ORIGINAL RESEARCH ARTICLE

Automated Volumetric Analysis of Mammographic Density with Digital Breast Tomosynthesis in Comparison with Visual Assessments According to Breast Imaging Reporting and Data Systems (BI-RADS) and its Correlation with Breast Cancer

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ABSTRACT

Introduction: Mammographic density is a radiological representation of dense fibroglandular tissue in the breast. This study aims to compare the mammographic density by automated volumetric method, Volpara (quantitative method) with visual assessment by radiologists according to breast imaging reporting and data systems (BI-RADS) (qualitative method) and to establish its potential usage in clinical practice.

Methods: This was a cross-sectional analytical study conducted between November 2019 to November 2020 which included women aged between 35 to 65 years having clinical sign and symptoms of breast disease. Each mammogram was assessed for breast density according to the BI-RADS breast density categories by two radiologist and compared with volumetric breast density assessed by Volpara, an automated software.

Results: A total of 110 women were included in the study with mean age 46.8 years. Of the total, 53.64% women's breast had spiculated margins and 41.82% women had BI-RADS V. According to Volpara, observer 1 and 2 a total of 47.3%, 53.6% and 43.6% breasts were heterogeneously dense, respectively. A total of 90% women had high breast density. A total of 47% women had right breast malignancy and 36% had left breast malignancy. A fair agreement was observed between two observers (κ=0.384); however, moderate agreement was seen between Volpara and observer 1 (κ=0.539) and Volpara and observer 2 (κ=0.469).

Conclusion: Overall, it was found that Volpara has moderate agreement with radiologists' visual assessment supporting the potential use of Volpara as an adjunct tool for breast screening.

Keywords: BI-RADS, Computer Assessment, Mammography, Radiological Density, Volpara, Mammographic Breast Density.

INTRODUCTION

Cancer prevalence and death are rapidly mounting worldwide. Non-communicable diseases (NCDs) are now accountable for the mainstream of global deaths, and cancer is anticipated to rank as the foremost cause of death and the single most chief barrier to increasing life expectancy in every country of the worldwide.[1] Breast cancer is the second-most common form of cancer in females after lung cancer.[2] Mammographic breast density (MBD) defines the amount/quantity of radiologically dense fibroglandular tissue in the breast. Dense tissue comprises the functional glandular tissue (mammary lobules and ductal system) and the fibrous stromal tissue (including blood vessels, collagen fibers and immune cells) of the breast. Fibroglandular tissue appears white on a mammogram due to high attenuation and adipose or fatty tissue appears dark, this is due to different attenuation properties. Abundant factors including age, ethnicity, endogenous and exogenous hormones, menopausal status, body mass index (BMI) and parity forming effect on breast density. MBD is genetically determined, which shows significant heritability, twin studies show approximately 60% associations. Thus, MBD assessment is important for detecting women at increased risk of developing breast cancer.[3]

Mammographic density represents the percentage/proportion of dense tissue of the entire breast. The percent mammographic density is the appearance of mammographic density in accordance to the different radiographic attenuation features of the composition of breast tissue.[4] Mammographic density is defined as fibroglandular mammary tissue consisting of fibroblasts, epithelial cells and connective tissue.[5] Breast imaging reporting and data systems (BI-RADS) is the most commonly used tool for assessment of mammographic density on a mammogram. Volpara is

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an automated density measure used for the calculation of volumetric density for each breast separately and overall for a woman.

The aim of this study was to compare the mammographic density by automated volumetric method (quantitative method) with visual assessment by radiologists according to BI-RADS (qualitative method). This study also evaluated the association between high mammographic density (Type C, Type D) and risk of breast cancer. Further, the present study evaluated the feasibility of this software by comparing it to the qualitative BI-RADS density category, and to determine the factors influencing the agreement and disagreement between Volpara and the BI-RADS density category.

MATERIAL AND METHODS

This was a prospective study conducted in Department of Radio diagnosis Government medical college Kota , Rajasthan.

Study period **:** 1 year- from November 2019 to November 2020.

Sample size : 110.

Inclusion cirietria

1. Patients between age group 35 to 65 years.
2. Patient with < 35 years with clinical sign and symptoms shows breast disease)

Exclusion criteria

1. Patient with age < 35 years and > 65 years.
2. History of mastectomy (one or both breast) .
3. History of breast conservative surgery or any other breast surgery.
4. History of radiotherapy / chemotherapy.

Equipments

- Digital breast tomosynthesis – FUJIFILM AMULET INNOVALITY
- Ultrasound -ALPINION CUBE 15
- Automated breast density software -(VOLPARA, VERSION 3.3/1.5.3.0 ; VOLPARA SOLUTIONS)

Procedure of study

Measurements of fibroglandular volume (absolute density), breast volume, and Volumetric breast density (percent density) were obtained from raw data by using an automated software (Volpara, version 3.3/1.5.3.0 ; Volpara Solutions).[6] The density values represented the average value for a screening examination, which typically consisted of four images (craniocaudal and mediolateral oblique views of each breast). The Volpara Density Grading (VDG) is graded according to the percentage volumetric breast density as follows:

VDG 1, less than 3.5%;
VDG 2, 3.5% to less than 7.5%;
VDG3, 7.5% to less than 15.5%;
VDG 4, 15.5% or more.[7]

$$\text{Volumetric breast density (\%)} = \frac{\text{Volume of dense tissue}(cm^3)}{\text{Volume of dense tissue } (cm^3) + \text{Volume of fat tissue } (cm^3)^{8}}$$

All mammographic images were downloaded to a soft-copy review workstation (in BARCO Monitor) with soft-copy reading software. Two radiologists independently reviewed and interpreted mammography and soft-copy review of digital mammography images at the review workstation. Both the radiologists were blinded to each other's assessments and to the volumetric breast density. Each mammogram was assessed for breast density according to the BI-RADS breast density categories (category A, almost fatty; category B, scattered areas of fibroglandular densities; category C, heterogeneously dense, and category D, extremely dense).

The categorical and ordinal variables are assessed using Pearson's chi-square test, Cohen's kappa reliability test, unpaired t-test, Pearson's correlation test. The test was considered significant if the p value was <0.05. The concordance between BI-RADS score (qualitative) and VOLPARA score (quantitative) was assessed using sensitivity, reliability, incidence and diagnostic accuracy of the technique.

RESULTS

A total of 110 women were included in the study with age group between 35 to 65 years. The mean age was 46.8 years and the majority 34.5% of women aged ≤40 years followed by 32.5% between 41-50 years. Of the total, 53.64% women's breast had spiculated margins followed by 17.27% had well circumscribed margin, 10.91% had micro-lobulated margins. A total of 41.82% women had BI-RADS V followed by 25.45% BI-RADS IV C (Table 1).

According to Volpara, observer 1 and 2 a total of 47.3%, 53.6% and 43.6% breasts were heterogeneously dense, respectively, which may obscure small masses (C); 34.5%, 16.4% and 9.1% breasts were extremely dense, respectively, which lowers the sensitivity of mammography (D) (Table 2). A total of 99 (90%) women had high breast density, of which

Parameter	N=110
Age (years), mean (SD)	46.8 (9.8)
Age (years)	
≤40	38 (34.5)
41-50	36 (32.7)
51-60	19 (17.3)
≥61	17 (15.5)
Margins	
Indistinct	10 (9.09)
Micro Lobulated	12 (10.91)
Obscured	4 (3.64)
Spiculated	59 (53.64)
Others	6 (5.45)
Well Circumscribed	19 (17.27)
BI-RADS	
Type II	6 (5.45)
Type III	10 (9.01)
Type IV A	5 (4.55)
Type IV B	15 (13.64)
Type IV C	28 (25.45)
Type V	46 (41.82)
Data presented as n (%), unless otherwise specified.	

Table-1: Mean age and distribution according to age, margin and BI-RADS

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	Volpara	Observer 1	Observer 2
The breasts are almost entirely fatty (A)	4 (3.6)	4 (3.6)	4 (3.6)
There are scattered areas of fibro glandular density (B)	16 (14.5)	29 (26.4)	48 (43.6)
The breasts are heterogeneously dense, which may obscure small masses (C)	52 (47.3)	59 (53.6)	48 (43.6)
The breasts are extremely dense, which lowers the sensitivity of mammography (D)	38 (34.5)	18 (16.4)	10 (9.1)
Chi-square =36.7886; P-value=<0.0001			

Table-2: Distribution of women according to density of breast

		≤40 years		41-50 years		51-60 years		≥61 years	
		N	%	N	%	N	%	N	%
Right	Benign (18)	11	28.9	7	19.4	0	0	0	0
	Malignant (47)	12	31.6	11	30.6	12	63.2	12	70.6
Left	Benign (9)	5	13.2	4	11.1	0	0	0	0
	Malignant (36)	10	26.3	14	38.9	7	36.8	5	29.4
Total		38	100	36	100	19	100	17	100

Table-3: Distribution of benign and malignant cases according to age

	A	B	C	D	Kappa (95% CI)
Between observer					
A	4	0	0	0	0.384 (0.243 - 0.525)
B	0	27	2	0	
C	0	21	32	6	
D	0	0	14	4	
Observer 1 and Volpara					
1	4	0	0	0	0.539 (0.406 to 0.671)
2	0	16	0	0	
3	0	13	39	0	
4	0	0	20	18	
Observer 2 and Volpara					
1	4	0	0	0	0.469 (0.340 to 0.599)
2	0	16	0	0	
3	0	22	30	0	
4	0	2	16	20	
Kappa <0, no agreement; 0.00-0.20, sight agreement; 0.21-0.40, fair agreement; 0.41-0.60, moderate agreement; 0.61-0.80, substantial agreement; 0.81-1.00, almost perfect agreement.					

Table-4: Summary of reliability

Density grade	With HRT	Without HRT
Observer 1		
A	0	4 (5.13)
B	7 (21.88)	22 (28.21)
C	19 (59.38)	40 (51.28)
D	6 (18.75)	12 (15.38)
Observer 2		
A	0	4 (5.13)
B	8 (25.00)	32 (41.03)
C	18 (56.25)	28 (35.90)
D	6 (18.75)	14 (17.95)
Volpara		
1	0	4 (5.13)
2	2 (6.25)	14 (17.95)
3	19 (59.38)	33 (42.31)
4	11 (34.38)	27 (34.62)

Table-5: Distribution of patient's density grade according to HRT

the majority were aged less than 50 years. A total of 47 women had right breast malignancy and 36 had left breast malignancy (Table 3). A negative correlation ($p<0.05$) was found between age and volumetric density of right and left breast (Figure 2). When the reliability between observers was evaluated it showed fair agreement between two observers ($\kappa = 0.384$); however, moderate agreement was seen between Volpara and observer 1 ($\kappa = 0.539$) and Volpara and observer 2 ($\kappa = 0.469$) (Table 4).

Of the total 110 women, 32 (29.1%) women received hormone replacement therapy (HRT). Among women who received HRT, the breast density was significantly higher than those who did not receive HRT (right breast: 660.46 [206.99] vs. 608.10 [156.78]; p<0.0001; left breast: 663.07 [241.16] vs. 603.47 [160.02]; <0.0001). Among women who received HRT, 59.38% were graded as the Type C by observer 1; 56.25% were graded as the Type C by observer 2; and 59.38% were graded as type 3 according to Volpara (Table 5).

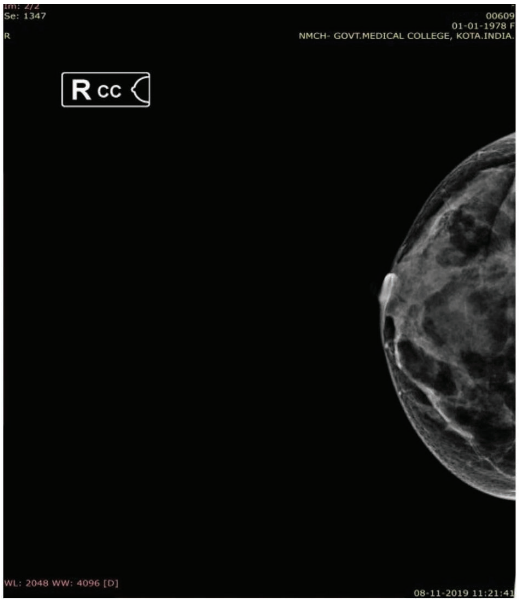

Figure: 1a

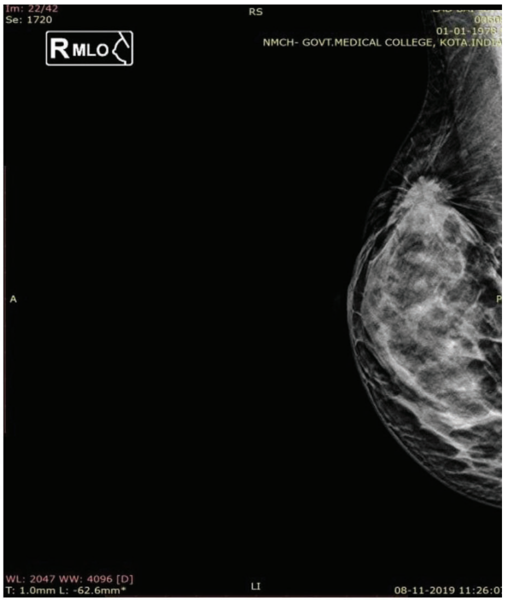

Figure:1b

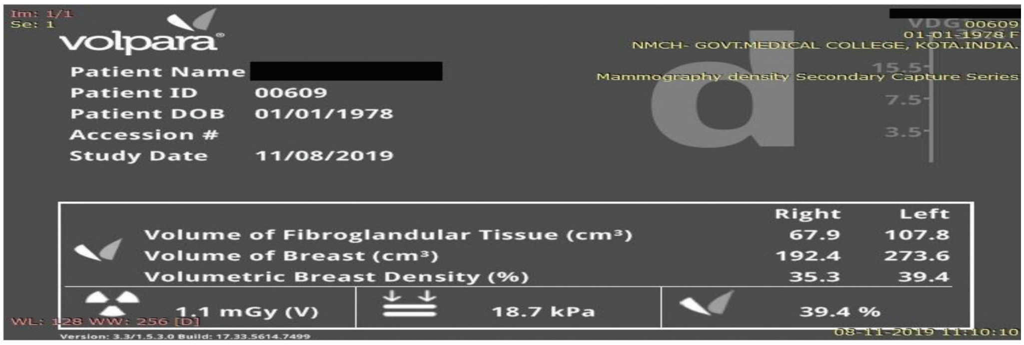

Fig: 1c

Figure-1A & 1B: Right breast, (CC) and (MLO) views shows shows extremely dense fibroglandular tissue(Type-D breast density- according to BIRADS) high density lesion in right upper outer quadrant , lesion is irregular in shape with spiculated margins and architectural distortion of adjacent breast parenchymal tissue (BIRADS-IV C). Figure 1c: Automated volumatric analysis (Volpara software) breast tissue density is Grade-4 (VDG-4)

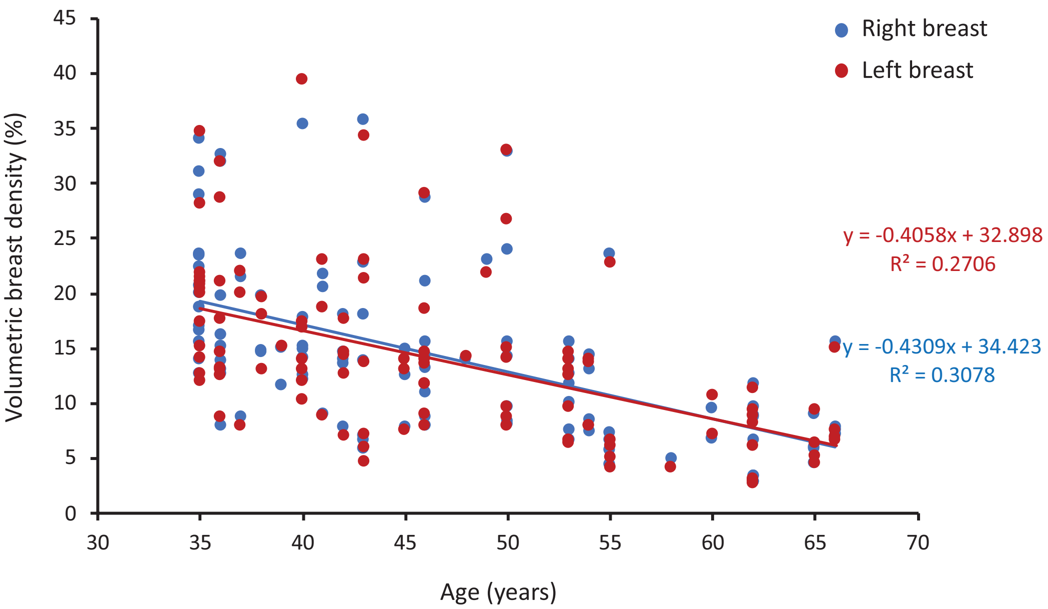

Figure-2: Pearson's correlation between age and volumetric breast density

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DISCUSSION

The effect of breast density on breast cancer risk is applicable for primary and secondary prevention, where it can potentially be used as a risk stratification factor. There is limited published evidence on the association between volumetric density and breast cancer risk, although previous studies have suggested that volumetric density may be more strongly associated with breast cancer risk due to its predicted biological association.[9,10] According to the meta-analysis of McCormack et al, women with extremely dense breasts based on the BI-RADS classification have higher breast cancer risk compared with women with fatty breasts.[11]
Focus on quantitative measurement of breast density is important for estimation of breast cancer risk. There are many studies reported a direct association between increased mammographic density and the increased risk of breast cancer.[12,13,14,15] Area-based quantitative density assessment methods are reliable, but most of these semi-automated methods, which is time-consuming.[16]
Volumetric assessment of three-dimensional dense tissue volume is more reliable than an area-based estimation of breast density, because of there are some limitations with fully automated area-based density measurements.[17]
Fully automated area-based density measurements those methods adopt a binary system, which classifies each pixel to either glandular tissue or fat without accounting for the actual depth of the pixel. Other one is changes in the imaging parameters may influence the image contrast or background density in influencing changes in density over time. Furthermore area-based density does not represent three-dimensional glandular tissue, thus actual glandular tissue may be higher or lower than the density according to the total breast volume. Thus, our present study measures breast density using Volpara, which is an automated volumetric breast density assessment.

In the present study the mean age of the participants was 46.8 years with 34.5% aging ≤40 years and 32.5% aged between 41-50 years demonstrating higher prevalence breast cancer in 4th and 5th decade of life. In our study out of total malignant cases, 22.9% were in age group 51-60 years followed by 20.5% cases in age group ≥61 years. National cancer institute reported 276,480 new breast cancer cases in 2020 and suggest that age is one of the risk factors for breast cancer with observed facts that 20.1% were aged 44–55 years and 25.6% were aged 55–64 years.[18] In another report by Anders et al observed that of all cancers diagnosed among women, more than 40% is breast cancer by the age of 40[19]; however, Youk et al found mean age of 51.4 years with 313 women 30–83 years.[20]

In the present study, according to Volpara 47.3%, according to observer 1 53.6% and observer 2 43.6% women's breasts were heterogeneously dense, which may obscure small masses; however, 34.5%, 16.4% and 9.1%, respectively, women's breasts were extremely dense, which lowers the sensitivity of mammography according to Volpara, observer 1 and observer 2, respectively. Rahmat et al used Quantra software for breast density assessment and found that Quantra assign 44% patients in B category followed by 41.8% in C category.[21] In their study, there were 3 observers, according to observer 1, 2 and 3 a total of 45.8%, 53.4%, and 37.4%, respectively, women had category B.

In the present study, a total of 75.5% women had malignancy and 24.5% had benign breast, of which 53.64% had spiculated margins and 17.27% had well circumscribed margins. In a study by Rotstein and Neerhut majority of the patients showed that carcinoma patients showed spiculated, microlobulated, and angular margins.[22] In another study by Sannomiya et al, it was showed that invasive ductal carcinoma with well-defined and rough margins on ultrasound.[23]

There is a greater risk of breast cancer among women with dense breasts than those with fatty breasts. Breast density has to be considered along with other risk factors, such as age, family history, and any personal history of breast changes that increase cancer risk. Nazari and Mukherjee reported that mammographic dense breast tissue is among the important factor that is associated with breast cancer burden.[24] Among women aged <50 years half of the women have high mammographic density. Breast imaging reporting and data systems (BI-RADS) is the most commonly used tool for assessing mammographic density worldwide.

In the present study, the majority (41.82%) had BI-RADS category V followed by 25.45% category-IV C. There was a negative correlation between age and volumetric density of breast. Rahmat et al also found an inverse correlation between age and volumetric breast density.[21] The possible reason for such correlation could be post-menopausal involution where fat slowly replaces fibro-glandular tissues.[25]

In the present study, the agreement between two observers was fair, the agreement between software and observer 1 and 2 moderate. Similar to our study Rahmat et al also calculated kappa value but found a fair agreement between software and each reader in all density categories with visual density assessment, the subjectivity and variability of readers in different setting may contribute to different values obtained.[21] In a study by Youk et al which evaluated visual assessments of mammographic breast density by BI-RADS (4th and 5th editions) and compared with automated volumetric breast density and found moderate to substantial agreement with the use of BI-RADS 4th edition (κ = 0.58–0.63) and substantial agreement with the 5th edition (κ = 0.63– 0.66). Volumetric density has several positives than using qualitative scales and area-based density measures. These volumetric software's calculate the breast density using on 3D information rather than with of 2D also include tissue thickness.[9,10] Additionally, volumetric measurements are generally easy for implementation in screening programmes. In our study, around 29% women received HRT has high breast density than those who didn't. In a study by Azam et al[26] also found a significantly positive relations between HRT use and mammographic density and breast cancer risk. They also found breast cancer risk was around 10% in HRT receiving patients. Finally, the overall adverse effect of HRT on breast cancer was greater in women with higher mammographic density.

Limitation of study

We authors acknowledging few limitations of our current study. The sample size was small so care must be taken when generalizing the results. Study with larger sample size may be needed to validate these results. Women with dense breast are more likely to experience both false positives and false negatives in mammography interpretations. Given these challenges, multi-modal screening strategies (ultrasonography and MRI) should be included for women with dense breast, which will improve the sensitivity of breast cancer detection.

CONCLUSION

Breast malignancy has emerged to be a global epidemic. The only key to successfully deal with this is to diagnose the cases early and providing early and prompt management. Mammography is an essential tool in this approach. Overall results from this study showed that Volpara has moderate agreement with radiologists' visual assessment supporting the potential use of Volpara as an adjunct tool for breast screening programmes. It is important to note that computer assessed breast density is mostly reproducible and hence may be favored than visual grouping. Still, all that we know about the value of breast density as an individual risk factor or as a determinant of mammography lower sensitivity is based on visual classification. If studies certainly demonstrate that breast density is important for evaluating performance or could be useful for risk stratification, then Volpara may be considered.

Author contribution

All the authors that are listed have contributed to the preparation of the article.

Conflict of interest

There is no conflict of interest

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