


Evaluation of automated volumetric breast density software in comparison with visual assessments in an Asian population

A retrospective observational study

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Abstract

This study aims to compare Quantra, as an automated volumetric breast density (Vbd) tool, with visual assessment according to ACR BI-RADS density categories and to determine its potential usage in clinical practice.

Five hundred randomly selected screening and diagnostic mammograms were included in this retrospective study. Three radiologists independently assigned qualitative ACR BI-RADS density categories to the mammograms. Quantra automatically calculates the volumetric density data into the system. The readers were blinded to the Quantra and other readers assessment. Inter-reader agreement and agreement between Quantra and each reader were tested. Region under the curve (ROC) analysis was performed to obtain the cut-off value to separate dense from a non-dense breast. Results with P value $< .05$ was taken as significant.

There were 40.4% Chinese, 27% Malays, 19% Indian and 3.6% represent other ethnicities. The mean age of the patients was 57.15%, 45.6%, 30.4%, and 9% of patients fall under BI-RADS A, B, C and D density category respectively. Fair agreement with Kappa (κ) value: 0.49, 0.38, and 0.30 were seen for Reader 1, 2 and 3 versus Quantra. Moderate agreement with κ value: 0.63, 0.64, 0.51 was seen when the data were dichotomized (density A and B to “non-dense”, C and D to “dense”). The cut-off Vbd value was 13.5% to stratify of dense from non-dense breasts with a sensitivity of 86.2% and specificity of 83.1% (AUC 91.4%; confidence interval: 88.8, 94.1).

Quantra showed moderate agreement with radiologists visual assessment. Hence, this study adds to the available evidence to support the potential use of Quantra as an adjunct tool for breast density assessment in routine clinical practice in the Asian population. We found 13.5% is the best cut-off value to stratify dense to non-dense breasts in our study population. Its application will provide an objective, consistent and reproducible results as well as aiding clinical decision-making on the need for supplementary breast ultrasound in our screening population.

Abbreviations: Abd = area breast density, ACR- BIRADS = American College of Radiology Breast Imaging Reporting and Data System, AEC = automatic exposure control, AUC = area under the curve, BI-RADS = Breast Imaging Reporting and Data System, CC = craniocaudal, K = Kappa, kVp = kilovoltage peak, mAs = milliampere-seconds, MLO = mediolateral oblique, MRI = magnetic resonance imaging, ROC = region under the curve, Vbd = volumetric breast density.

Keywords: Quantra, ACR BI-RADS breast density, automated volumetric breast density software, mammography, visual assessment

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Written informed consent was waived by institutional ethical boards due to retrospective nature of study.

The authors or institution have no conflicts of interest to declare.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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1. Introduction

Mammographic density is a radiographic representation of dense fibroglandular tissue in the breast in comparison to fatty tissue.^[1] Wolfe in 1976 was the first to define and categorize breast density on mammogram and to hypothesize the association between parenchymal patterns and breast cancer risk.^[1] There have been several breast density classifications system developed since then, however, the most widely used classification for a qualitative breast density classification is the American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS) lexicon,^[2] which categorizes breast density into 4 categories. Heterogeneously dense breasts and breasts with extremely dense fibroglandular tissue are categorized as “dense,” while breasts with scattered fibroglandular tissue and largely fatty breasts are considered “non-dense”.^[3]

The importance of breast density came into limelight through the case of Nancy Cappello in 2004, who was diagnosed with advanced breast cancer despite regular screening and recent normal mammograms. She has never been informed that she had dense breasts and its implications.^[4] Currently, at least 38 states in the United States of America have legislation that requires notification to patients about breast density.^[5]

Dense breast parenchymal patterns have been associated with an increased risk of breast cancer.^[6–8] Furthermore, higher breast density imposes a masking effect in the detection of breast lesions and microcalcifications.^[9] There is a higher number of interval cancer in women with dense breast due to reduced sensitivity of mammography in these patients. Mammographic sensitivity is reduced from 80% to 98% in women with fatty breasts to 30% to 64% in women with extremely dense breasts.^[10]

There is some limitation to radiologists visual assessment of breast density. This method is subjective and is influenced by many factors including over/underestimation tendency, bias due to defensive practice and reading room conditions.^[3] Inter- and intrareader variabilities are also noted to be considerable in published studies.^[11–13]

An objective, reliable and consistent method is important in assessing breast density to stratify patients into dense and non-dense categories with no ambiguity. The results from this method will provide evidence to support the decision for supplemental screening to mammography. All patients with dense breast on screening mammogram will be offered supplemental screening, either with ultrasound or rarely MRI. Majority of patients falls under density category B or C, but concurrently, reclassification between these 2 groups frequently reported.^[14] Inconsistency in supplemental screening requirement and information on breast density and breast cancer risk may cause patients to lose confidence in the system.

Quantra is a fully automated Vbd software produced by Hologic (Hologic Inc., Bedford, Massachusetts, USA) with breast density reference population from the USA. It is designed as an adjunct tool to facilitate radiologists to make consistent breast density assessment decision. Automated computer-based density measurements, such as in Quantra, are not limited to the constraint of visual assessment and thus will provide a more accurate, reliable and reproducible method of density assessment. Thus, quantitative assessment method may be preferred over the subjective visual estimation. Few studies have proven reproducibility of quantitative mammographic density assessment compared to radiologist visual assessment.^[15–17] The published studies also reported a wide range of cut-off values in discriminating dense from non-dense breasts.^[16,18–23]

Hence, in this study, we would like to compare Quantra, as an automated Vbd measurement tool, with visual assessment by radiologists using ACR BI-RADS breast density category in the Asian population. Furthermore, we would also clarify which cut-off value best applies to the breast density in our multi-ethnic study population to best stratify dense and non-dense breasts.

2. Methodology

2.1. Patients and methods

This was a retrospective study involving 500 screening and diagnostic mammograms in randomly selected female patients who present to the Department of Biomedical Imaging, University of Malaya Medical Centre (UMMC) between November 2016 and April 2017. The study was conducted in adherence with the approved guidelines from the Medical Ethics Committee of University Malaya Medical Centre. This study was supported by University Malaya Postgraduate Research Fund.

Mammography images in craniocaudal (CC) and mediolateral oblique (MLO) views were acquired with automatic exposure control (AEC) (Selenia Dimension machine (Hologic Inc., Bedford, Massachusetts, USA). Three readers; MR, FF and SK, with a minimum of 8 years in breast imaging, visually assessed the mammographic breast density images independently in multiple sessions in a research setting. Breast density assessments by radiologists were according to ACR BI-RADS 5th edition lexicon, which categorised breast density into 4 categories (density A, B, C, and D).^[2] The mode of density category was calculated, and data were dichotomized to “non-dense” (density A and B) and “dense” groups (density C and D) for statistical analysis. Only the remaining breast was included for post-mastectomy patients. 391 patients had bilateral mammograms, whilst 109 patients were post-mastectomy patients with a unilateral mammogram (left; 52 and right; 59) (Fig. 1). The breast density assessment was made per patient for both Quantra and visual density assessment. The readers were blinded from the Quantra and other readers assessment.

The software package used to assess the volumetric density of each mammogram was Quantra™ 2.0 (Hologic, Bedford, Massachusetts). The software calculated the volumetric and area breast density from CC and MLO views of digital mammogram images. Vbd was derived by dividing the fibroglandular volume to the breast volume. The area breast density (Abd) was derived from the ratio of areas the pixels selected as dense to the total area of the breast.^[24]

Vbd assessment used the physical imaging chain, based on the physical parameters of the breast and imaging system and individual x-ray exposure. This included the breast attenuation coefficient, x-ray spectrum of the target material, kilovoltage peak (kVp), milliampere-seconds (mAs) and thickness of the compressed breast. It then produced BI-RADS like scores, which was a four-point scale, by estimating the overall breast composition in relation to a reference population, which were taken from multiple centres in the United States.

Abd assessment was a ratio of the area of pixels selected as dense divided by the total area of the breast, by standard mammographic breast segmentation.

2.2. Statistical analysis

Inter-reader agreement and agreement between Quantra and readers were tested for each density group using Cohens Kappa test and Intraclass correlation coefficient (ICC). The breast

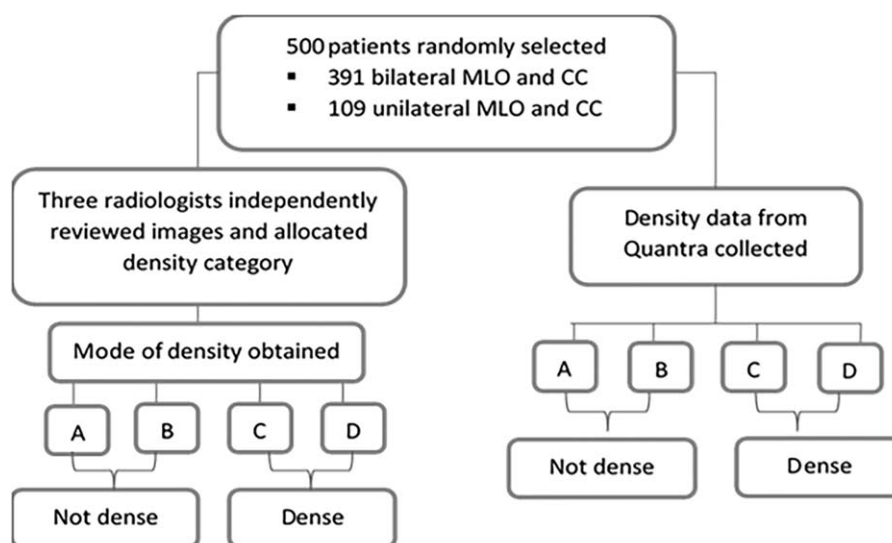


Figure 1. Algorithm for methodology.

density groups were then dichotomized into 2 groups, A and B into non-dense and C and D into dense, and agreement between Quantra and each reader was again tested. Kappa (κ) value ranges and its indications were; <0.0 (poor), 0.00 – 0.20 (slight), 0.21 – 0.40 (fair), 0.41 – 0.60 (moderate), 0.61 – 0.80 (substantial), and 0.81 – 1.00 (almost perfect agreement).^[25] Interclass Correlation Coefficient (ICC) was computed to test inter-reader reliability using absolute agreement, 2-way mixed model. ICC value ranges and its indications were; <0.5 (poor), 0.5 – 0.75 (moderate), 0.75 – 0.9 (good), >0.90 (excellent reliability).^[26] Mode of density was also categorized according to age and race. Pearson's correlation test was performed between the mode of readers visual density assessment and Vbd values by Quantra, and between Vbd, and Abd values.

Using ROC analysis on 400 patients from the study population, Vbd were used to establish the cut-off value to separate dense and non-dense breasts. For internal validation, we tested the cut-off value on the rest of the study sample of 100 mammograms.

All statistical analyses in this study utilised SPSS 21 (IBM SPSS Statistical software). Statistical tests with P values $>.05$ were considered to indicate statistical significance.

The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

3. Results

Of the 500 women recruited in this study, majority of were Chinese (40.4% ($n=252$)) followed by Malay (27% ($n=135$)), Indian (19% ($n=95$)) and others (3.6% ($n=18$)). The patients age ranged between 33 and 87 with the mean study population age of 57. In 50.6% ($n=253$) of the patients, the indication was for screening, 36% ($n=180$) for surveillance post-treatment of carcinoma and 13.4% ($n=67$) for diagnosis.

3.1. Visual breast density assessment

Using the mode of density between 3 radiologists; there were 15% ($n=75$), 45.6% ($n=228$), 30.4% ($n=152$), and 9% ($n=$

45) of patients within density A, B, C and D categories respectively. There were 11.6% ($n=58$) patients age 60 and above within the dense breast category, which comprised of 29% of density C and D. Age distribution in each density group was illustrated in Figure 2.

In the density C and D groups, there was higher breast density distribution in the Chinese ethnicity, which comprised of 60.4% ($n=119$), compared to the Malays; 24.8% ($n=49$) and the Indians; 11.1% ($n=22$). Ethnicity to density distribution was shown in Figure 3. Other ethnicities in this study population were too variable to be computed.

3.2. Quantra software density assessment

The Vbd values computed by Quantra in this study population ranged from 3% to 41% (mean = 14.5%). The Abd ranged from 0% to 71% (mean = 15.65%).

The volume of the breast in this study population ($n=500$) averaged 1473.0 cm^3 ($s=732.88$), with a minimum volume of 7 cm^3 and maximum volume of 5078 cm^3 . The volume of fibroglandular tissue averaged 205.41 cm^3 ($s=138.89$), with a minimum volume of 3 cm^3 and maximum volume of 1123 cm^3 .

Vbd was inversely related to age. Pearson correlation test yielded small correlation; $r=-0.292$ ($P<.001$). There was a strong linear correlation between Vbd and Abd, with correlation test results $P=0.754$ ($P<.001$).

3.3. Agreement between readers and Quantra

The majority of cases were in density B and C for Quantra and all readers. Table 1 showed the percentages of density category for each reader and Quantra. There was a strong positive correlation between the mode of readers density assessment and Quantra ($P = .711$, $P<.001$) (Fig. 4).

A fair agreement between Quantra and each reader were observed in all density categories. When the density data were dichotomized into density A+B (not dense) and C+D (dense), there was a stronger (moderate) agreement between all readers and Quantra, as tabulated in Table 2. Moderate reliability was

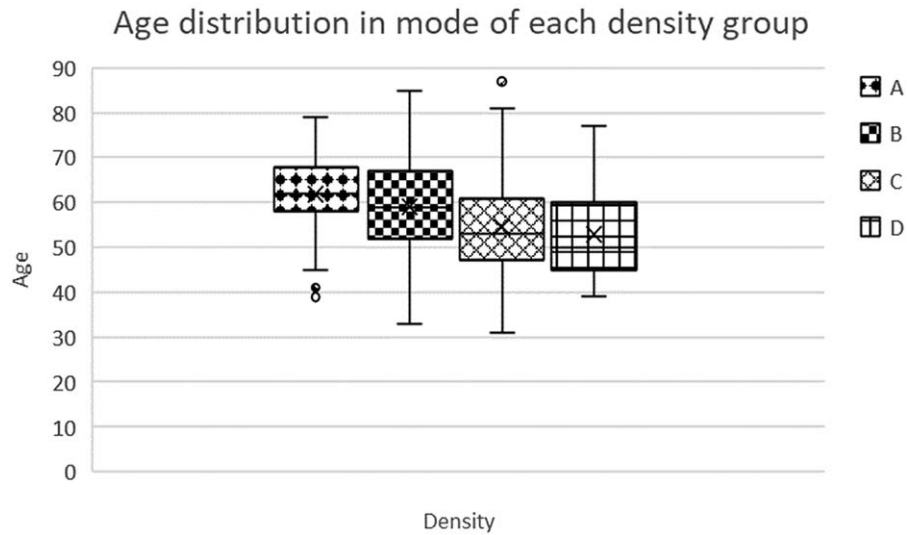


Figure 2. Age distribution in each density category (mode of visual assessment).

observed between all readers with ICC of 0.77 (95% CI: 0.74–0.799, $P < .001$) for non-dichotomized data and 0.85 (95% CI: 0.824–0.876, $P < .001$) for the dichotomized data.

On applying ROC analysis to the 400 patients, we found the best cut-off Vbd value of 13.5% by using Youden index to stratify the mammograms into dense and non-dense categories, with a sensitivity of 86.2% and specificity of 83.1% (AUC 91.4%; confidence interval: 88.8, 94.1, P value $< .001$) (Fig. 5). Applying this value to the rest of the sample as validation data set ($n = 100$), we were able to stratify the mammograms into dense and non-dense categories with a sensitivity of 79.6% and specificity of 82.6%.

4. Discussion

Mammographic breast density is a risk factor for breast cancer^[27,28] with an inverse relationship to mammographic

sensitivity.^[29] The sensitivity of mammography with almost entirely fatty breasts (density A) is 88% as compared to 82% for scattered fibroglandular densities (density B), 69% for heterogeneously dense breasts (density C) and 62% in extremely dense breasts (density D).^[9,30] Asians are reported to have higher breast density compared to the general population.^[31] To our knowledge, the present study is the first study on automated Vbd assessment in a multi-ethnic Asian population.

The study population age group is wide (age 33–87), which is reflective of the patients age group that attend our breast imaging unit. The density distribution according to age is as reported previously, with density category inversely related to age.^[9,32] This is due to post-menopausal involution, whereby the fibroglandular tissues are gradually replaced by fat.^[33] However, it is prudent to note that within density C and D groups in this study population, almost a third were age 60 and above. Hence, generalizing higher age to lower breast density, which is not

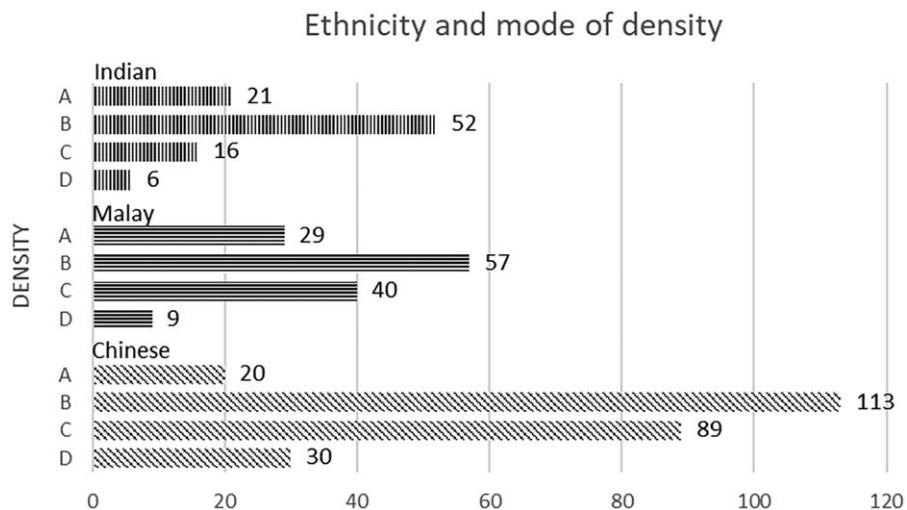


Figure 3. Ethnicity distribution of density category (mode of visual assessment).

Table 1
Breast density classification for Quantra and each reader.

BIRADS density category	QUANTRA	R1	R2	R3
The breasts are almost entirely fatty (A)	2.8% (n=14)	9.8% (n=49)	15% (n=75)	21.8% (n=109)
There are scattered areas of fibroglandular density (B)	44% (n=220)	45.8% (n=229)	53.4% (n=267)	37.4% (n=187)
The breasts are heterogeneously dense, which may obscure small masses (C)	41.8% (n=209)	32.2% (n=161)	23.4% (n=117)	33.4% (n=166)
The breasts are extremely dense, which lowers the sensitivity of mammography (D)	11.4% (n=57)	12.2% (n=61)	8.2% (n=41)	7.6% (n=38)

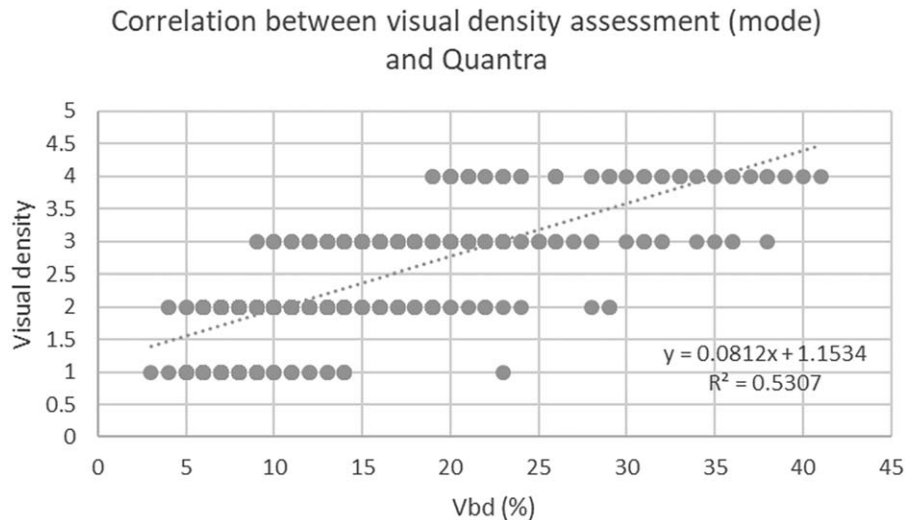


Figure 4. Correlation between visual density assessment and Vbd (Quantra).

always the case, may lead to inaccurate presumptive breast density assessment. In such cases, Quantra will be advantageous in comparison to visual assessment, as age is not factored in Quantra assessment.

There is a higher number of Chinese within the dense breast group in our study population in comparison to Malay and Indian. Previous studies have reported mixed results in the association between ethnicity and breast density in the Malaysian population. Studies that reported a significant association between ethnicity and density group reported similar findings as ours, whereby Chinese ethnicity was noted to have the highest breast density.^[34,35] Other studies reported no significant association between ethnicity and breast density in the Malaysian population.^[36–38] However, western studies have reported that Chinese ethnicity as having the highest breast density,^[32] as well as in Asian women.^[39,40] Hence, more studies are needed to evaluate whether there is a significant difference in breast density between the ethnic groups in Malaysia.

Vbd percentage in Quantra is derived by dividing the fibroglandular volume to the breast volume. As the assessment

is based on volume estimations, in comparison to visual radiologists interpretation by masking effect, the Quantra volumetric density estimation tends to be lower.^[24] This is the reason why several published papers reported similar findings of lower density estimation by Quantra in comparison to visual assessment.^[16,21] This is also the reason why establishing the best cut-off value is crucial.

Previously studies have shown that there is potential usage of Quantra in a clinical setting and proposed breast density cut-off value to separate dense and non-dense breasts. The cut-off values from these studies are tabulated in Table 3. Regini et al and Ciatto et al obtained cut-off values of 21%, and 22%. These studies were utilising an earlier version of Quantra, which included skin in its volumetric density assessment.^[16,18] As automated Vbd assessment technology evolved and software are upgraded, further studies testing the later versions yielded lower cut-off values of 10% and 14%,^[19,23] which are similar to our study which obtained cut off value of 13.5%. However, it is important to note that studies using the earlier version of Quantra by van der Waal et al and Rafferty et al also noted a cut-off value of

Table 2
Agreement test between Quantra and readers in non-dichotomized and dichotomized data.

	Reader 1 vs Quantra	Reader 2 vs Quantra	Reader 3 vs Quantra	P value
Kappa value for non-dichotomized data	0.49	0.38	0.30	<.001
Kappa value for dichotomized data	0.63	0.64	0.51	<.001

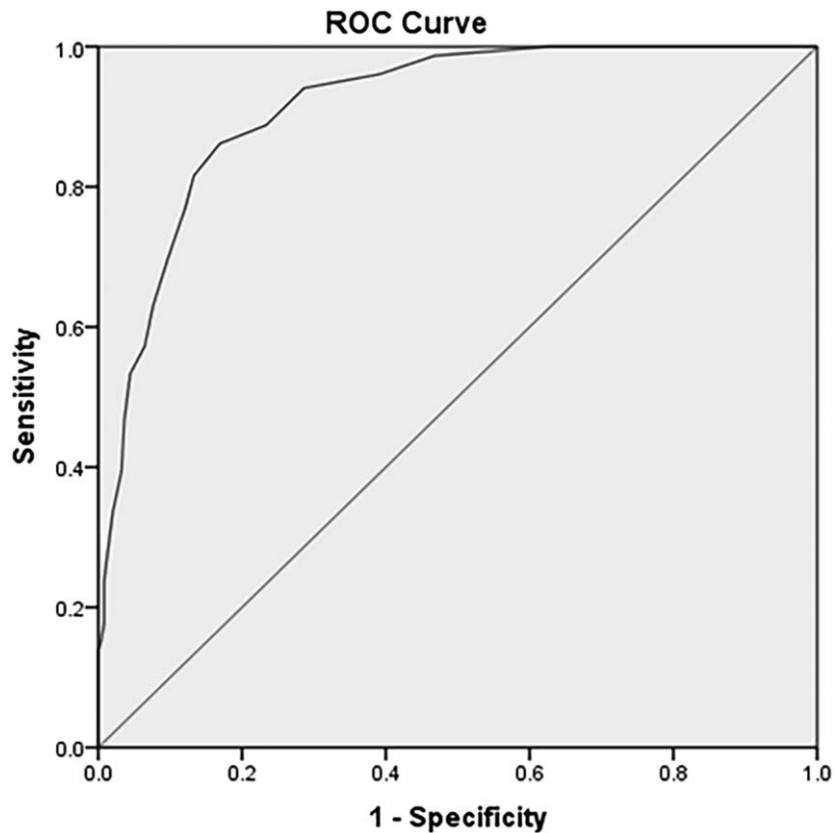


Figure 5. ROC curve of Vbd estimation of Quantra and visual assessment (mode).

Table 3

Cut-off values from Quantra in previous studies with origin of study population, range of Vbd in each study and number of subjects recruited.

Author, Journal, Publication year	Title	Country	Cut-off value	Range of density (Vbd) (n= number of subject)
Regini et al, 2014 ^[18] Radiologia medica.	Radiological assessment of breast density by visual classification (BI-RADS) compared to automated volumetric digital software (Quantra): implications for clinical practice	Turin, Italy	21%	8% to51% (n=200)
Ciatto et al,2012 ^[11] The Breast	A first evaluation of breast radiological density assessment by QUANTRA software as compared to visual classification	Turin, Italy	22%	7% to 50.5% (n=418)
Richard Davis et al, 2018 ^[19] Breast Cancer: Basic and Clinical Research	Evaluation of Quantra Hologic Volumetric Computerized Breast Density Software in Comparison With Manual Interpretation in a Diverse Population	USA	14%	Not provided (n=385)
Rafferty et al, 2009 ^[20] Radiological Society of North America 2009 Scientific Assembly and Annual Meeting (unpublished)	Comparison of 3 methods of estimating breast density: BI-RADS density scores using full field digital mammography, breast tomosynthesis, and Vbd	USA	13%	Not provided (n=264)
Van der waal et al, 2015 ^[40] PLOS ONE	Comparing Visually Assessed BI-RADS Breast Density and Automated Vbd Software: A Cross-Sectional Study in a Breast Cancer Screening Setting	Amsterdam, Netherlands	13.8%	5.9% to 38.1% (n=992)
Pahwa et al, 2015 ^[21] Indian Journal or Radiology Imaging.	Evaluation of breast parenchymal density with QUANTRA software	New Delhi, India	19.6%	7% to 42% (n=545)
Ekpo et al, 2016 ^[22] British Journal of Radiology	Quantra should be considered a tool for two-grade scale mammographic breast density classification	Sydney, Australia	20%	1% to44% (n=1314)
Osteras et al, 2016 ^[23] Acta Radiologica	Classification of fatty and dense breast parenchyma: comparison of automatic volumetric density measurement and radiologists classification and their interobserver variation	Oslo, Norway	10%	Not provided (n=537)

Vbd = volumetric breast density.

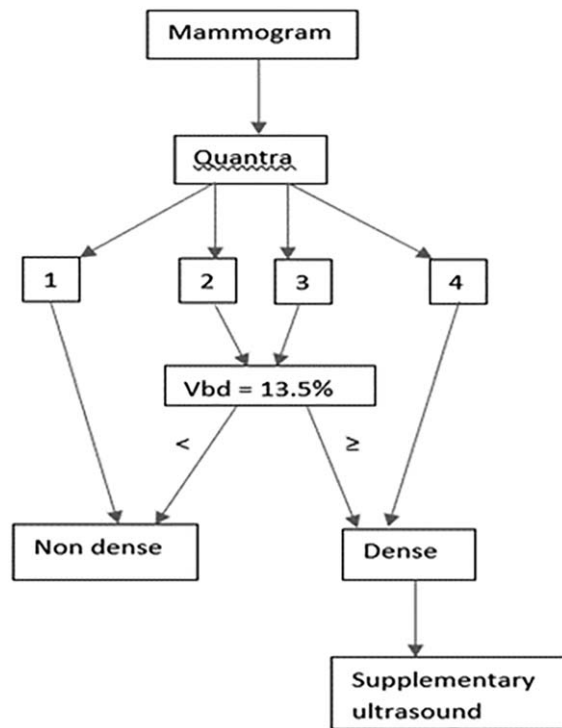


Figure 6. Algorithm for supplementary ultrasound in screening mammogram patients, with application of the cut-off value.

13.8% and 13% respectively.^[20,41] Hence, the different cut-off values are likely due to a few factors and are not particularly related to the versions of software used.

For visual density assessment, the subjectivity and variability of readers in different setting may contribute to different values obtained. Years of experience, the number of cases reported per year and level of training may play a role. All the readers in our study have a minimum of 8 years of breast radiology training. Readers in Osteras et al study, for example, have a range of 1 to 34 years of experience, and the median of visual density assessment was used to compare with Vbd.^[23] Regini et al study compared one reader of 23 years experience to Quantra.^[18]

Richard-Davis et al commented that different race and ethnicity may cause a disparity in cut-offs values obtained.^[19] This may be the cause too, as previous studies were from a different population than ours, which involves a multi-ethnic population of the Asian population. As breast volume and compression thickness are the parameters in producing Vbd value, different cut-off value may be expected in different population. Mariapun et al concluded that there was a difference in the non-dense area of the breast, which can be correlated to volume, between different ethnicity.^[35]

The sensitivity of mammography is reduced in the dense breast, and adding ultrasound to screening in patients with dense breast detects early-stage, invasive carcinoma.^[42] In our setting, screening mammography patients must wait for decisions by the radiologist in-charge on whether supplemental breast ultrasound is required. Erroneous classification of non-dense

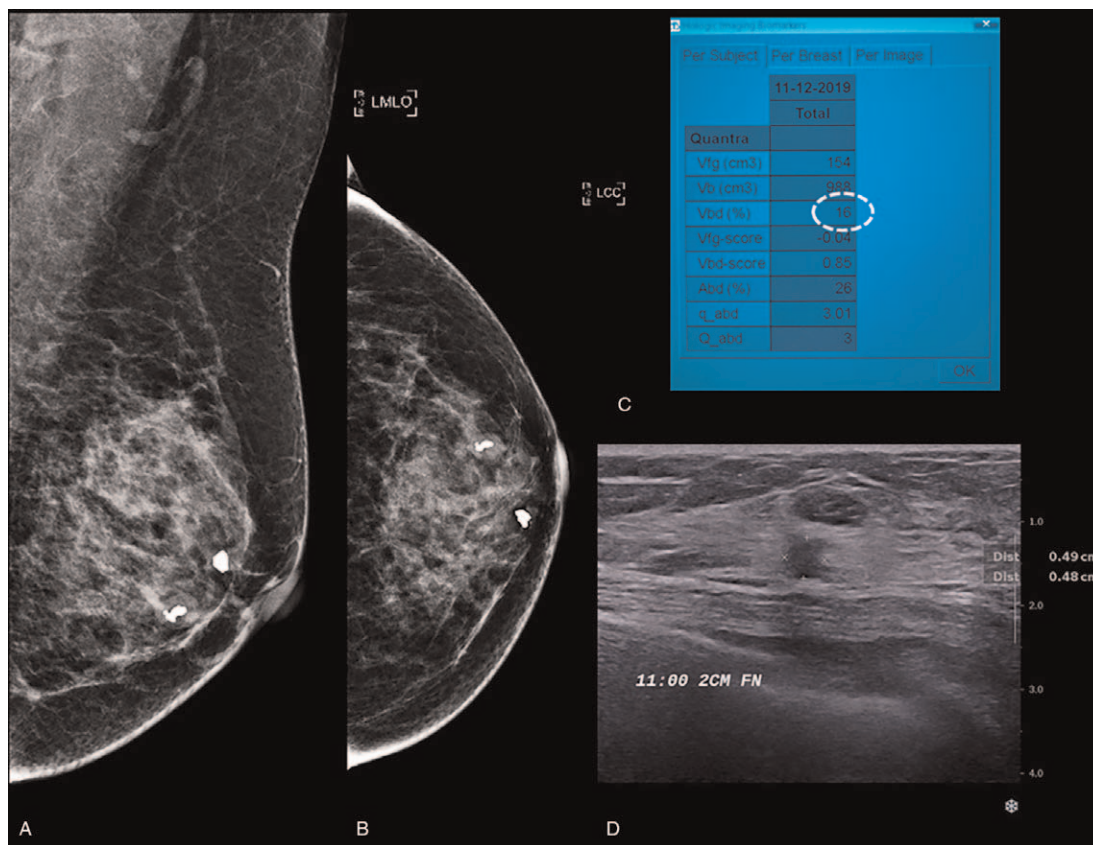


Figure 7. Left MLO (A) and CC (B) view of a 60 year old asymptomatic patient for screening. No suspicious lesion seen in the mammogram. With Vbd of 16% (C), patient was sent for supplementary ultrasound which detected a subcentimeter suspicious lesion (white circle) at left 11 o'clock position (D). Histopathology confirmed invasive carcinoma.

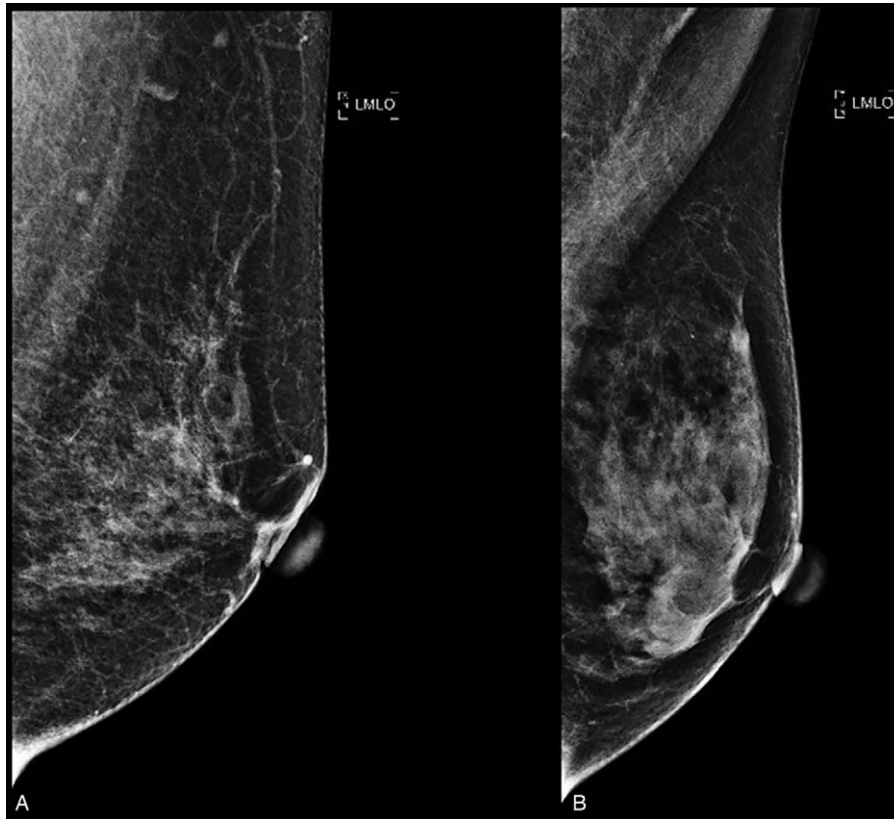


Figure 8. (A) showing left MLO view of a patient from study population. The visual density assessment from two readers were discordant; density B and C. Vbd by Quantra was 14%. In clinical setting, by applying the cut-off value in this case as a problem solver, patient is categorized as C (dense). (B) Showing left MLO view of a patient from study population, which all readers were concordant and categorized the patient in dense group. The Vbd by Quantra is 18%, which further supported the readers findings.

mammography as dense will lead to call back of patients for a supplemental ultrasound. With the application of Quantra and the cut-off value of 13.5%, the decision on the need for supplemental ultrasound can be made with confidence pending radiologists review. The following algorithm is what we proposed to be applied in the screening population setting to assist radiologists breast density assessment (Fig. 6).

Example of cases which can benefit from the application of this algorithm is as illustrated in Figures 7 and 8.

A study by Ekpo et al concluded that Quantra is a useful tool to assess mammographic breast density into dense and non-dense categories, instead of 4 distinct categories.^[22] This is similar to our study findings, that shows greater agreement between Quantra with readers when the density data were dichotomized. Although breast density assessment is purely subjective with the elimination of numerical percentiles as recommended by ACR-BIRADS 5th edition, the cut-off value can be applied to stratify dense from the non-dense breast when radiologists are in doubt. Results from our study showed that Quantra has its role in assisting the radiologist in decision making tree as depicted in Figure 6 and as case examples in Figures 7 and 8.

The example demonstrated in Figure 8(b) may not be clinically significant in our clinical setting for Quantra to decide whether supplementary US study is required as it is an obvious density C category on visual assessment. However, future application of numerical Vbd in risk stratification and personalised medicine

may come into practice, whereby Vbd of a certain percentage carries a certain risk of breast cancer. A study by Brandt et al noted an association between Vbd and cancer risk.^[43] Hence patients with a known Vbd may require a different screening protocol or further supplemental study.

Our study has its limitation, which includes it being a single centre study, using a single automated breast density software and involving a limited number of patients and readers. Other breast cancer risks factors were not included in the data collection process, hence the association between Vbd and other risk factors were not able to be computed. The data from this study is not reflective of other breast density software which include Volpara, Cumulus, LIBRA, PowerLook iCAD, Densitas, and others.

Future development for a more accurate breast density estimation software is the way forward in the era of artificial intelligence and machine learning. This subsequently will alleviate radiologists reporting burden and classify patients breast density accurately, for better tailoring of screening protocol depending on individual risk factors and breast density.^[44]

5. Conclusion

Quantra showed moderate agreement with radiologists visual assessment. Hence, this study adds to the available evidence to support the potential use of Quantra as an adjunct tool for breast

density assessment in routine clinical practice in the Asian population. We found 13.5% is the best cut-off value to stratify dense to non-dense breasts in our study population and its clinical application may provide automation and assistance for supplementary breast ultrasound in our screening population.

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Author contributions

K Rahmat contributed to the conception and design of the study, and N Ab Mumin, M Ramli, and F Fadzli on acquisition of data. N Ab Mumin and Ng WL analysed and interpreted the data. K Rahmat, N Ab Mumin and F Fadzli contributed to the drafting of article. Figure 6 is by Ng WL. Figures 1–5 and Figures 7 and 8 and Tables 1–3 are by N Ab Mumin. K Rahmat, M Ramli, N Muhammad Gowdh and Ng WL revisited it critically for important intellectual content. All authors approved the final version of the manuscript submitted for publication and take responsibility for the statements in the article.

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