0.037**
	Range: 0.9–15.9		Range: 0.5–4.2		Range: 0.56–5.3	
Luminal B	4.7 (4.2–5.8)	0.634	2.6 (2.2–2.8)	0.587	2.43 (2.2–3.8)	0.683
	Range: 3.9–8.5		Range: 2–3.4		Range: 2–4.5	
Triple negative	3.41 (1.6–4.5)	0.259	2.27 (0.8–2.6)	0.477	2.6 (1–3)	0.544
	Range: 1.6–4.5		Range: 0.8–2.6		Range: 1–3	
HER2/Neu	9.1 (6.6–9.9)	**0.003**	4.07 (3.17–5)	**0.005**	3.83 (3–5.5)	**0.014**
	Range: 6.7–11.2		Range: 2.2–6.62		Range: 2.44–7.46	

Bold means that the *p* value < 0.05 and there is a significant relation

subtype tumors than among triple negative, luminal A and B subtype tumors. This finding agrees with Noda et al. [22] who concluded a positive correlation between tumor to liver SUV_{max} of the lesion with the molecular subtype ($P = 0.0049$) and agreed also with AbdElaal et al. [23] who concluded that "the mean TLR values were much higher in Her2neu+, GIII and TN molecular subtype patients ($P = 0.002$, 0.0476, 0.005 and 0.018 respectively)

In our study we found positive correlation between TLR and TSR and the number of breast lesions (P value = 0.037 and 0.010 respectively), the axillary lymph node activity (P value = 0.048 and 0.041 respectively) and negative correlation between TLR and TSR and size of the axillary lymph nodes (P value = 0.025 and 0.028 respectively), this finding agree with AbdElaal et al. [23] who founded that the median of TLR

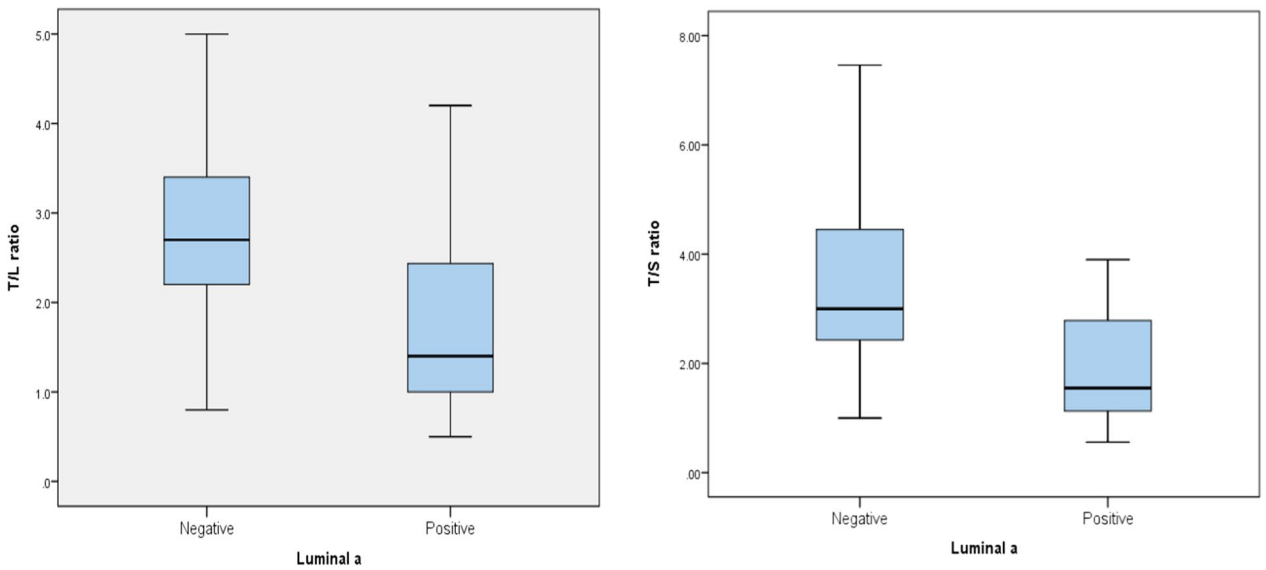

Fig. 4 Relation between the TLR and TSL and luminal a molecular subtype

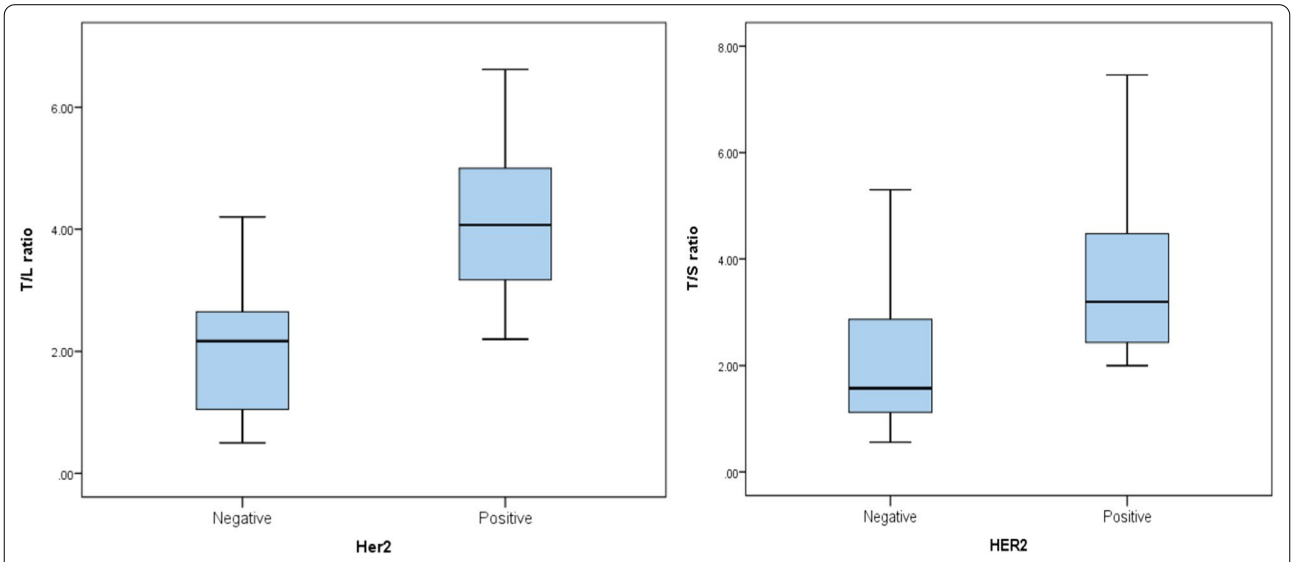

Fig. 5 Relation between the TLR and TSR and HER2 molecular subtype

values was significantly higher in patients with positive axillary lymph nodes (P value = 0.022) and also agree with Önner et al. [14] who founded that the TLR value seems to be more informative than the tumor SUVmax in predicting axillary lymph nodes involvement.

There were a few limitations in our study. First, since this was a retrospective study with a small sample size and was conducted in a single medical center, there was a higher risk of selection bias. More clinical trials with larger sample sizes may be required to confirm our

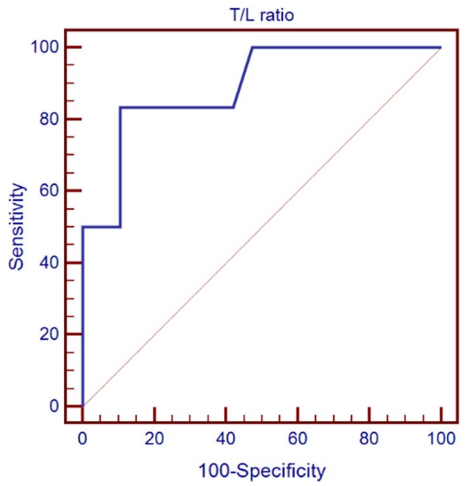

Fig. 6 ROC curve of TLR as a predictor of Her2 molecular subtype

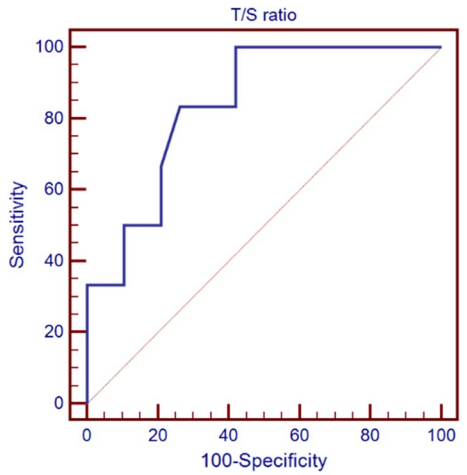

Fig. 7 ROC curve of TSR as a predictor of Her2 molecular subtype

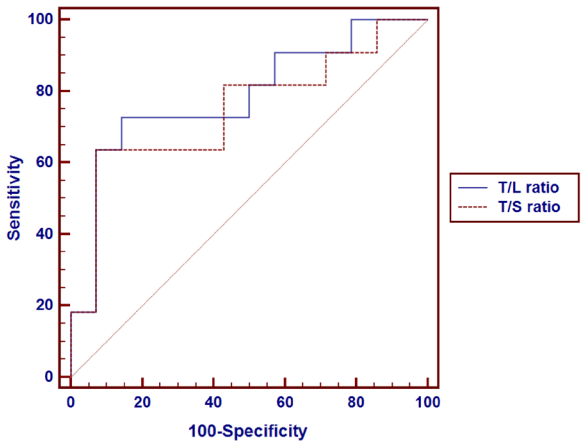

Fig. 8 ROC curve of TLR and TSR as a predictor of luminal a molecular subtype

Table 5 Correlation between TLR and TSR and PET/CT findings

	TLR		TSR	
	r	*P* value	*r*	*P* value
Number of breast lesions	0.419	0.037	0.507	0.010
Axillary LN activity	0.447	0.048	0.461	0.041
size of axillary LN	− 0.500	0.025	− 0.490	0.028

preliminary findings. Second, our study included small tumors which are more susceptible to partial volume effect. Hence, the SUVmax may be underestimated.

Conclusions

TLR and TSR appeared to be valuable for HER2- and luminal A molecular subtype detection. thus, 18F-FDG PET/CT could be a beneficial tool for prediction of

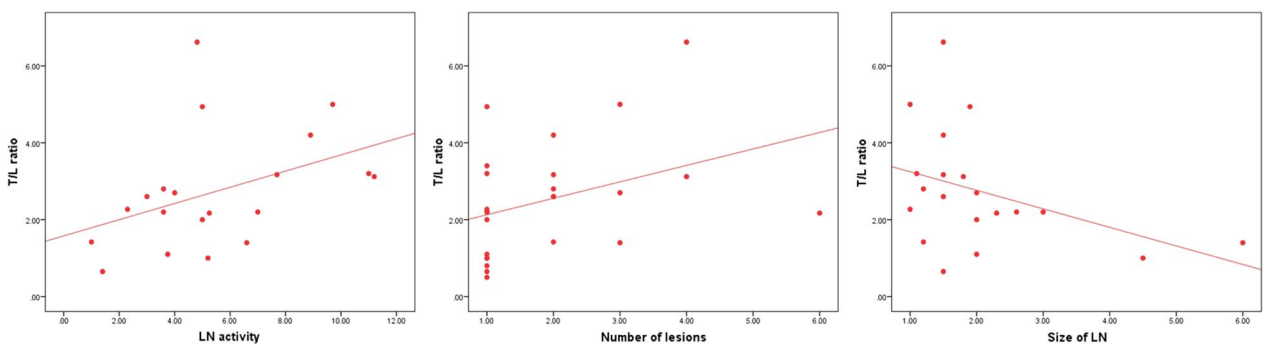

Fig. 9 Correlation between TLR and LN activity, number of breast lesions and the size of the LN

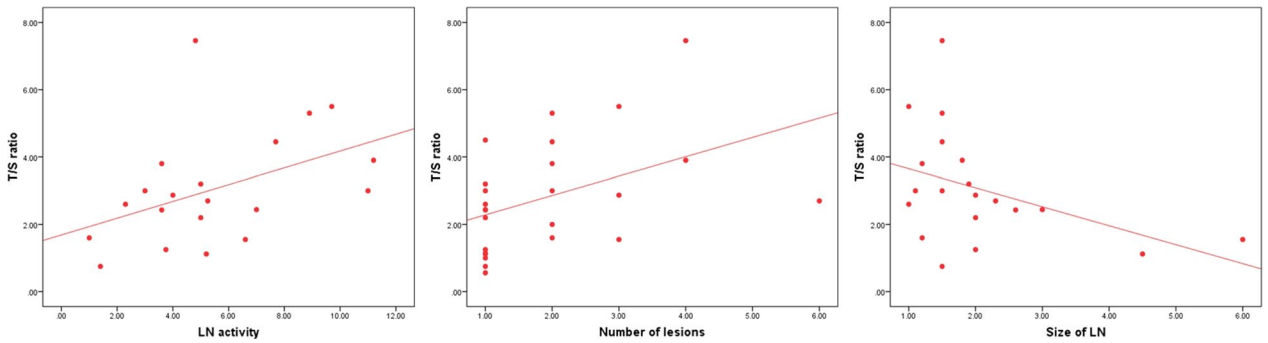

Fig. 10 Correlation between TSR and LN activity, number of breast lesions and the size of the LN

tumor biological characteristics that help in management of breast cancer patients.

Abbreviations

(18F) FDG-PET/CT: Fluorodeoxyglucose positron emission tomography/computed tomography; FDG: Fluorodeoxyglucose positron; SUV max: Maximum mean standard uptake values; IBC: Invasive breast carcinoma; ER: Estrogen receptor; PR: Progesterone receptor; HER2: Human epidermal growth factor receptor 2; TLR: Tumor-to-liver ratio; TSR: Tumor-to-spleen ratio; LN: Lymph node.; Ki-67: Ki-67 labelling index; ROI: Region of interest; AUC: Area under the curve.

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Author contributions

NE: the corresponding author, collected the patients' data, interpreted the findings and analyzed the data. FM: the co-author revised the data collected. AA: the co-author revised and interpreted the data collected. NK: the co-author revised, interpreted, and analyzed the data collected. All authors read and approved the final manuscript.

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Availability of data and materials

The data and material used in this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The study was reviewed and approved by Ain Shams University ethical and scientific committee "The committee's reference number is MD203/2019". A written informed Consent is obtained from all patients before the procedure.

Consent for publication

Consent for publication was obtained for every individual person's data included in the study.

Competing interests

There are no competing interests in this study.

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