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Original Article, PET/CT.

Could Visceral Fat Metabolic Activity and Primary Tumor Metrics of 18 F-FDG PET/CT Predict the Clinical Staging of Breast Cancer at Initial Presentation?

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ABSTRACT:

Aim of work: To explore the association between clinical staging and various factors, including body mass index (BMI), adipose tissue metabolic activity, and primary tumor metabolic parameters extracted from $^{18\text{-}F}$ FDG PET/CT in breast cancer. **Methods**: One hundred thirty-eight newly diagnosed BC patients underwent 18-F FDG PET/CT for initial staging. SUVmax, MTV, and TLG of the primary tumor were extracted. The average SUVmax for the subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT), and visceral/subcutaneous ratio (V/S ratio) were calculated. Univariate and multivariate analyses were utilized to determine the significant factors predicting clinical staging. **Results**: Ninety-two patients (67%) presented with advanced tumor stages (stage III, IV), while 46 patients (33%) were classified with low stages (stage I, II). In univariate analysis, the significant predictors associated with late-stage included a decrease in SAT (OR = 0.01, $p < 0.001$), as well as an elevation in V/S ratio (OR = 14.60, $p < 0.001$), TLG (OR = 1.01, p = 0.017), and MTV (OR = 1.05, p = 0.003). BMI was not associated with a significant predictive value for late-stage presentation (OR: 0.97, p=0.157). In multivariate analysis, a decrease in SUVmax SAT (OR=0.013, p=0.002), elevated V/S ratio (OR=10.48, p=0.002), and elevated TLG (OR=1.01, 95% CI: 1.01-1.013, p=0.012) were identified to be reliable advanced tumor staging predictors.
Conclusion: Tumor TLG and V/S ratio are significant predictors for advanced tumor stage at initial presentation in BC patients.

Keywords: Visceral fat, SUVmax, MTV, TLG, FDG, PET, breast cancer, BMI.

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INTRODUCTION:

Breast cancer in females represents a significant global health concern, accounting for 11.6% of all new malignancies [1]. It represents the most common cancer mortality rate in the female population [2]. Precise clinical staging is crucial for determining management plans [3]. The NCCN guidelines advise utilizing 18-FDG-PET/CT for advanced clinical staging as well as in specific situations where other imaging modalities yield equivocal findings [4]. Obesity is a substantial contributing factor to BC's prognosis. Obese patients typically present with a larger tumor size at diagnosis and a higher incidence of lymph node metastases [5,6]. Obesity leads to VAT dysfunction, which induces inflammatory mediators' release [7]. Prior research examined the correlation between the inflammatory environment produced by adipose tissue, prognosis, and metastatic status in BC cases [8,9]. 18-F FDG-PET/CT is essential for the noninvasive evaluation of SAT and VAT [10]. VAT metabolic activity normalized to subcutaneous tissue metabolic activity, called the V/S ratio [11]. The association between metastatic status and visceral metabolic activity has been investigated across several cancer types, including endometrial, breast, colorectal, and thyroid carcinoma [11–14]. In contrast, primary tumor metabolic metrics derived from 18-F FDG PET/CT may serve a predictive function for clinical and pathological staging [15]. This study examined the correlation between clinical staging in BC cases and VAT metabolic activity and primary tumor volumetric measures.

PATTIENTS and METHODS:

Ethical approval for this retrospective study was obtained from the South Egypt Cancer Institute/Institutional review (IORG0006563, No: 692). We enrolled 138 patients with recently diagnosed infiltrating ductal breast carcinoma who had an 18-F FDG PET/CT study before receiving any treatment during the period of Jan. 2021 to Dec. 2023. We included only female patients because the behavior of breast carcinoma in males is different than in females and downregulated BC incidence in the male population [16]. Two nuclear medicine physicians with significant experience analyzed 18-F FDG PET/CT for clinical staging as per the NCCN clinical practice guidelines published in 2024 [17]. Patients' age, weight, height, and fasting blood glucose were retrieved from their clinical records. BMI calculation was done according to the formula weight in Kg/ height in m^2.

PET/CT protocol

18-F FDG PET/CT study was conducted following the routine protocol established by the European Association of Nuclear Medicine [18]. All study subjects underwent a fasting period of no less than 6 hours before tracer injection and were advised to drink plenty of water. FBG was obtained immediately before tracer injection (mean ± SD was 111 ± 27). Individuals with FBG levels> 200 mg/dl were excluded. Afterward, subjects received 3.7 MBq/kg of 18-F FDG. Imaging utilizing a 20-slice PET/CT scanner (Siemens Biograph mCT at least 30 minutes after tracer injection. Whole-body scans were obtained from the skull cap to the mid-thigh. Subsequently, PET emission scans (per bed position) ranged from 1 to 3 minutes. The CT scan was conducted using intravenous contrast administration. Patients with known allergies or elevated renal chemistry did not receive contrast.

Image analysis:

DICOM PET/CT images were introduced to Osirix MD software version 8 [19]. A semi-automated volume of interest (VOI) with a 40% threshold was drawn for primary breast lesions extracting SUVmax, TLG, and MTV as indicated in **Figure 1**. In 18-F FDG PET/CT images, fat density was determined utilizing CT Hounsfield unit (HU) range from -110 up to -70, and then regions of interest (ROI) using the pencil tool were drawn over VAT and SAT. For VAT, ROIs were applied in the retroperitoneal space at the lumbar spine level across three consecutive images. In the SAT, ROIs were applied in three images located in the buttocks or beneath the anterior abdominal wall if there was interference from adjacent metabolic activity over intramuscular injections. SUVmax values for VAT and SAT were recorded, followed by the calculation of average values. The V/S ratio was determined by dividing the mean VAT by the mean SAT, as demonstrated in **Figure 1**. Hepatic reference mean metabolic activity was recorded. The tumor SUVmax was normalized to hepatic reference activity by dividing the tumor SUVmax over the hepatic reference activity, referred to as the tumor/liver ratio (T/L ratio).

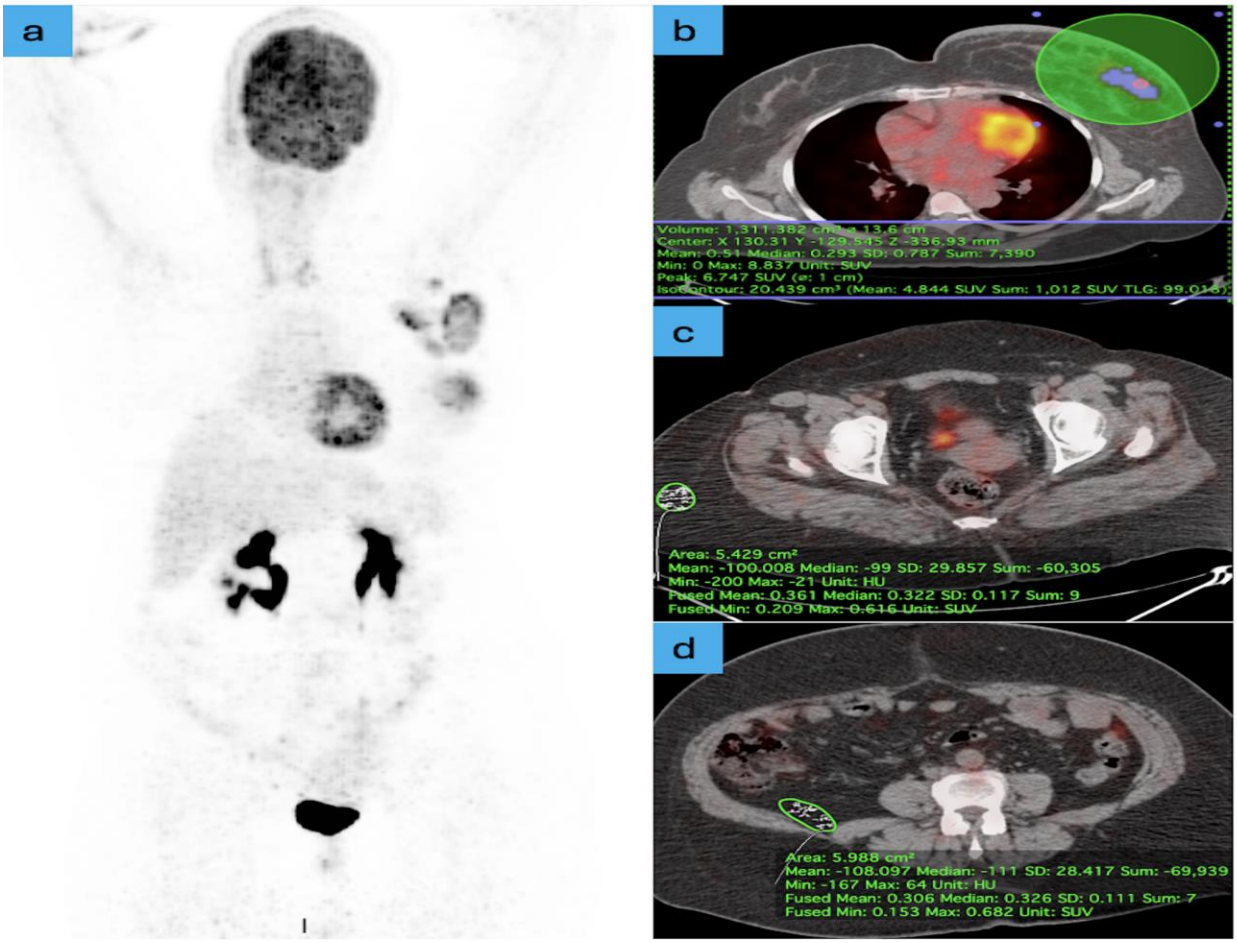

Figure 1: A 49-year-old female was diagnosed with infiltrating ductal carcinoma (left breast), exhibiting positive ipsilateral axillary lymphadenopathy, classified as clinical stage T2N2aM0. (a) Maximum intensity projection illustrates the primary left breast neoplasm alongside ipsilateral axillary lymphadenopathy. (b) Axial-fused PET/CT image displays the volume of interest applied to the primary breast neoplasm. (c) Axial-fused PET/CT image displays the region of interest applied to VAT.(d) Axial-fused PET/CT image displays a region of interest applied to SAT.

Statistical methods:

Data analyses were done utilizing V26 of the SPSS software. Categorical data were expressed in terms of percentages as well as frequencies. Numerical data normality was determined utilizing the Shapiro-Wilk test and are presented as SD and mean or IQR and median, depending on their distribution. The Mann-Whitney U test and the independent sample t-test were employed to compare the differences in median and mean between the two groups. The Pearson/Spearman correlation analysis was conducted to identify relationships between BMI, adipose tissue metabolic activity, and semi-quantitative tumor measures among the studied patients. Logistic regression analyses,

both multivariate and univariate, were conducted to determine the significant predictors linked to late-stage tumor presentation. The significance level was set at a P-value< 0.05.

RESULTS:

Patient characteristics:

One hundred thirty-eight female patients with recently diagnosed infiltrating ductal breast carcinoma underwent a pre-therapy 18-F FDG PET/CT study. Among the subjects, 121 (87.7%) exhibited a BMI of > 25 kg/m^2. The mean age was 57 years (range: 32-82). The TNM staging for patients is presented in **Table 1**. Distant metastases as well as regional lymph nodes were detected in 34.8% and 78.3% of patients, respectively. Stage IV was the most prevalent stage, accounting for 34.8%, followed by stage III at 31.9%, stage II at 26.1%, and stage I at 7.2%.

Table (1): Patients characteristics (N=138)

▪ Weight (kg)	81.65±16.50 (45-142)
▪ Height (cm)	157.57±6.73 (137-176)
▪ BMI (Kg/m^2)	33.01±6.75 (17.26-59.11)
▪ ≤25	17 (12.3 %)
▪ >25	121 (87.7 %)
Fasting blood glucose	
Mean± SD (range)	111.13±27.21 (63-199)
TNM clinical staging	
T Status	
▪ T 1	19 (13.8%)
▪ T 2	55 (39.9%)
▪ T 3	8 (5.8%)
▪ T 4	56 (40.6 %)
N Status	
▪ N0	30 (21.7 %)
▪ N+	108 (78.3 %)
M Status	
▪ M0	90 (65.2%)
▪ M+	48 (34.8%)
Clinical staging	
▪ I	10 (7.2 %)
▪ II	36 (26.1 %)
▪ III	44 (31.9 %)
▪ IV	48 (34.8 %)

Adipose tissue metabolic activity, TNM, and clinical staging in BC patients:

VAT metabolic activity demonstrated a substantial positive association with M status (0.32±0.12 for M0 versus 0.42±0.14 for M1, p <0.001). In contrast, T, N, and overall staging exhibited insignificant associations (p = 0.710, 0.970, and 0.171, respectively). SAT metabolic activity exhibited a marked inverse correlation with M staging (0.39±0.13 for M0 versus 0.26±0.08 for M1, p <0.001) and with advanced staging (0.41±0.14 for early stage versus 0.31±0.11 for late stage, p <0.001). No substantial relationship was observed with T and N staging (p = 0.127 and 0.105, respectively). The V/S ratio exhibited a significant positive correlation with M status (0.84±0.26 for M0 versus 1.71±0.91 for M1, p <0.001) and clinical staging (0.82±0.25 for early stage versus 1.30±0.80 for late stage, p <0.001). Conversely, the V/S ratio did not significantly correlate with T and N status (p = 0.420 and 0.175, respectively).

Primary tumor metabolic parameters with TNM and clinical staging. Higher tumor SUVmax showed a marked positive association with nodal metastases (p = 0.036*)*, distant metastases (p = 0.027), and advanced clinical staging (p = 0.044). Nevertheless, it did not exhibit a marked association with T staging (P value = 0.254). MTV and TLG showed substantially higher values in advanced T staging (P <0.001 and <0.001, respectively), nodal metastases (p = 0.006 and 0.001, respectively), distant metastases (p = 0.015 and 0.013, respectively), and overall clinical staging (P value <0.001, and <0.001 respectively). With respect to the T/L ratio, the higher ratio showed a marked positive association with nodal metastases (p = 0.049), distant metastases (p = 0.018), and advanced clinical staging (p = 0.028). **Table 2** illustrates the association of TNM with the primary tumor's adipose tissue and metabolic parameters.

Table 2: Association of adipose tissue metabolic activity and tumor metabolic parameters with TNM and clinical staging

	T stage		N stage		M stage		Final stage	
	Early (T1, T2) (n=74)	Late (T3, T4) (n=64)	N0 (n=30)	N+ (n=108)	M0 (n=90)	M1 (n=48)	Low stage (I, II) (n=46)	High stage (III, IV) (n=92)
Average SUVmax VAT								
▪ Mean ± SD	0.36±0.14	0.35±0.13	0.35±0.15	0.35±0.13	0.32±0.12	0.42±0.14	0.33±0.14	0.37±0.13
▪ P-Value	0.710		0.970		<0.001		0.171	
Average SUVmax SAT								
▪ Mean ± SD	0.36±0.14	0.33±0.11	0.38±0.14	0.34±0.12	0.39±0.13	0.26±0.08	0.41±0.14	0.31±0.11
▪ P-Value	0.127		0.105		<0.001		<0.001	
V/S ratio								
▪ Mean ± SD	1.10±0.61	1.19±0.80	0.99±0.48	1.19±0.75	0.84±0.26	1.71±0.91	0.82±0.25	1.30±0.80
▪ P-Value	0.420		0.175		<0.001		<0.001	
tumor SUVmax								
▪ Median (IQR)	5.36 (2.94-9.80)	7.92 (4.71-12.50)	5.36 (2.94-9.80)	7.92 (4.71-12.50)	6.02 (3.85-10.90)	9.21 (4.98-13.13)	5.36 (3.61-10.33)	8.19 (4.71-12.25)
▪ P-Value	0.254		0.036		0.027		0.044	
tumor MTV								
▪ Median (IQR)	4.62 (2.77-18.08)	11.32 (5.78-25.76)	4.62 (2.77-18.08)	11.32 (5.78-25.76)	8.95 (4.23-16.52)	15.08 (5.95-34.73)	5.26 (2.85-12.03)	13.46 (6.97-31.29)
▪ P-Value	<0.001		0.006		0.015		<0.001	
tumor TLG								
▪ Median (IQR)	19.25 (6.02-51.91)	53.95 (22.16-130.39)	19.25 (6.02-51.91)	53.95 (22.16-130.39)	36.14 (16.12-97.67)	61.15 (23.38-171.20)	23.73 (6.40-53.08)	58.99 (24.35-162.77)
▪ P-Value	<0.001		0.001		0.013		<0.001	
Tumor/Liver ratio								
▪ Median (IQR)	2.02 (1.32-3.39)	2.52 (1.62-4.52)	2.02 (1.32-3.39)	2.52 (1.62-4.52)	2.07 (1.35-3.743)	3.01 (1.83-4.52)	1.86 (1.29-3.47)	2.69 (1.69-4.22)
▪ P-Value	0.074		0.049		0.018		0.028	

Correlation between BMI, visceral metabolic activity, and clinical staging:

BMI displayed an insignificant correlation with VAT metabolic activity (r = -0.051, p = 0.558). Conversely, it displayed a marked positive correlation with SAT metabolic activity (r = 0.23, p = 0.007). There was a marked negative inverse correlation with the V/S ratio (r = -0.179, and p = 0.037).

Table 3 indicates no marked correlation between BMI, T, N, and M status, as well as clinical staging (r = -.0032 (p=0.707), r = -0.056 (p= 0.514), r = -0.007 (p= 0.937), and r = 0.092 (p= 0.289), respectively).

Table 3: Correlation between BMI and adipose tissue, primary tumor metabolic activity and clinical staging

	BMI	
	r	P-Value
Average SUVmax VAT	-0.051	0.558
Average SUVmax SAT	0.230**	0.007
V/S ratio	-0.179*	0.037
Tumor SUV max	-0.060	0.488
Tumor MTV	0.042	0.626
Tumor TLG	-0.010	0.904
T/L ratio	-0.141	0.101
T status	-.0032	0.707
N Status	0.056	0.514
M Status	-0.007	0.937
Clinical stage	-0.092	0.289

Logistic regression analyses, both univariate and multivariate, for predicting late-stage presentation at initial diagnosis:

Univariate analysis identified significant predictors for late-stage occurrence: a decrease in SUVmax SAT (OR = 0.01, 95% CI: 0.001-0.059, p < 0.001), an increase in V/S ratio (OR = 14.60, CI: 3.97-53.60, p < 0.001), an increase in tumor MTV (OR = 1.05, CI: 1.01-1.09, p = 0.003), and an increase in tumor TLG (OR = 1.01, CI: 1.001-1.011, p = 0.017). Age reduction demonstrated borderline significance for late-

stage presentation (OR = 0.97, 95% CI: 0.93-1, p = 0.050). The BMI and T/L ratio displayed insignificant predictive value for late-stage presentation. The multivariate regression analysis included significant predictors identified in univariate logistic regression. These predictors were decreased SUVmax SAT (OR=0.013, 95% CI: 0.001-0.58, p=0.025), elevated V/S ratio (OR=10.48, 95% CI: 2.34-46.84, p=0.002), and elevated tumor TLG (OR=1.01, 95% CI: 1.01-1.013, p=0.012), as depicted in **Table 4.**

Table (4): logistic regression analyses, multivariate and univariate, for the prediction of late-stage among studied patients

	Univariate analysis		Multi-variate analysis	
	OR (95% CI)	P-Value	AOR (95% CI)	P-Value
Age	0.97 (0.93-1.00)	0.050	0.96 (0.92-1.003)	0.071
BMI	0.96 (0.91-1.02)	0.157		
Average SUVmax VAT	6.42 (0.44-92.66)	0.171		
Average SUVmax SAT	0.01 (0.001-0.059)	<0.001	0.013 (0.001-0.58)	0.025
V/S ratio	14.60 (3.97-53.60)	<0.001	10.48 (2.34-46.84)	0.002
Tumor SUVmax	1.05 (0.98-1.13)	0.110	0.96 (0.88-1.06)	0.501
Tumor MTV	1.05 (1.01-1.09)	0.003		
Tumor TLG	1.01 (1.001-1.011)	0.017	1.01 (1.01-1.013)	0.012
T/L ratio	1.17 (0.96-1.42)	0.106		

DISCUSSION:

Breast cancer staging is the key to determining disease extent, aggressiveness, prognosis, and management [20]. 18-F FDG PET/CT is advised for initial staging, particularly in cases of locally advanced and inflammatory breast carcinoma, due to its higher accuracy in detecting extra-axillary nodal and distant metastases [4]. Obesity is a modifiable risk factor for BC progression in a post-menopausal state [21]. The relationship between obesity and breast carcinoma lacks a definitive mechanism. A potential explanation for this phenomenon is that adiposity enhances the secretion of hormones, inflammatory mediators, and growth factors that trigger the growth of the tumor microenvironment [22]. BMI is not an accurate marker of obesity; thus, it is imperative to investigate additional factors, such as dysfunctional adipose tissue [23]. The functional state of the adipose tissue has been investigated in the 18-F FDG PET/CT [24]. Few studies have explored the relation between adipose tissue metabolic activity in 18-F FDG PET/CT and cancer prognosis [14,25]. Furthermore, metabolic parameters (e.g., TLG, SUVmax, and MTV) derived from 18-F FDG PET/CT are significant for disease risk stratification[26,27]. This study examined the association of metabolic activity in adipose tissue and primary tumor metrics extracted from pre-therapy 18-f FDG PET/CT and advanced-stage occurrence of breast carcinoma in the initial presentation. Our results revealed that increasing the V/S ratio and tumor TLG were positive predictors of advanced-stage presentation. Younger age was borderline significant for advanced-stage presentation. BMI was not associated with the advanced stage. To our knowledge, a limited number of studies focused on visceral metabolic activity derived from 18-F FDG PET/CT in BC as a predictor tool in staging [14,25]. **Pahk** et al. investigated the association between BMI and V/S ratio derived from pre-therapy 18-F FDG PET/CT in BC patients with axillary lymph node metastasis; the V/S ratio was markedly elevated in cases with pathologically proven axillary nodal metastases [14]. Our results partially support their findings; the V/S ratio is significantly positively correlated with M status and clinical staging. However, there was no significant association with N status. One possible explanation is that this study examined the association using clinical rather than pathological staging. **Kim** et al. investigated 148 patients with stage I-III

based on the AJCC 8th edition [25]. They classified their subjects based on VAT metabolic activity into high and low groups. Their results did not reveal significant associations with VAT metabolic activity, lymph node metastases, and AJCC staging. Our study demonstrated no significant association with VAT metabolic activity, nodal metastatic status, and clinical staging, consistent with their findings. However, our results showed that the normalization of VAT to SAT (V/S ratio) had a significant association with M status and clinical staging. Regarding tumor metabolic parameters and clinical staging, **Yilmaz** et al. enrolled 113 patients with pre-therapy 18-F FDG PET/CT. Among them, 43 cases with biopsy-proven axillary lymph node metastasis [28]. Their findings displayed a marked positive relationship between tumor SUVmax and TLG with T, N, and M states. Similarly, **Fikri** et al. illustrated that high tumor SUVmax was associated with advanced TNM staging [15]. The results indicated comparable findings; SUVmax, MTV, and TLG exhibited significant positive correlations with N and M status, as well as clinical staging, although SUVmax displayed insignificant positive correlations with T status. Our analysis of obesity and TNM status revealed no significant correlation between BMI and clinical staging (r= -0.092 and p= 0.289). Similar findings were reported by **Fikri** et al. [15]. A study examining various cancers, like-small cell lung carcinoma, BC, soft tissue sarcoma, and neck and head squamous cell carcinoma, investigated the relationship between obesity and tumor glucose metabolism [29]. Their study examined the association between SUL max and BMI in patients diagnosed with breast cancer. Their findings indicated a positive correlation between BMI and glucose uptake in primary breast lesions (r=0.36, p = 0.02). This study did not normalize tumor metabolic activity to lean body mass. Our findings revealed a weak inverse correlation between BMI, tumor SUVmax, and TLG (r = -0.060 and -0.010, p = 0.488 and 0.904). Our findings indicate that BMI is an inadequate measure of obesity, necessitating consideration of dysfunctional VAT[14].

Limitations of the research:

First, there is no detailed pathological staging analysis and classification of primary breast neoplasms and axillary lymph nodes. We utilized 18-F FDG PET/CT for clinical staging, which presents several challenges, particularly in assessing axillary lymph nodes. Additionally, we did not account for significant biomarkers indicative of systemic

inflammation, including the erythrocyte sedimentation rate. Nonetheless, these inflammatory biomarkers lack specificity. Future research should focus on pathological staging, subtypes, and systemic inflammation biomarkers.

CONCLUSIONS:

Our findings suggest that an increase in the V/S ratio and TLG are predictive of advanced-stage breast carcinoma.

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