Breast Density Assessment with High-resolution Ultrasonography: A Reliability Study

Deeksha Bhalla[1], Tulika Singh[2], Veenu Singla[3], Shruti Kumar[4]

Received on: 01 July 2021; *Accepted on:* 10 July 2021; *Published on:* 31 December 2022

Abstract

Objective: To determine the accuracy of ultrasonic (US) assessment of breast density vs mammography, and its interobserver reliability.

Methods: One hundred consecutive adult women were scanned using a high-frequency ultrasound transducer in the upper outer quadrant of a single breast. Breast density was recorded as one of four categories: < 25%, 25–50%, 50–75%, and > 75% by two radiologists. Digital mammography was performed on the same day and density was assigned to one of four breast imaging-reporting and data system (BI-RADS) categories by a third radiologist. Cohen's Kappa was used to compute inter-rater reliability for US assessment and intermodality agreement among mammographic and US density.

Results: The most frequent mammographic density group was ACR B (43%). US density category B had the highest frequency of readings (49% and 51% readings of radiologists 1 and 2, respectively). Excellent interobserver agreement was seen for the measurements of US density; k = 0.968 [95% confidence interval (CI): 0.925–1]. Substantial intermodality agreement was seen for both radiologists 1 and 2; k = 0.675 (95% CI: 0.552–0.798) and 0.673 (95% CI: 0.551–0.796) respectively ($p < 0.001$). The US overestimated breast density in 14.5%, while underestimation was seen in 6.5% of cases.

Conclusion: The US provides accurate and reproducible estimates of breast density. This enables personalized screening, particularly in young women and high-density breasts.

Keywords: BI-RADS, Breast density, Breast neoplasms, Mammography, Mass screening, Ultrasonography.

Journal of Postgraduate Medicine, Education and Research (2022): 10.5005/jp-journals-10028-1587

Introduction

Breast density in women is a dynamic variable with manifold implications for not just cancer risk assessment but also for the detection of potentially cancerous lesions. American College of Radiology (ACR) classifies mammographic breast density into four categories, and it is required that this classification be applied to mammography reports as it potentially affects the sensitivity of the screening examination.[1] In addition, multiple studies have estimated a significant increase in breast cancer risk among women with dense breast tissue compared to those with fatty breasts, independent of other risk factors.[2,3] However, breast density in itself is influenced by multiple factors such as age and hormonal therapy among others.[4,5]

Significant interobserver variability has been recorded in the mammographic assessment of breast density.[6] Breast imaging-reporting and data system (BI-RADS) edition 5 has also abolished the use of objective, percentage cut-offs for the same, and now relies on a more subjective interpretation by the radiologist. US assessment of breast density has been studied in the past with a description of parenchymal patterns similar to those found on mammography.[7,8] Classification into four categories based on the extent of fibroglandular parenchyma (less than 25%, 25–50%, 50–75%, and more than 75%) was performed. Low frequency, low-resolution transducers were used in these studies, and comparisons were mostly in retrograde fashion with previously acquired digital or xeromammography films. Prospective evaluation of interobserver agreement among US breast density measurements, as well as the performance of US in comparison to mammography, has been performed on a small cohort of patients in a relatively recent study.[9]

The purpose of our study was to prospectively evaluate the inter-rater reliability of US assessment of breast density; and its accuracy compared to mammography on a larger cohort of patients, using high-resolution sonomammography.

[1–4]Department of Radiodiagnosis, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Corresponding Author: Tulika Singh, Department of Radiodiagnosis, Postgraduate Institute of Medical Education and Research, Chandigarh, India, Phone: +91 2147483647, e-mail: tulikardx@gmail.com

How to cite this article: Bhalla D, Singh T, Singla V, *et al.* Breast Density Assessment with High-resolution Ultrasonography: A Reliability Study. J Postgrad Med Edu Res 2022;56(4):160–164.

Source of support: Nil

Conflict of interest: None

Materials and Methods

Study Design

This was a prospective study, performed at our institution, in which 100 consecutive adult women (over 18 years ago) undergoing screening or diagnostic mammography were recruited (mean age 49 years). Informed consent was taken from the patients. Patients were included if they had a minimum of one breast that had not been previously operated on or undergone breast biopsy within 14 days of the study. Patients were excluded if they were lactating at the time of the study, had breast implants, or had received chemotherapy or radiotherapy to the breast. Other criteria for exclusion were patients who did not give consent or had contraindications to mammographies such as pregnancy, tender, or inflamed breasts. Prior to the examination, a questionnaire about weight, height, body mass index (BMI), menopausal status and parity, family history, and intake of hormonal therapy was filled out by the participants.

Image Acquisition and Analysis

Two independent radiologists with 3 years and 10 years of experience (henceforth referred to as Rad 1 and Rad 2, respectively), performed the real-time US on one breast for assessment of density. Hand-held high-frequency US transducer was used (Supersonic Aixplorer Multiwave Ultrasound System with 4–15 MHz linear array transducer). Patients were scanned in a sequential manner by one radiologist followed by the other. A uniform radial scanning technique was applied using both longitudinal and transverse views. The left breast was scanned in case of both breasts fit into the inclusion criteria. In other situations, the right breast was scanned. The US still images of the upper outer quadrant (9'o clock–12'o clock) in the transverse plane were acquired and stored. The scanning time taken by each radiologist was approximately 3–7 minutes.

Patients underwent full-field digital mammography the same day on the Siemens MAMMOMAT Novation DR system. Standard views, that is, craniocaudal (CC) and mediolateral oblique (MLO) views were acquired for each breast.

Image Analysis

For US classification of breast density, the echogenic fibroglandular tissue in a particular field was marked out. The maximum length of fibroglandular tissue was measured. The length of the entire breast tissue from the inner margin of the skin to an outer wall of the chest wall was measured; this included subcutaneous fat, fibroglandular parenchyma, and retromammary fat. Following this, the length of fibroglandular tissue was calculated as a percentage of the breast tissue. An average of three readings at different clock positions was taken. The final assessment was recorded as one of four categories–A: < 25%, B: 25–50%, C: 50–75%, and D: > 75% (Fig. 1). The readings of both radiologists were independently recorded.

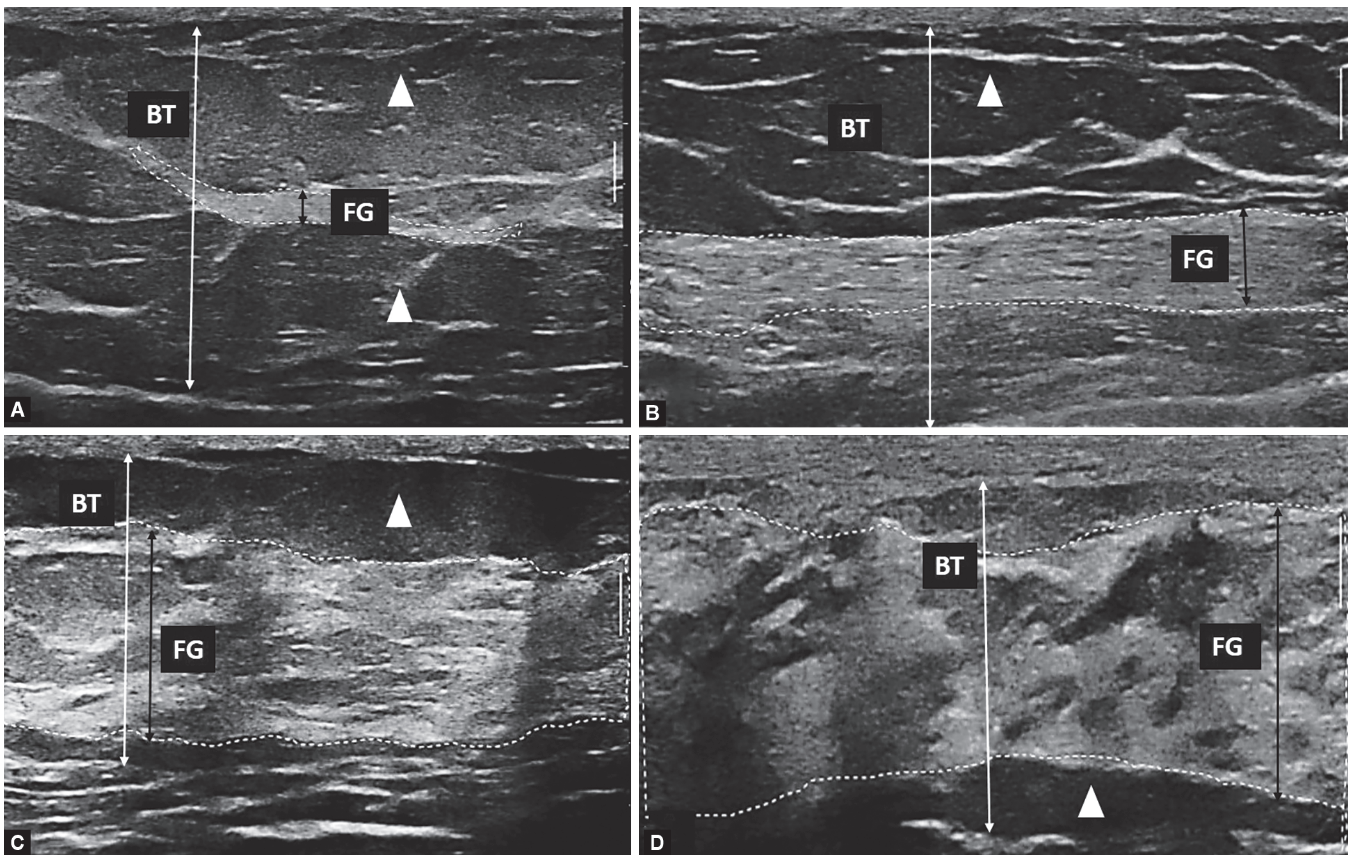
Mammographic density was assessed by a third trained radiologist to avoid recall bias from the US examination. Density was allotted to one of the four categories (ACR A, B, C, or D) under the BIRADS 5 lexicon (Figs 2 and 3).

Statistical Analysis

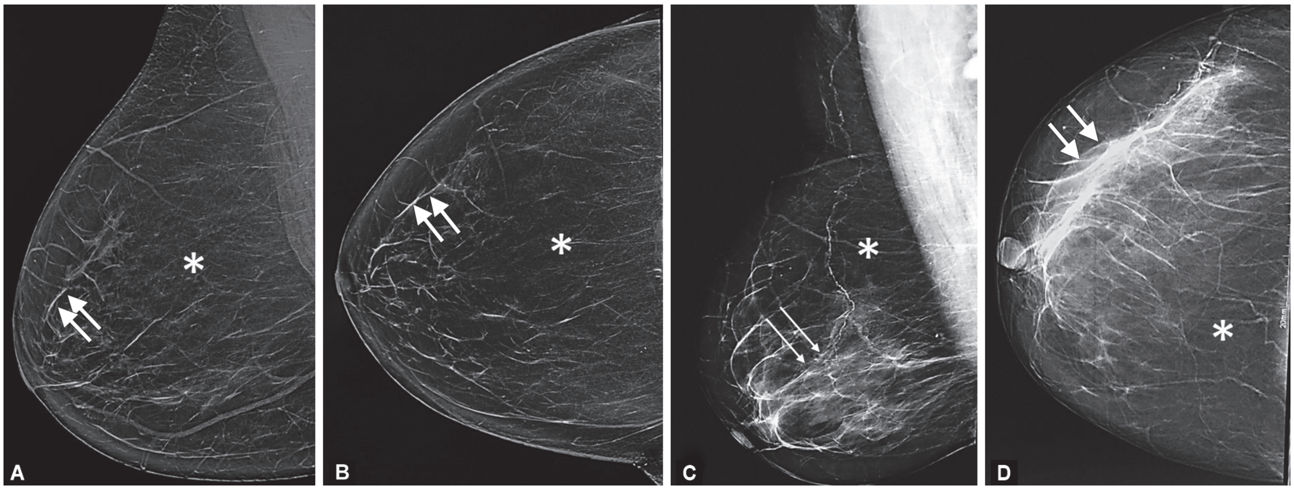
Statistical analysis was performed using IBM SPSS Statistics (version 22.0). Mean and standard deviation was calculated for continuous variables such as age, height, weight, and BMI. Discrete variables such as family history, prior history of breast malignancy, intake of hormone replacement, menopausal status, parity, and the US and mammographic breast density were expressed in terms of their frequencies and percentages.

Pearson Chi-square test was used to test the significance of the relationship between recorded US breast density and all demographic variables age, menopausal status, and parity, respectively. In addition, the relationship of breast density with familial breast malignancy was also computed. p-value < 0.05 was taken as significant.

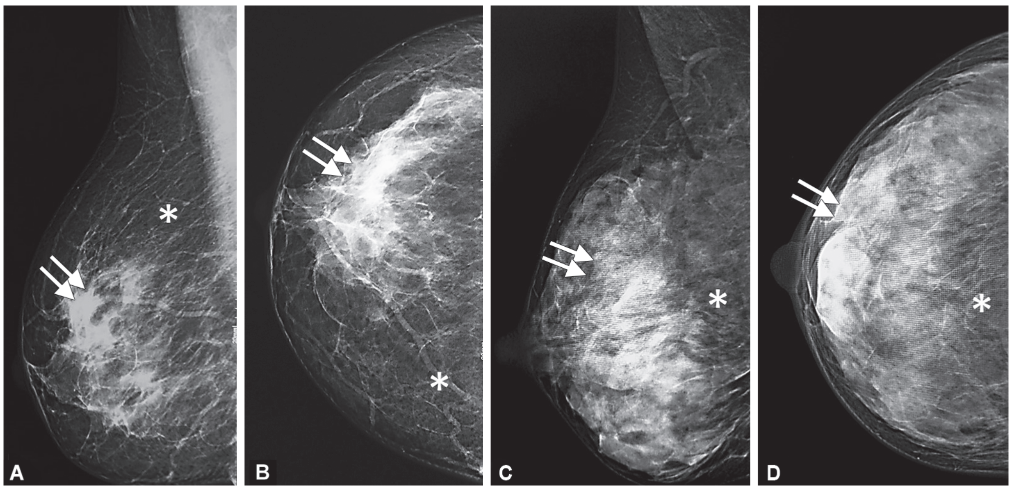
Cohen's kappa was used to measure the interobserver agreement in US breast density. Intermodality agreement between mammographic density and US density was also computed. The k value strength was defined as follows "< 0.0: poor agreement,



Figs 1A to D: Breast density was calculated by measuring the length of fibroglandular tissue (FG, black arrow) as a percentage of length of entire breast tissue (BT, white arrow). (A) Category A: < 25% FG; (B) Category B: 25–50% FG; (C) Category C: 50–75% FG; (D) Category D: > 75% FG



Figs 2A to D: ACR A: MLO (A) and CC (B) views of the right breast show a predominantly fatty (*) composition of the breast. Sparse FG seen in upper outer breast (arrow). ACR B: MLO (C) and CC (D) views show scattered FG (arrows). Fat is in abundance (*)



Figs 3A to D: ACR C: MLO (A) and CC (B) views show a heterogeneously dense breast (arrows). The relative amount of fat (*) is reduced. ACR D: MLO (C) and CC (D) views show an extremely dense breast (arrows). Only thin rim of retromammary fat (*) is seen

0.0–0.20: slight agreement, 0.21–0.40: air agreement, 0.41–0.60: moderate agreement, 0.61–0.80: substantial agreement and > 0.81: excellent agreement." A 95% CI was also computed.

Results

Demographics

The mean age of the examined women was 49 years, with a range of 64 years (22–86 years). The mean weight was 59.3 + 6.2 kg. The mean height was 160.57 + 3.1 cm and the mean BMI was 23.01 + 2.5 kg/m^2.

Risk Assessment

About 3% (3 of 100) of patients had a family history of breast malignancy (1% in first-degree relatives, 2% in second-degree relatives). Around 1% (1 of 100) patients had a prior history of malignancy in the opposite breast. Another 1% of patients had a family history of carcinoma endometrium in a first-degree relative. Nearly 3% of patients were on hormonally active therapy. About 40% of patients were postmenopausal, while another 9% of patients had undergone prior hysterectomy. A total of 98% of patients were multiparous, while 1% of each patient were uniparous and nulliparous, respectively.

Mammographic and Ultrasonographic Breast Density

The distribution of mammographic and US breast density among study subjects is shown in Table 1.

On application of Chi-square test, US breast density was not found to vary significantly with either BMI ($p = 0.32$), parity ($p = 0.92$), menopausal status ($p = 0.08$) or family history of malignancy ($p = 0.76$). The only variable with which it did vary significantly was the age of the participant at the time of the study ($p = 0.02$).

Interobserver Agreement in Ultrasonographic Density

Table 2 shows the concurrence among readings of both radiologists. Rad 1 showed agreement with Rad 2 in 98% of scans. The readings differed in 2% scans, where Rad 1 selected higher density grades in patients who were assigned Category B by Rad 2. Among these two scans, the density variable was within one category in one scan and differed by two categories in the other. When the density variable was dichotomized (fatty–grade A and B) and dense (grade C and D)—a similar 98% of scans were in exact agreement. On the

Table 1: Number of patients in each assessment category A, B, C, and D on mammography and ultrasound by each radiologist independently

Categories	*Mammography (N = 100)*	*US (radiologist 1) (N = 100)*	*US (radiologist 2) (N = 100)*
A	9	9	9
B	43	49	51
C	38	33	32
D	10	9	8

Table 2: Cross tabulation density readings of ultrasonic breast density by both radiologists

	Radiologist 2 (n = 100)			
Radiologist 1 (n = 100)	*A (n = 9)*	*B (n = 51)*	*C (n = 32)*	*D (n = 8)*
A (*n* = 9)	9 (100%)	0	0	0
B (*n* = 49)	0	49 (96.1%)	0	0
C (*n* = 33)	0	1 (2%)	32 (100%)	0
D (*n* = 9)	0	1 (2%)	0	8 (100%)

Table 3: Cross tabulation of readings of mammographic breast density vs ultrasonic breast density assessed by both radiologists. Disparity in readings in each category are highlighted in bold letters

	Mammography			
	A (n = 9)	*B (n = 43)*	*C (n = 38)*	*D (n = 10)*
Radiologist 1				
A	8 (88.8%)	1 (2.3%)	0	0
B	1 (11.1%)	38 (88.3%)	9 (23.7%)	1 (10%)
C	0	3 (6.8%)	27 (71.1%)	3 (30%)
D	0	1 (2.3%)	2 (5.3%)	6 (60%)
Radiologist 2				
A	8 (88.8%)	1 (2.3%)	0	0
B	1 (11.1%)	39 (90.7%)	10 (26.3%)	1 (10%)
C	0	3 (6.8%)	26 (68.4%)	3 (30%)
D	0	0	2 (5.3%)	6 (60%)

computation of Cohen's Kappa, excellent agreement was found between the density recordings of both observers with k = 0.968 (95% CI: 0.925–1, $p < 0.001$).

Intermodality Agreement among Mammographic and Ultrasonographic Breast Density

Table 3 shows the concurrence among readings in both modalities. The agreement among the US and mammographic density for Rad 1 and Rad 2 was 79% each. When the density variable was dichotomized, there was disagreement in 1% scans of Rad 1, while Rad 2 showed complete agreement. Ultrasound overestimated breast density in 14.5% of scans: 14% (14 of 100) of Rad 1, and 15% (15 of 100) of Rad 2. On the other hand, ultrasound underestimation of breast density was lower, seen in 6.5% of patients: 7% (7 of 100) readings of Rad 1 and 6% (6 of 100) readings of Rad 2.

When the ultrasound showed discordant readings with mammographic density, the readings were within one category of each other in 92.8% of scans (39 of 42 for both radiologists). There was higher discordance in denser breasts; 11.1% each in category A, 11.6% (Rad 1) and 9.3% (Rad 2) in category B, 28.9% (Rad 1), and 31.5% (Rad 2) in category C and 40% each in category D. On the computation of Cohen's Kappa, substantial agreement was found between the density recordings of both observers compared with mammography. The values were k = 0.675 (95% CI: 0.552–0.798) and 0.673 (95% CI: 0.551–0.796) for Rad 1 and 2, respectively ($p < 0.001$).

Discussion

Annual screening mammograms for women in their 40s (40–49 years' age group) remain controversial. Guidelines vary across nations, while the American College of Radiology and American Cancer Society guidelines recommend annual screening of women above 40 years of age,[10] others such as the United States Preventive Services Task Force[11] and the Netherlands recommend routine screening mammograms only above 50 years of age.[12] These guidelines cite the low risk/benefit ratio, that is, any modest mortality benefit is outweighed by the increased rate of false positives and additional testing. Therefore, screening in younger women is recommended only for those with at least a twofold risk; either a first-degree relative with breast cancer; or very high breast density.[13] Breast density of the ACR category D has been associated with a twofold risk of breast cancer while ACR category C increases the risk to about 1.5 to two times.[14]

Thus in this era of personalized screening, particularly in light of the Dense Breast Notification laws,[15] ultrasound-based breast density screening may benefit the decision of when to screen and how often to screen women: particularly in the younger age group. Because of the non-ionizing nature of the modality, it lends itself to easy longitudinal follow-up of breast density changes with age in women. In addition, there is recent interest in both primary and secondary preventive therapy in women using breast density as imaging biomarker.[16,17]

We hence set out to perform a prospective evaluation of hundred patients by both full-field digital mammography and high-resolution sonomammography in order to categorize breast density. A substantial intermodality agreement was found (k = 0.67) when using the ACR-BIRADS categories of breast density on mammography and similarly classifying the US breast density into four patterns. Around 79% of readings showed exact agreement when using this classification, while near perfect agreement was seen when the patterns were reduced to two, that is, "fatty" or "dense." Similar values for the intermodality agreement were obtained in a previous study,[9] though the number of readings showing exact agreement was higher in our study. Even among discordant scans, the density readings were within one category of each other in the vast majority of cases (92.8%). Breast density readings in the US also showed excellent interobserver agreement (k = 0.968). This was substantially higher than the value reported by previous investigators,[9] who had an inter-rater agreement of substantial level (k = 0.63). The highest interobserver variability was seen in intermediate categories of density. In addition, similar readings of density as well as intermodality and interobserver agreement were seen among both radiologists, despite differing experiences in breast imaging.

Our study suffered from some limitations. A fewer number of trained radiologists were engaged to test interobserver reliability. Longitudinal follow-up of breast density assessments of the US was not done to estimate the risk of breast cancer with changing US density groups, or the temporal revolution with age. In addition, the small sample size in our study also is a potential limiting factor to large-scale application, though, to the breast of our knowledge, our study is the largest of its kind in the literature.

To conclude, the US shows promise as a modality for fast and reproducible estimates of breast density. If our results can be validated in population-based studies, sonomammography may be used for longitudinal follow-up of changes in breast density with age and suggest mammographic screening when appropriate. In addition, the direct relationship of US breast density to breast cancer may also be evaluated.

Orcid

Deeksha Bhalla https://orcid.org/0000-0003-0478-6859

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