Can Dual-Energy Contrast-Enhanced Digital Mammography Change The Final BI-RADS Category of Equivocal Breast Lesions Characterized by Sonomammography in Women with Dense Breast?

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ABSTRACT

Background: Equivocal and indeterminate breast lesions which are detected on sonomammography should be further evaluated by either biopsy or follow-up. Contrast-enhanced digital mammography can act as a problem-solving tool to avoid biopsies of some problematic breast lesions and help clinicians to take a proper decision about these lesions in the same setting. **Objective:** This study aimed to evaluate the complementary role of contrast-enhanced digital mammography (CEDM) to characterize indeterminate and equivocal breast lesions detected on sonomammography and its role to downgrade or upgrade the final BI-RADS category of these lesions.

Patients and Methods: This prospective study included 35 females with mean age of 48.26 years. Ladies were referred from the clinic for screening mammograms during the period from august 2020 to September 2021.

Results: Contrast-enhanced digital mammography showed higher specificity (86.4%), PPV (80.0%), NPV (95.0%), and accuracy (88.6%). While sonomammography revealed specificity of 63.6%, PPV of 60.0%, NPV of 93.3%, and accuracy of 74.29%. However, both showed a comparable sensitivity of about 92.3%. Fourteen lesions (40%) were downgraded by CEDM and proved to be benign lesions and five lesions (14.2%) were upgraded and proved to be malignant lesions.

Conclusion: Contrast-enhanced digital mammography is a promising technique in the characterization of equivocal and indeterminate breast lesions (BI-RADS 3 and 4). It can be utilized to help in the final assessment of these findings in the same setting and offer assistance in avoiding biopsies in numerous patients with more prominent specificity and precision than sonomammography.

Keywords: Mammography, Indeterminate, Equivocal, Breast cancer, Contrast-enhanced digital mammography (CEDM), Dual-energy.

INTRODUCTION

Abnormalities recognized at screening mammography are reviewed for complementary more diagnostic imaging modalities, counting MRI, and US [(1)]. MRI has many limitations due to its low specificity, spatial resolution, high cost, and long examination time [(2)]. Ultrasound is operator-dependent and many lesions could be missed during the examination. Subsequently, other imaging modalities are needed to decide the likelihood of malignancy of these abnormalities. CEDM is progressively being utilized for the final assessment of these query findings [(1)].

Structured reporting was developed to establish reliable and detailed reporting for both radiologists and clinicians [(3-5)]. One of them was the BI-RADS categorization of breast lesions. (BI-RADS 3) lesions are categorized as probably benign lesions and this subsequently confuses the final decision of clinicians. In clinical practice, 0.9–7.9% of potentially benign findings on mammography are upgraded and subsequently, a histopathological biopsy was done [(6)]. Equivocal or suspicious findings cause a clinical dilemma either by follow-up or biopsy [(5)]. Breast mammography and MR imaging may result in an increase in the number of false-positive cases and lead to unnecessary biopsies [(7-8)].

Contrast-enhanced digital mammography is a new imaging modality that could be used as a complementary tool to usual digital mammography in the diagnosis of breast cancer [(1)]. CEDM has a great ability to detect and characterize lesions even in dense breasts, and stereotactic biopsy can be performed in the same setting [(9)].

This study aimed to evaluate the complementary role of (CEDM) to characterize indeterminate and equivocal breast lesions detected on sonomammography and its role to downgrade or upgrade the final BI-RADS category of these lesions.

PATIENTS AND METHODS

Patients: This prospective study included ladies referred from the clinic for screening mammograms during the period from august 2020 to September 2021. 35 females with ages ranging from 24 – 77 years (mean age 48.26) were included in our study.

Digital mammography was done for all the patients. Women with dense breasts classified as ACR C or D on mammography were subjected to further ultrasound evaluation. Lesions were detected by sonomammography and classified according to the ACR BI-RADS system. BI-RADS 3 and 4 lesions were considered as equivocal and indeterminate breast lesions. Fifteen lesions were classified as BI-RADS 3 lesions, and twenty lesions were classified as BI-RADS 4 lesions. Afterwards, complementary CEDM was done for all these patients. Sonomammography results were reported by an experienced radiologist with ten years of experience in women's imaging. Another different experienced radiologist with 10 years of experience in women imaging analyzed the

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CEDM results independently in another independent session to avoid bias. A final evaluation by histopathology was done for all the lesions and was performed in our institution.

Exclusion criteria: Patients with a history of allergic reaction to contrast media or severe renal disease, pregnant patients, patients with breast implants and patients with known breast cancer or under treatment.

The technique of Sonomammography and CEDM:

Imaging was done (on Senographe Pristina) as FDA-approved mammography and relatively delivers CEDM at the same dose as 2D digital mammogram. Digital mammography craniocaudal (CC) and mediolateral oblique (MLO) views were done for all participants. Afterward, ultrasound was done for all the patients (using the GE logic p5 machine or Samsung RS85). Lesions were categorized according to the ACR BI-RADS scoring system. Patients with BI-RADS 3 or 4 lesions were subjected to complementary CEDM on the same day. Contrast media was administrated, and imaging was done. A catheter was inserted into the antecubital vein of the contralateral arm to the diseased breast. Infusion of non-ionic iodinated contrast media (Ultravist) iopromide was done intravenously as a single shot at a dose of 1.5-mmol/Kg body weight. Imaging by CEDM was done 2 min after the contrast administration. The normal breast was compressed in CC and MLO views and both low- and high-energy images (dual-energy) were obtained. Then CC and MLO views for the potentially diseased breast were acquired. The low energy (26–30 kVp) image is a usual 2D mammogram image while the high energy (45–49 kVp) image is a high kV mammography image. Processing and combination of the two images were done to visualize enhancing lesions. The total duration of the examination was about 6 to 10 min.

Imaging analysis and interpretation: Sonomammography was reported according to the Breast Imaging Reporting and Data System (BI-RADS) by the American College of Radiology (ACR) as the following: site of the lesions, type (mass, focal asymmetry, architecture distortion and calcification) then each finding was categorized and had its BI-RADS scoring. Lesions with BI-RADS 3 and 4 were only selected for complementary CEDM.

There is no CEDM assigned lexicon, so CEDM were evaluated by using criteria related to the degree of contrast enhancement and morphology related to the MRI part in the BI-RADS lexicon. Subsequently, lesions were evaluated and reported into non-enhancing lesions, mildly enhancing lesions, or well-defined uniformly enhancing lesions and moderately or markedly enhancing lesions showing malignant criteria. Lesions detected on sonomammography and showed non-enhancement on CEDM were downgraded to BI-RADS 2. Uniformly well circumscribed oval enhancing lesions were categorized on CEDM as BI-RADS 3. Lesions detected on sonomammography with suspicious criteria and enhanced on CEDM were upgraded to BI-RADS 5. Lesions that were diagnosed as BI-RADS 3 on sonomammography and showed heterogeneous faint , moderate enhancement or any suspicious query finding on CEDM were upgraded to BI-RADS 4. Ultrasound-guided, stereotactic-guided core biopsy or excisional biopsy was done for all lesions with suspicious findings. Ultrasound-guided fine-needle aspiration cytology was done for cystic lesions.

Ethical consent:

An approval of the study was obtained from Ain Shams University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Data were analyzed using a statistical package for social science (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Parametric quantitative data were expressed as mean ± standard deviation (SD). Median and range were used to report the non-parametric quantitative data. Qualitative data were described as frequency and percentage. The diagnostic performance of the categorical variable was performed using cross-tabulation. The sensitivity, specificity, PPV, NPV, and accuracy were then calculated. P-value < 0.05 was considered statistically significant.

RESULTS

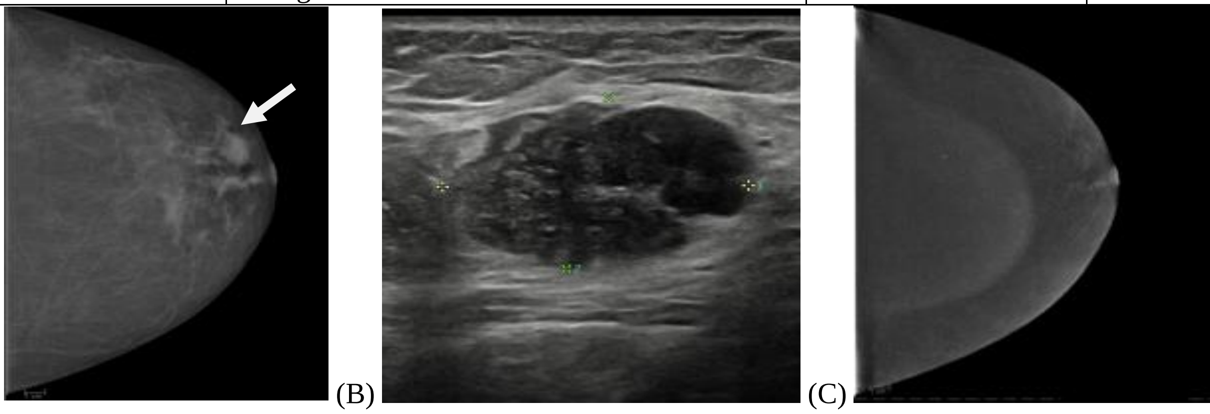
Our study included thirty-five participates. Their age ranged from 24 – 77 years with a mean age of 48.26 years. The mean size of the lesion was 19.14 ± 9.68 mm.

Lesions were classified and categorized by sonomammography according to ACR BI-RADS classification as the following: 15 lesions as BI-RADS 3 lesions and 20 lesions as BI-RADS 4 lesions**.** Complementary CEDM was done and subsequently, lesions were classified as the following: 14 lesions as BI-RADS 2, 6 lesions as BI-RADS 3, 12 lesions as BI-RADS 4, and 3 lesions as BI-RADS 5.

Based on the pathological results, there were 22 benign lesions (62.9 %) as the following: 10 fibroadenomas (Figs. 1 & 3), 3 cystic lesions, 3 adenosis, 2 abscess, 1 mastitis, 1 fibrosis/scar tissue (Fig. 4), 1 atypia/hyperplasia and 1 fat necrosis. While, 13 lesions were diagnosed as malignant lesions and comprised 9 IDC (Fig. 2), 1 ILC and 3 mucinous carcinoma (37.1%) (Table 1).

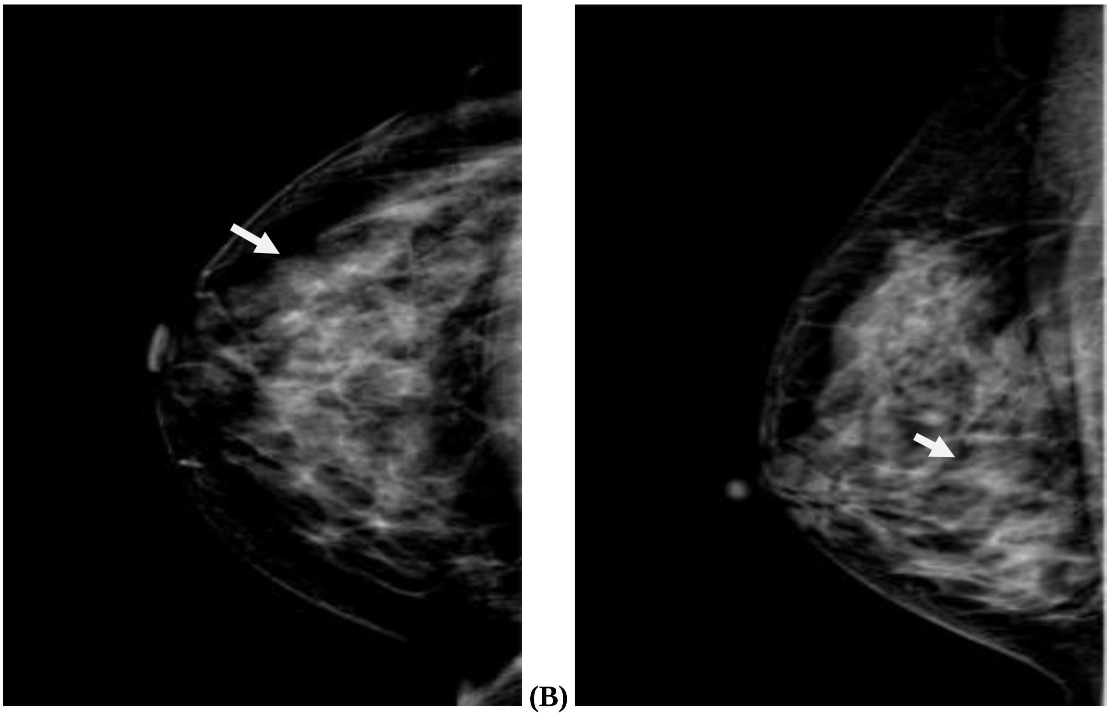
Table (1): Pathology results

Pathology		No.	%
Findings	IDC	9	25.7%
	ILC	1	2.9%
	Mucinous c	3	8.6%
	Fibroadenoma	10	28.6%
	Cysts	3	8.6%
	Adenosis	3	8.6%
	abscess	2	5.7%
	mastitis	1	2.9%
	Fibrosis/scar tissue	1	2.9%
	Atypia/ hyperplasia	1	2.9%
	Fat necrosis	1	2.9%
Results	Benign	22	62.9%
	Malignant	13	37.1%



(A) (B) (C)

Figure (1): A 62-years-old patient with a left retro areolar breast lump. (A): DM of the left breast in CC view revealed retro areolar small oval lesion partially obscured by glandular tissue. (B): Ultrasound showed a macrolobulated lesion showing more than 3 lobulations with 3 microcalcific foci and the lesion was categorized as a suspicious lesion (atypical fibroadenoma) (BI-RADS 4). (D): CC complementary CEDM view revealed No enhancement of the lesion. The lesion was downgraded to BI-RADS 2). An excisional biopsy revealed fibroadenoma.



(A) **(B)**

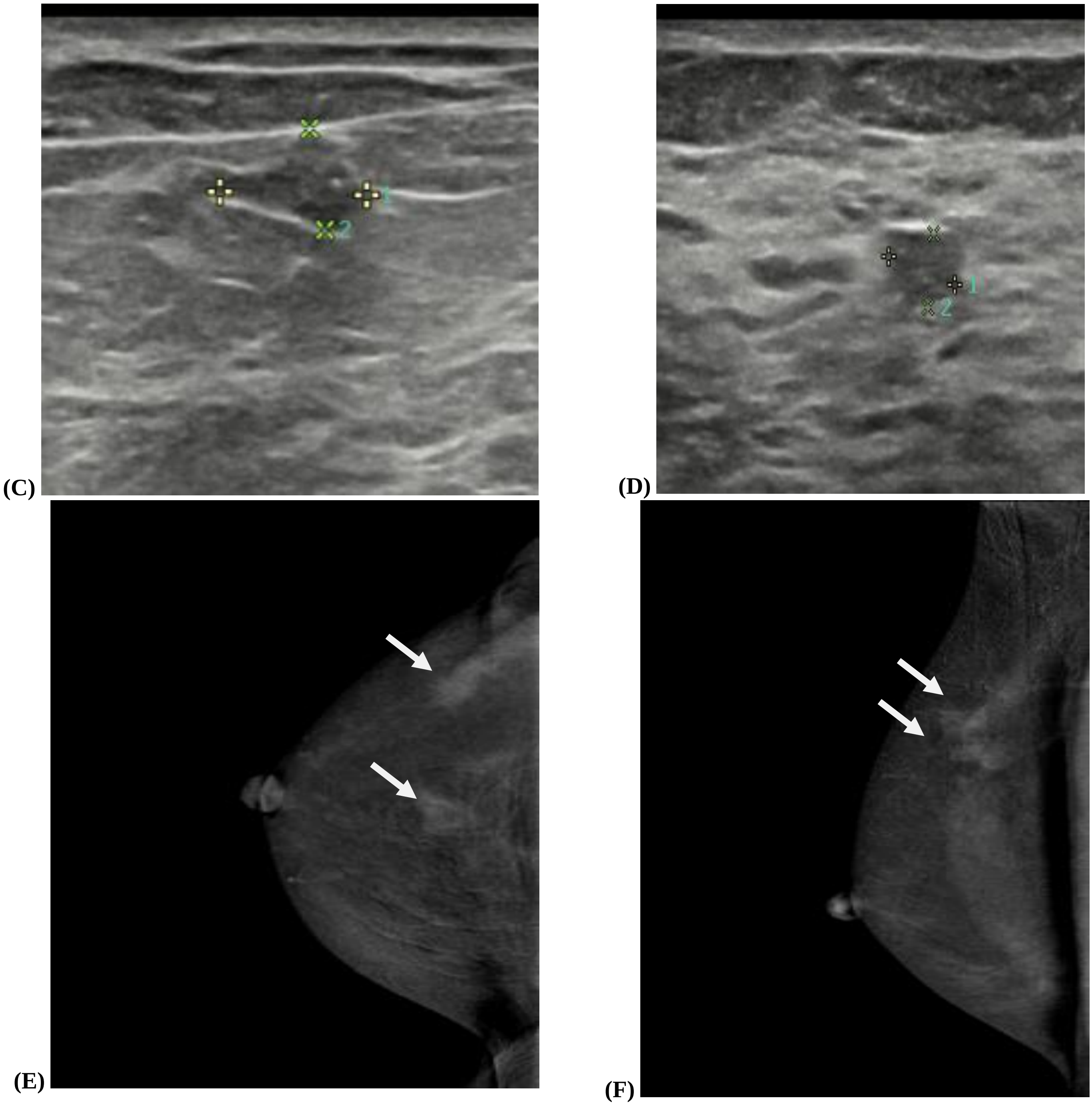
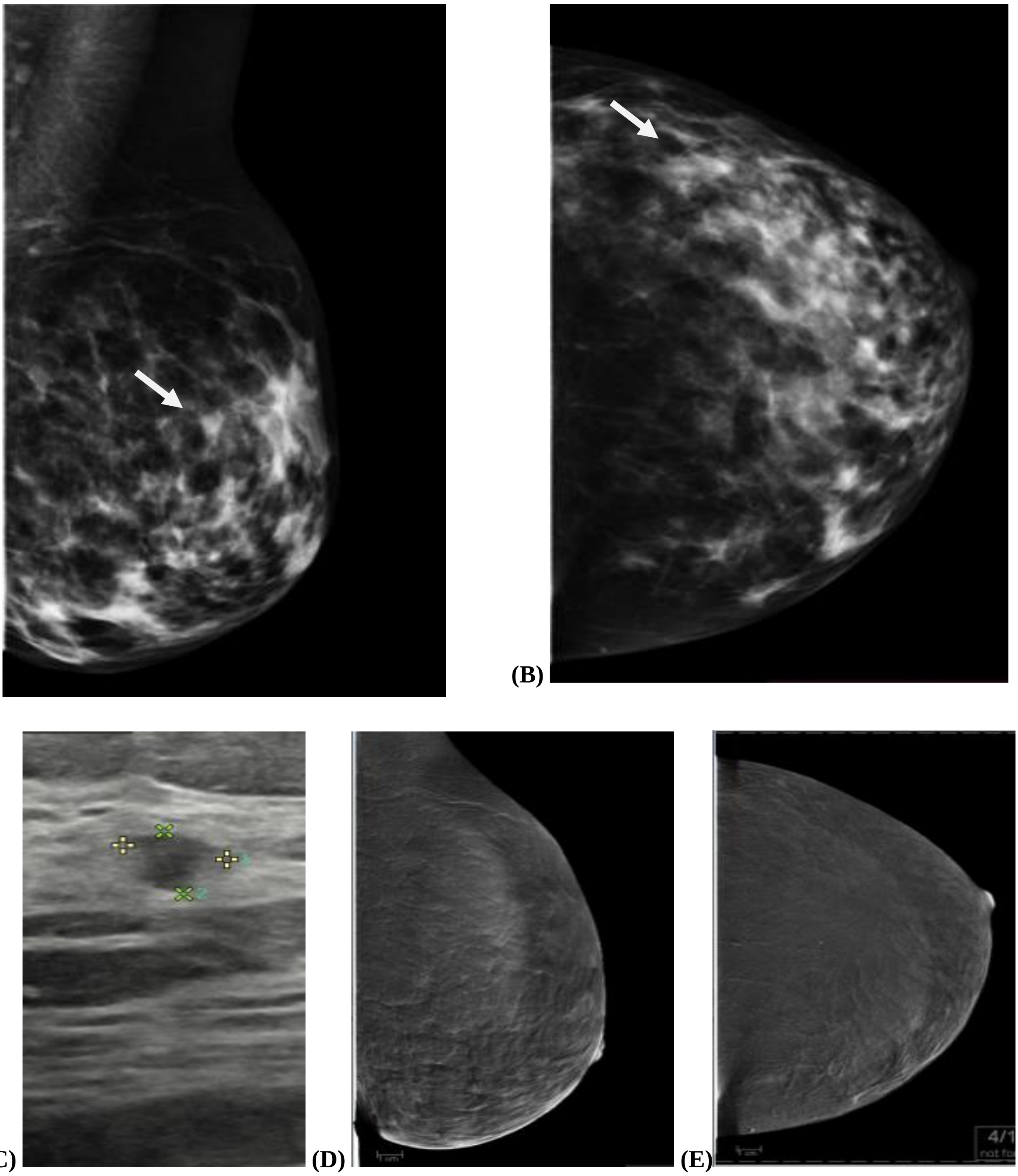


Figure (2): A 65-years-old female coming for breast screening. (A-B) CC, MLO of DM of right breast revealed right upper central quadrant ill-defined lesion partially obscured by condensed glandular tissue. (C-D): ultrasound revealed ill-defined 2 oval lesions with angular and microlobulated margins and they were categorized as BI-RADS 4. (E-F): CEDM of the right breast in CC and MLO views revealed 2 enhancing irregular lesions. The lesions were upgraded to BI-RADS 5. Tissue core biopsy revealed multifocal invasive ductal carcinoma.



(A) (B) (C) (D) (E)

Figure (3): A 52-years-old female on screening. (A-B): DM: MLO and CC views of the left breast revealed upper outer ill-defined partially circumscribed lesion obscured by condensed glandular tissue. (C): ultrasound revealed a small well-defined lesion with an angular border taller more than wider categorized as BI-RADS 4. (D-E): CC views of CEDM of right breast revealed no enhancement of the lesion. The lesion was downgraded and categorized as BI-RADS 2. Pathology result was fibroadenoma.

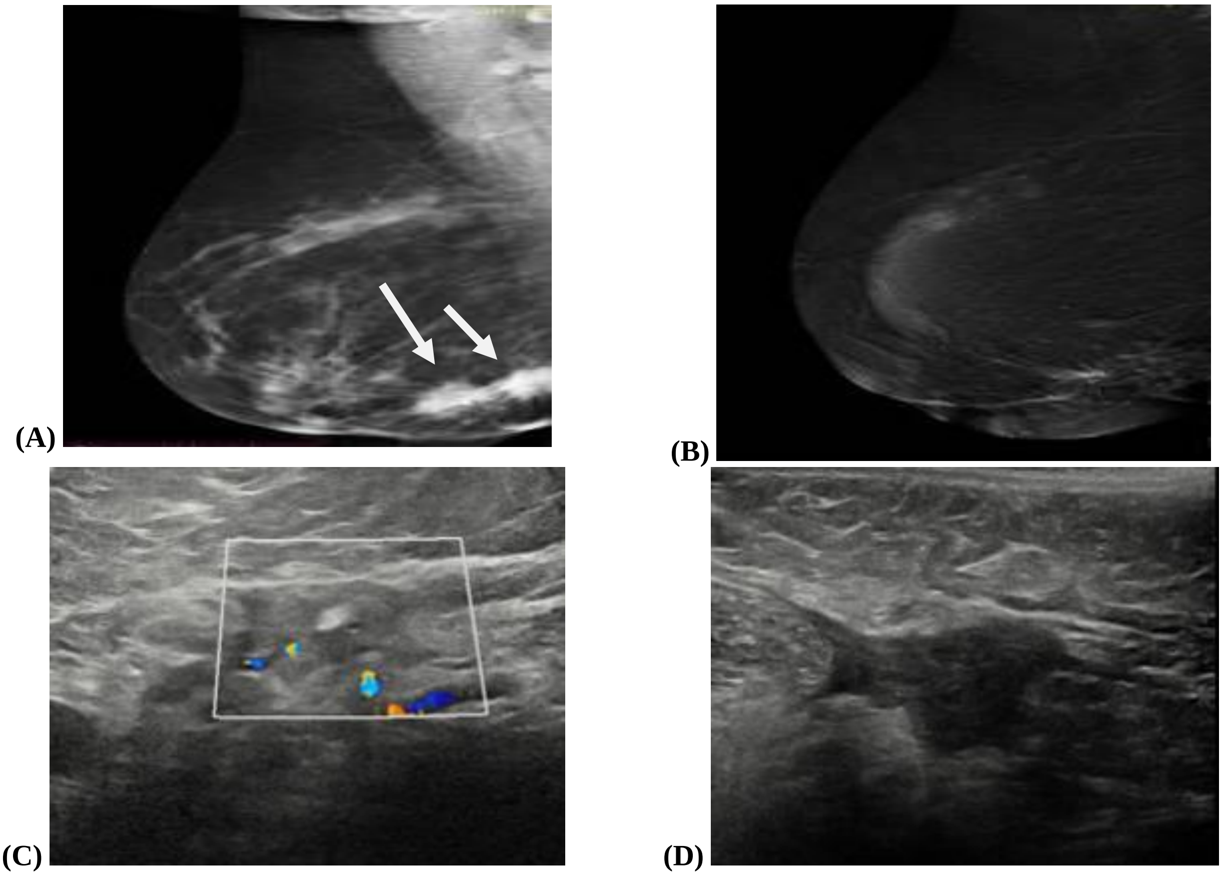


Figure (4): A 73-years-old female underwent right conservative breast surgery on follow-up. (A): DM: (MLO) of the right breast revealed two suspicious irregular lesions on the right operative bed. (C-D): ultrasound revealed two suspicious lesions at operative bed with internal vascularity (BI-RADS 4), (B): MLO view of CEDM of right breast revealed no enhancement of these lesions suggestive of post-operative scar tissue and were categorized as BI-RADS 2. Pathology result was fibrous scar tissue.

Comparison between the histopathological results and sonomammography or CEDM was done (Table 2). BI-RADS 2 and 3 lesions were considered as potentially benign lesions while BI-RADS 4 and 5 were considered as potentially malignant lesions.

Table (2): Comparison between histopathological results and CEDM/Sonomammography results

		Pathology		Test value	P-value	Sig.
		Benign	**Malignant**			
		No. = 22	**No. = 13**			
Sonomammography	Benign	14 (63.6%)	1 (7.7%)	10.443*	0.001	HS
	Malignant	8 (36.4%)	12 (92.3%)			
Contrast-enhanced digital mammography	Benign	19 (86.4%)	1 (7.7%)	20.651*	<0.001	HS
	Malignant	3 (13.6%)	12 (92.3%)			

P>0.05: Non-significant; P < 0.05: Significant; P <0.01: Highly significant

In our study, 40 % (14/35) of lesions were downgraded by CEDM and proved by histopathology to be benign lesions.

On the other hand, upgrading occurred for 14.2 % (5/35) lesions by CEDM done and was proved by histopathology to be malignant lesions. However, three false-positive cases were upgraded by CEDM from BI-RADS 3 to 4 and proved to be benign lesions (sclerosing adenosis, fibroadenoma and breast abscess). Furthermore, one false-negative case was downgraded from BI-RADS 4 to 2 by CEDM and proved by histopathology to be invasive ductal carcinoma. While, twelve lesions had the same BI-RADS scoring on both sonomammography and CEDM (Table 3).

Table (3): Comparison between the final BI-RADS scoring of CEDM and sonomammography**.**

No of lesions	Sonomammography	CEDM	Grading
5	BIRADS 3	BIRADS 2	Downgrading
2	BIRADS 3	BIRADS 4	Upgrading
8	BIRADS 4	BIRADS 2	Downgrading
3	BIRADS 4	BIRADS 5	Upgrading
1	BIRADS 4	BIRADS 3	Downgrading

According to our results CEDM showed higher specificity (86.4%), PPV (80.0%), NPV (95.0%), and accuracy (88.6%). While, sonomammography revealed specificity of 63.6%, PPV of 60.0%, NPV of 93.3%, and accuracy of 74.29%. But, both showed comparable sensitivity 92.3% (Table 4).

Table (4): Comparison between CEDM and sonomammography as regard: True positive, true negative, false positive, false negative sensitivity, specificity, PPV, NPV, and accuracy.

	TP	TN	FP	FN	Sensitivity	Specificity	PPV	NPV	Accuracy
Sonomammography	12	14	8	1	92.3%	63.6%	60.0%	93.3%	74.29%
Contrast-enhanced digital mammography	12	19	3	1	92.3%	86.4%	80.0%	95.0%	88.6%

DISCUSSION

Digital mammography is significant in breast cancer screening and the evaluation of symptomatic patients, even though it has a restricted accuracy in ladies with dense breast tissue. CEDM has risen as a practical effective tool in the detection of breast cancer especially in dense breasts and allows diminishing examination time. Intravenous iodinated differentiate materials are utilized in CEDM to improve the visualization of tumor neovascularity and subsequently supportive in resolving equivocal findings recognized at ordinary breast imaging [10].

Beginning clinical encounter has appeared the capacity of CEDM to outline the conveyance of neovasculature actuated by cancer utilizing mammography. Additionally, the role of CEDM complementary to standard mammography revealed a higher ability to evaluate and characterize breast lesions for final BI-RADS' evaluation compared to mammography alone. The potential clinical applications are the clarification of mammographically occult findings and the detection of query lesions on standard mammography, especially in dense breast [11].

According to our results CEDM showed higher specificity (86.4%), PPV (80.0%), NPV (95.0%), and accuracy (88.6%). While, sonomammography revealed specificity of 63.6%, PPV of 60.0%, NPV of 93.3%, and accuracy of 74.29%. However, both showed a comparable sensitivity of about 92.3%. A lesser specificity of CEDM 42.9 % and higher sensitivity of 100% was reported by **Chalabi *et al.*** [11]**.** However, both are still higher than the sonomammography evaluated in this study. In concordance to our results, several studies revealed higher specificity, PPV, NPV, and accuracy of CEDM than mammography in categorizing indeterminate breast lesions. **Saraya *et al.***[12] conducted a study in 2017 on 34 patients and the results was in favor of CEDM with higher specificity (91.3%), PPV (88.2%), NPV (95.4%) and accuracy (92.3%) than in mammography (69.5%, 61.1%, 76.1% and 69.2% respectively). **Abdel-Magied and Khalifa** [13] conducted a study on indeterminate breast lesions on patients with conservative breast surgery and revealed a higher specificity (71.4%), PPV (92.3%), and NPV (71.4%) for CEDM compared to mammography results which showed 71.4%, 90.9%, and 55.6% respectively. **Hashem *et al.*** [14] concluded a higher specificity of contrast mammography (71.43 %), compared to digital mammography (59.05%). Yet, all of them showed higher sensitivity of CEDM than our study. An initial clinical experience was done by **Chalabi *et al.*** [15]**.** Indeterminate and equivocal breast lesions were included as a part of this study and were analyzed retrospectively. According to this study, CEDM revealed a higher sensitivity of 92.7%, specificity of 82.4% and accuracy of 89.7% than sonomammography as the latter showed a sensitivity, specificity, and accuracy of 82.9%, 76.5%, and 81.0% respectively. However, these results were for the whole breast lesions detected (with all BI-RADS categories) and not only the indeterminate breast lesions. **Helal *et al.*** [16] reported a comparable sensitivity (92.7%) and accuracy (85.5 %), yet lesser specificity than our results. However, CEDM results were still higher than utilized sonomammography which revealed about 71.5%, 51.8%, and 65.9% respectively. A comparable result as regards the high specificity of CEDM was reported by **Yasin & El Ghany** [17]. Yet, the latter study compared the result of CEDM to MRI. The study concluded that CEDM had less sensitivity (94.1%) than MRI (100%) but a higher specificity (100%) than MRI (95.5%).To put in consideration that the study included only lesions categorized as BI-RADS 4.

In contrast to our study, **Mokhtar and Mahmoud** [18] specified that the sensitivity of CEDM was higher compared to mammography (97.7% vs.

93.2%) with nearly proportionate specificity. Furthermore, A multileader multicase study by **Domain *et al.*** [19] reported that there was a higher average per lesion sensitivity for CEDM complementary to mammography than for sonomammography alone (0.78 vs. 0.71 using BIRADS, p = 0.006).

In our study, 14 lesions (40 %) were downgraded by CEDM and proved by histopathology to be benign lesions. On the other hand, upgrading of 5 lesions (14.2 %) by CEDM was done and proved by histopathology to be malignant lesions. However, three false-positive cases (8.5%) were upgraded by CEDM from BI-RADS 3 to 4 and proved to be benign lesions. Additionally, one false-negative case was downgraded from BI-RADS 4 to 2 by CEDM and proved by histopathology to be invasive ductal carcinoma. While, twelve lesions had the same BI-RADS scoring on both sonomammography and CEDM. This is in concordance with a study done by **Saraya *et al.*** [12]**,** which identified five lesions (12.8%) classified as BI-RADS 4 by DM, yet they were downgraded by CEDM to BI-RADS 3. Nine lesions (23 %) were classified as BI-RADS 3 lesions by DM and then were upgraded to BI-RADS 4 by contrast mammography. Additionally, in a study done by **Chalabi *et al.*** [11], where disagreement around the BI-RADS category was watched in 25% of the inspected lesions counting upgrading and downgrading of lesions in 11.36% and 13.6% respectively. 100% of up/down evaluated lesions demonstrated CEDM to be redressed about the ultimate conclusion.

In our study the sonomammography showed higher false positive (22.8 %) than CEDM (8.57%). While, both of them revealed equal false-negative results (2.8%). In a study done by **Chalabi *et al.*** [15] mammographies revealed a considerable number of false-negative (36%) and false positive (48%) cases. However, already detected, and classified BI-RADS 3 and 4 lesions were included in our study while the previously mentioned study was for screening.

To our knowledge, there are two techniques for CEDM; the dual-energy and temporal subtraction technique. **Domain *et al.*** [19] and **Jong *et al.*** [20] conducted the temporal subtraction CEDM technique in a way comparable to that of breast MRI. These preliminary studies examined a limited number of patients and revealed that CEDM was able to highlight tumor neoangiogenesis. The most advantage of temporal subtraction is its capacity to analyze the time-intensity curve. However, these curves failed to illustrate any clinical significance [20]. Moreover, the dual-energy technique has greater patient compliance and acceptance than the temporal subtraction technique. In our study, we conducted a dual-energy technique, and this was in concordance and established by many other studies [14-16, 21-25].

Concurring to our results and other studies' results CEDM was demonstrated to be more valuable within the discovery of the nature of the breast lesions compared to the sonomammography. Also, it helps within the distinguishing proof of the illness extent on the same setting. The fundamental drawback of CEDM is the requirement for intravenous infusion of contrast media, which may be refused by some patients and contraindicated to others. Another drawback to put into consideration, CEDM is a radiation-dependent technique. In any case, controlled measurements are conveyed to the patient, which is around identical to two ordinary mammography examinations.

There were several limitations in our study such as the limited number of cases, and the additional cost of the study. Additionally, many cases refused to receive contrast and weren't included in our study. Other limitations and pitfalls of CEDM was based on clinical encounter (including more radiation exposure, contrast infusion components, plausibility of unfavorably allergic responses, relative contraindications and the required fasting).

CONCLUSION

CEDM appeared to have a more noteworthy diagnostic accuracy compared to sonomammography in categorizing indeterminate and equivocal breast lesions detected on dense breast. It can be utilized to help in the final assessment of these problematic findings in the same setting and help in avoiding biopsies in numerous patients with more prominent specificity and precision than sonomammography alone.

List of abbreviations:

Contrast-enhanced digital mammography (CEDM), Digital mammography (DM), Positive predictive value (PPV), Negative predictive value (NPV), Ultrasound (US). Magnetic renounce imaging (MRI).

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Author contribution: Authors contributed equally in the study.

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