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Elastography Ultrasound for Breast Tumors: Gland-to-Lesion Strain Ratio or Fat-to-Lesion Strain Ratio?

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Introduction: To evaluate the diagnostic efficiency of the gland-to-lesion strain ratio versus the fat-to-lesion strain ratio for breast tumor diagnosis.

Methods: The prospective study included 375 breast masses in 330 patients. B-mode ultrasound and elastography were performed for each mass. The gland-to-lesion strain ratio and fat-to-lesion strain ratio of the masses were calculated. The elasticity score of the lesions was also evaluated. The area under the curve, sensitivity, and specificity were calculated to compare the gland-to-lesion strain ratio with the fat-to-lesion strain ratio. Histopathological examination was considered the gold standard for final diagnosis.

Results: Three hundred and seventy-five breast masses were included in our study (298 benign and 77 malignant). The gland-to-lesion strain ratio (GLR) and fat-to-lesion strain ratio (FLR) of the malignant lesions were significantly higher than those of benign lesions ($P<0.0001$ for both). The sensitivity and specificity of fat-to-lesion strain ratio were significantly better than gland-to-lesion strain ratio, (sensitivity, 96.1% versus 72% and specificity, 93.3% versus 81.1%). The area under the curve values for the fat-to-lesion strain ratio (0.990) and the elasticity score (0.972) were significantly higher than those for the gland-to-lesion strain ratio (0.820) ($P < 0.0001$). However, there was no significant difference between the area under the curve of the fat-to-lesion strain ratio and the area under the curve of the elasticity score ($P=0.64$).

Conclusion: The fat-to-lesion strain ratio provided better diagnostic performance than the gland-to-lesion strain ratio in breast mass characterization.

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INTRODUCTION

With technological advances and improved image resolution, ultrasound is widely applied in the senological assessment for detection and characterization of breast lesions [1, 2]. In addition to the classical morphological criteria (shape, margin, boundary, orientation, echo pattern, posterior features), elastography, a non-invasive imaging technique, is available routinely in many ultrasound devices. This technique was developed to improve the specificity of breast ultrasound in B-mode (B-mode US) [3-10]. Elastography qualitatively evaluates tissue hardness through tissue displacement induced by compression (Elasticity score). The elastography images are acquired in real-time, in color, and

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classified according to the classification of Ueno and Itoh in five categories [3]. However, the elasticity score of a lesion can be influenced by various subjective factors [11]. The strain ratio (SR) providing a more objective assessment than the elasticity score [12]. It was used to measure breast lesion hardness semi-quantitatively. SR is the ratio between two regions of interest (ROIs) drawn in the mass and the surrounding normal breast tissue. It would therefore be more useful to know whether the glandular or fat tissue should be used as reference tissue for a better characterization of breast masses. Our study attempted to evaluate the diagnostic performance of the gland-to-lesion strain ratio (GLR) versus the fat-to-lesion strain ratio (FLR) in the characterization of breast masses.

METHODS

Patients and Lesions

This prospective study was approved by the Ethics Committee of our institution. All participants provided written informed consent. The study included 375 breast masses detected on clinical examination, B-mode ultrasound (US), and elastography between January 2017 and January 2020. The inclusion criteria were as follows: the presence of breast masses as assessed by B-mode ultrasound and elastography evaluation before core needle biopsy, and/or surgery. The exclusion criteria were: 1) previous history of breast cancer and 2) use of hormone therapy, radiotherapy, or neoadjuvant chemotherapy for adjacent lesions that may distort elastographic results. All ultrasound and elastography examinations were conducted by a radiologist with 16 years of experience in breast imaging and seven years of experience in elastography.

B-Mode Ultrasound

The ultrasound exams were performed using a Hitachi (HI Vision AVIUS) ultrasound machine equipped with a 6-14 MHz linear probe. The masses were classified according to the Breast imaging-reporting and data system (BI-RADS) ultrasound classification of the ACR [13], including shape, margin, boundary, echo pattern, presence of calcifications, orientation, and posterior acoustic features. The measurement of the largest sizes of mass in millimeters (mm) was obtained by measuring the mass in three planes of space.

Elastography

Elasticity score

The elasticity score for each breast mass was prospectively evaluated based on a five-point elasticity score proposed by Itoh et al., (Figure 1)[3]. The masses scored 1 to 3 are considered benign, and the ones scored 4 and 5 are considered malignant.

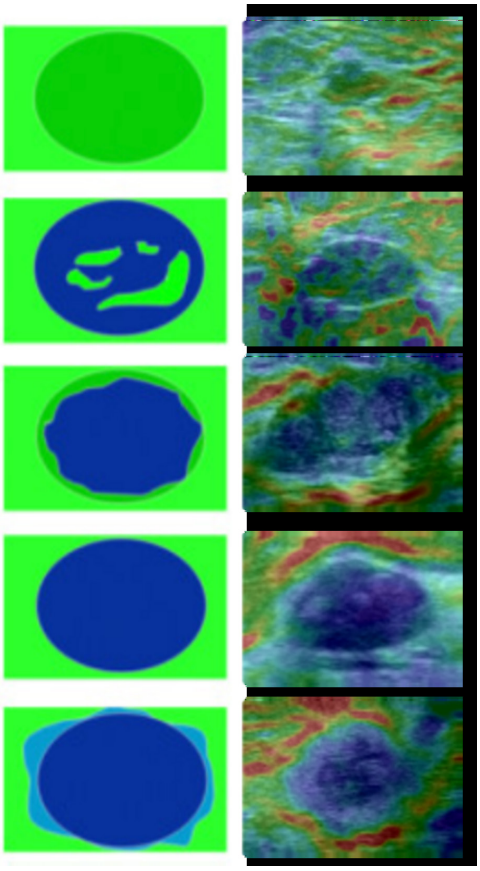

Figure 1: Elasticity Score Proposed by Itoh According to the Degree of Suspicion of Malignancy

Strain Ratio

We manually positioned regions of interest (ROIs) on the same color map for the semi-quantitative strain ratio, and two semi-quantitative parameters were obtained:

FLR, the first ROI was drawn on the color map of the lesion (L) and the second ROI was placed in the subcutaneous fat (F). The ratio F to L (FLR= F/L) was expressed as standard deviation (Figure 2A).

GLR, the first ROI was drawn on the color map of the lesion (L) and the second ROI was placed in the adjacent glandular tissue (G). The ratio G to L

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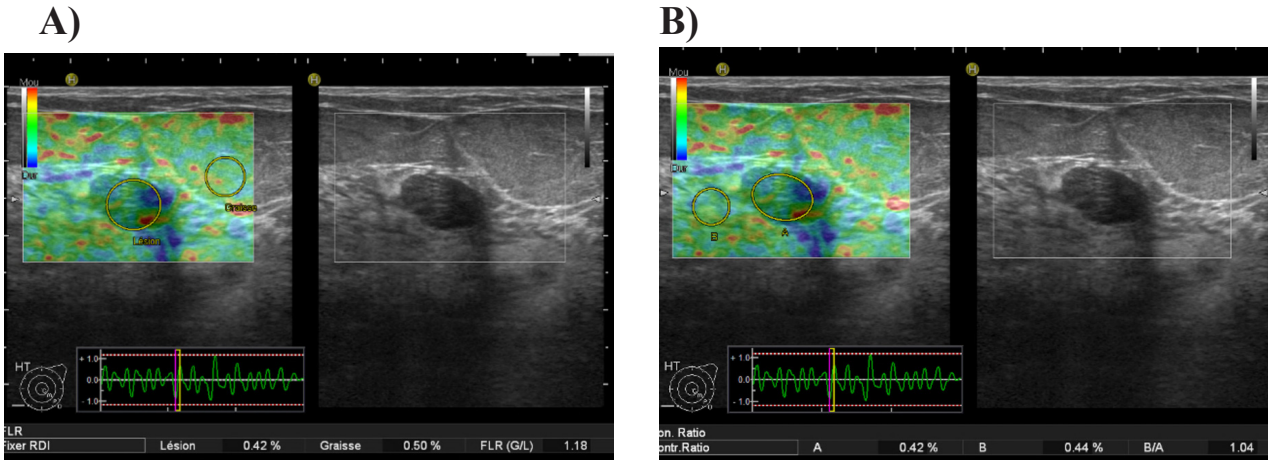

Figure 2: Strain Ratio
A) Fat to Lesion Ratio FLR, the first ROI drawn on the color map in the lesion (L) and the second ROI in the subcutaneous fat (F). In this example, the ratio F to L (FLR=F/ L) was calculated at 1.18; B) Gland-Lesion Ratio=GLR, the first ROI drawn on the color map in the lesion (L) and the second ROI in the glandular tissue (G). The ratio G to L (GLR=G/L), was calculated at 1.04. Histology: fibroadenoma.

(GLR= G/L) was expressed as standard deviation (Figure 2B).

Histology

The final diagnosis was determined by histopathology of lesions after core needle biopsy and/or surgery. The pathological findings of the lesions were divided into two groups: benign and malignant tumors.

Statistical Analysis

The statistical analysis was performed using SPSS 23. For all tests, a P value below 0.05 was considered statistically significant. B-mode ultrasound characteristics, lesion size, elasticity score, and strain ratio (FLR and GLR) of benign and malignant tumors were compared. Qualitative variables were represented as the number and the percentage of lesions, and quantitative variables as the mean±standard deviation (SD). Chi-square test or Fisher's exact test was used to compare percentages, and the student's t-test was used to compare the means. In the diagnostic performance analysis to distinguish between benign and malignant lesions, the positive test results for malignant mass were determined: BI-RADS category 4a or higher for B-mode US, and for each elastography parameter (elasticity score, GLR, and FLR), the positive results were acquired using the cutoff values identified by the Youden's index [14]. The sensitivity, specificity, and area under the curve (AUC) were calculated for each exam (B-mode US and elastography parameters). The Bennett's test, McNemar's test, and the $\chi 2$ test were conducted to compare the AUC, sensitivity, and specificity of B-mode US alone and the different elastography parameters (elasticity score, FLR, and GLR).

RESULTS

We reported a representative sample of 375 breast masses, of which 77 (20.53%) were malignant and 298 (79.47%) were benign masses. Fibroadenoma was the most common pathology of benign lesions in 189 cases (63.42%). Invasive breast carcinoma of no special type (ICNST) was often found in malignant masses (n=55/77, 73.55%). The distribution of masses according to histological results is reported in Table 1. The average age of patients with benign lesions was 41.80±12.30 years compared to 55.47±13.04 years for patients with malignant lesions (P<0.0001). The majority of patients with benign mass were detected on screening (44.57% of patients with benign mass vs. 18.06% of patients with malignant mass, P=0.00004), while patients with malignant lesions were often consulted for palpable mass (72.22% of patients with malignant lesions vs. 27.91% of patients with benign lesions, P=0.0001). The mean size of malignant masses was significantly larger than that of benign masses (24.46±11.53 mm vs. 17.74±10.64 mm, P<0.0001).

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Table 1: Distribution of Masses According to Histological Results

	Results, No.(%)
Benign Masses	298
Fibroadenoma	189(63.42)
Fibrocystic Mastopathy	55(18.46)
low-grade Phyllodes Tumor	30(10.07)
Diverse Lesions	24(8.25)
Malignant Masses	77
Invasive Carcinoma no Special Type in Situ	2(2.60)
Invasive Carcinoma no Special Type	55(71.43)
Lobular Invasive Carcinoma	9(11.69)
Diverse Lesions	11(14.28)

B-Mode Ultrasound Diagnostic Performance

The distribution of the BI-RADS categories classification and the two histological groups are summarized in Table 2. Benign lesions were often classified as BI-RADS 4 and 5 (74.50%). In terms of performance, the B-mode ultrasound shows 100% sensitivity. In contrast, the specificity and AUC were poor, 25.5% and 0.628, respectively (Figure 3A)

Table 2: Distribution According to the BI-RADS Category of Benign and Malignant Masses

	Benign, No.(%) (n=298)	Malignant, No.(%) (n=77)	P Value
BI-RADS Category			<0.0001
3	76(25.50)	0	
4a	190(63.76)	2(2.60)	
4b	7(2.35)	4(5.19)	
4c	23(7.72)	18(23.38)	
5	2(0.67)	53(68.83)	

Diagnostic Performance of Elasticity Score

Elasticity score two was found in most benign masses (71.14%), and malignant masses were more often scored 5 in 81.82% (Table 3). The best cutoff value of the elasticity score for differentiation between benign and malignant masses was between scores 3 and 4 with a sensitivity of 89.6%, specificity of 97.7% and an AUC of 0.972 (Figure 3B).

Table 3: Distribution of Elastography Between Benign and Malignant Masses[a]

	Benign (n=298)	Malignant (n=77)	P Value
Elasticity Score, No.(%)			<0.0001
1	10(3.36)	0	
2	212(71.14)	1(1.30)	
3	69(23.15)	7(9.09)	
4	3(1.01)	6(7.79)	
5	4(1.34)	63(81.82)	
Strain Ratio FLR, No. (mean±SD)	298(2.1±1.18)	77(32.7±39.89)	<0.0001
Strain Ratio GLR, No. (mean±SD)	247(1.5±0.67)	68(8.98±13.79)	<0.0001

[a] Abbreviations: FLR, fat-to-lesion strain ratio; GLR, gland-to-lesion strain ratio

Strain Ratio Diagnostic Performance

The mean FLR 32.7±39.89 (2.66-217.7) was higher in the malignant masses than the mean FLR in the benign masses 2.11±1.18 (0.62-13), with a significant difference (P<0.0001)(Figures 4, 5). Regarding the GLR, only 315 of the 375 masses were produced (84%) due to the absence of glandular tissue on the elastography image. The mean GLR 8.98±13.79 (0.68-77) for malignant masses was significantly higher than that of the benign masses 1.5±0.67 (0.08-5.46), (P<0.0001) (Figures 4, 5). In the malignant and benign groups, the mean FLR was considerably higher than the mean GLR (P<0.0001). The best cutoff for FLR and

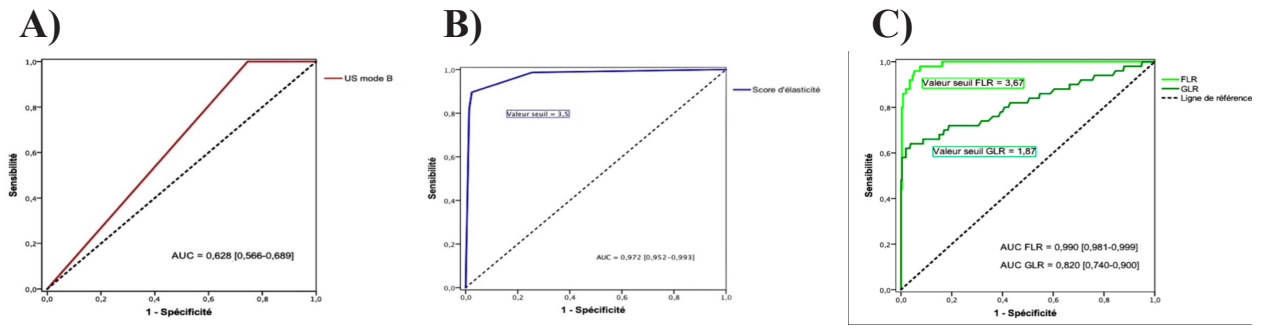

Figure 3: Receiver Operating Characteristic Curves for B-Mode US and Different Elastography Parameters
A) B mode US; B) elasticity score; C) FLR and GLR. The FLR (0.999) had the largest AUC compared to the GLR (0.820) and the elasticity score (0.972) but with no significant difference between the AUC of the FLR and the elasticity score (P=0.64).

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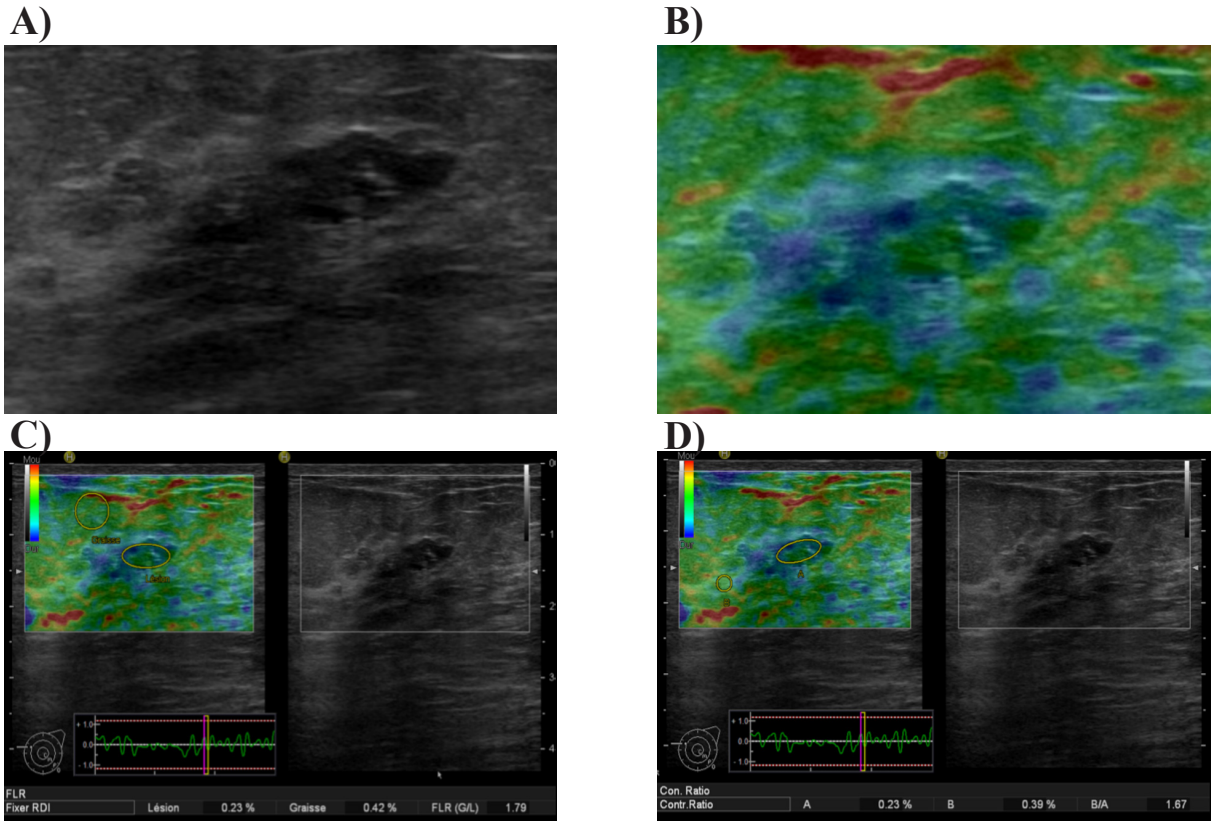

Figure 4: A 36-Year-Old Woman With a Fibroadenoma
A) The breast mass in the B-mode US image is categorized as BI-RADS 4a; B) in the elasticity score, the mass scored 2; C) FLR estimated at 1.79; and D) GLR at 1.67.

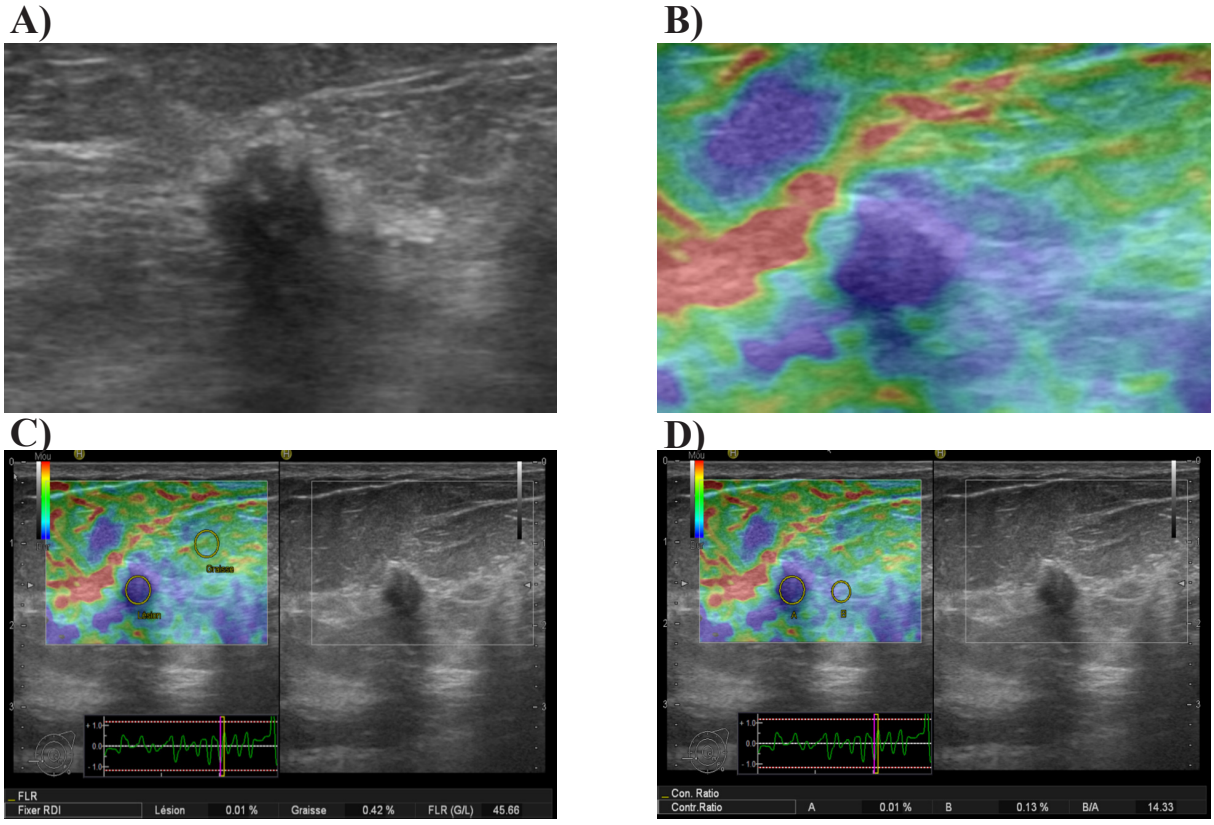

Figure 5: A 36-Year-Old Woman With an Invasive Carcinoma of No Special Type.
A) The breast mass in the B-mode US image is categorized as BI-RADS 5; B) Elasticity score. The mass scored 5; C) FLR estimated at 45.66; and D) GLR at 14.33.

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GLR to differentiate between malignant and benign breast masses was 3.67 (Youden index [IY]=0.881) and 1.87 (IY=0.531), respectively, with an AUC of 0.990 (0.981-0.999) and 0.820 (0.740-0.900 (Figure 3C). The FLR yielded higher sensitivity and specificity compared to the GLR (sensitivity, 96.1% versus 72%, and specificity, 93.3% versus 81.1%).

Comparison of the Diagnostic Performance of Different Elastography Parameters

The AUC values for elasticity score (0.972) and FLR (0.990) were higher than GLR (0.820) with a significant difference (P<0.001). However, there no significant difference between the AUC of the elasticity score and the AUC of the FLR (P=0.64). Our study has shown that the FLR yielded higher accuracy and specificity compared to the GLR (P<0.0001). The FLR had a lower specificity than the elasticity score (P=0.01), but no loss of sensitivity was found compared to the B-mode US (P=0.08). However, the elasticity score and GLR showed lower sensitivity compared to the B-mode US (P=0.004 and P<0.0001, respectively). The diagnostic performance of B-mode US and elastography parameters to differentiate between benign and malignant masses are summarized in Table 4.

DISCUSSION

In our study, we performed two strain ratio measurements: GLR and FLR. Our results showed that both the FLR and GLR were significantly higher in malignant than benign lesions (P<0.0001 for both). The findings of our study are consistent with the work of Zhou et al., [15], in which out of 193, masses 70 were malignant, and 123 were benign lesions. Moreover, the mean FLR of malignant masses was 3.91±1.42 (1.18-6.56) and 2.20±0.91 (0.70-4.80) for benign masses (P<0.0001). For GLR, the mean strain ratio was 2.15 ± 0.93 (0.66-5.19) for malignant lesions versus 1.45±0.48 (0.70-2.86) for benign lesions (P<0.0001). In a study by Graziano et al., [16] on159 lesions (106 benign lesions and 53 malignant lesions), malignant tumors were found to be harder than benign tumors in both methods of measuring FLR and GLR (8.28±7.5 vs. 3.69±4.4 and 7.18±8.1 vs. 2.15±1.7, P<0.0001). Similarly, in the Chee et al.,'s study [17], the mean FLR of malignant tumors was higher than that of benign tumors (5.37±1.63 (2.83-8.21) vs. 3.97±1.33 (1.23-6.89) (P<0.05). For GLR, the average strain ratio was 3.53±1.13 (1.97–5.67) for malignant masses and 2.74±1.10 for benign masses (1.02-5.7, P<0.05). FLR was considerably higher than GLR in both benign and malignant breast lesions (P<0.0001 for both) due to the elasticity difference between glandular and fat breast tissue. This difference was demonstrated in an in vitro study by Krouskop et al., [18], who reported that the elasticity modulus of glandular tissue was notably higher than that of adipose tissue. Moreover, Zhou et al., [19] used a shear wave elastography in an in vivo study and found that glandular tissue was harder than fatty tissue in benign and malignant breast lesions.

In terms of performance, FLR had a sensitivity of 96.1%, a specificity of 93.3%, and an AUC of 0.990 in the diagnosis of breast lesions, while GLR had a sensitivity of 72%, a specificity of 81.1% and an AUC of 0.820. The comparison of the two ratios showed that FLR delivered better diagnostic performance than GLR in differentiating benign and malignant breast masses (P<0.0001). In the literature, only three studies have examined the diagnostic performance of FLR and GLR. Similar results were published by Zhou et al., [15], in which the FLR with a cutoff value of 2.78 had 82.9% of sensitivity and 75.6% of specificity. However, the GLR with a cutoff value of 1.54 had a sensitivity of 77.1% and a specificity of 69.9%. In the Graziano

Table 4: Diagnostic Performance of Ultrasound and Different Elastography Parameters[a]

	AUC [CI 95%]	Sensitivity, % [CI 95%]	Specificity, % [CI 95%]
B-Mode US ≥BI-RADS 4a	0.628[0.566-0.689]	100[95.25-100]	25.5[20.9-30.7]
Elasticity Score ≥4	0.972[0.952-0.993]	89.61[82.8-94.6]	97.65[95.2-98.9]
Strain Ratio FLR ≥ 3.67	0.990[0.981-0.999]	96.1[89.2-98.7]	93.29[89.9-95.6]
Strain Ratio GLR ≥ 1.87	0.820[0.740-0.900]	72[61.4-82.7]	81.1[76.1-85.9]

[a] Abbreviations: AUC, area under the curve; BI-RADS, breast imaging-reporting and data system; CI, confidence interval; FLR, fat-to-lesion strain ratio; GLR, gland-to-lesion strain ratio

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et al., [16] study, the FLR with a cutoff value of 3, a sensitivity of 71.1% and a specificity of 75% had slightly better diagnostic performance than the GLR with a cutoff value of 2.15, a sensitivity of 83% and a specificity of 70.8%; however, this difference is not statistically significant. In a recent study by Chee et al., 53 masses (40 benign masses and 13 malignant masses) were studied, the FLR had a better specificity compared to the GLR (87.5% versus 37.5%, respectively)[17]. The fat tissue was considered the most appropriate structure for calculating the strain ratio because the stiffness of the breast fat tissue is stable, with less individual variation. However, the stiffness of glandular tissue could be impacted by multiple factors such as breast density, hormonal status, menstrual cycle, and lactation [20-24]. According to Jung et al., [25], FLR values were not influenced by the position of the ROI in the reference fat tissue, regardless of the depth of the lesion. To our knowledge, no publication has been made on comparing the FLR with the GLR using the same equipment in a large sample size.

CONCLUSION

The diagnostic performance of FLR was better than that of GLR in characterizing breast masses. The fat tissue was better than the glandular tissue as reference tissue to calculate the strain ratio in breast elastography. The use of fat tissue as a reference tissue to calculate strain ratio in breast elastography was better than that of glandular tissue.

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Not applicable

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ETHICS APPROVAL

The informed consent was obtained from all study participants or their guardians.

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