Review report

BSMMUJ-17.4 – 72500
Digital breast tomosynthesis in early detection of malignant breast microcalcification: A hospital-based cross-sectional study
Showkat MS *et al.* (syeeda.jany2019@gmail.com)

REVIEW COMMENTS		AUTHOR RESPONSE [Note: Please write the responses to each point here mentioning line number(s). You must change the manuscript as per your response.]
A. Technical review		
ROUND 1		
Reviewer's name: **A**		
ORCID: -		
Date assigned: **25-Apr-24**		
Date submitted: **26-Apr-24**		
Do you have any conflict of interest with the author/s? **No**		
Do you wish to be disclosed to the author? **No**		
Comments sent to author **(**Date: **29-Aug-24)**		Date: **11-Sep-24**
	Score	[Note: Please response if the score is below 6]
How would you rate the originality and depth of the manuscript?	7	-
Is the manuscript written in a scholarly manner?	7	-
Does the manuscript have the potential to make a valuable contribution to the world of knowledge?	9	-
Does the manuscript meet ethical standards?	10	-
1. Background: I suppose some information from the Bangladeshi context might be included.		We have now included information from the Bangladeshi context in the Introduction section from lines no. 127 to 133. We have also made necessary revisions in the reference section.
2. Method: I suppose a 95% confidence interval is high in a clinical setting. CI of 95% is used in epidemiological research. Thus, I suppose the author ought to take this into account and justify their actions in this specific study.		We used a 95% confidence interval (CI) in this study to provide a reliable estimate of the precision of our results. The 95% CI is a standard statistical tool that indicates the range within which we can be 95% confident that the true population parameter lies. We have now included this justification in the statistical analysis part of the methods section from lines no. 266 to 269.
3. Introduction and discussion: I couldn't find any information on sociodemographics, which I believe is a crucial factor in patients with breast cancer. Many errors are often found in in-text citations.		We have included sociodemographic information about breast cancer in the Introduction section from lines no. 133 to 140 Additionally, we have presented the socio-demographic information in Table 1 and in the relevant part of the Result section from lines no. 287 to 295. We have also added appropriate discussion in the Discussion section from lines no. 340 to 349. We have revised the text citations and corrected them.
Reviewer's recommendation: **Revisions Required**		
Reviewer's name: **D**		
ORCID: -		
Date assigned: **24-Jun-24**		
Date submitted: **26-Aug-24**		
Do you have any conflict of interest with the author/s? **No**		

REVIEW COMMENTS		AUTHOR RESPONSE [Note: Please write the responses to each point here mentioning line number(s). You must change the manuscript as per your response.]
Do you wish to be disclosed to the author? **No**		
	Score	[Note: Please response if the score is below 6]
How would you rate the originality and depth of the manuscript?	6	-
Is the manuscript written in a scholarly manner?	8	-
Does the manuscript have the potential to make a valuable contribution to the world of knowledge?	6	-
Does the manuscript meet ethical standards?	10	-
Major points:		-
1. DBT image acquisition: There is no mention of how standardization was ensured across different patients and technologists. Variability in compression, positioning, or interpretation could impact the results, so more information on quality control measures would be helpful.		We have included the standardization process of image acquisition in the methods section from lines no. 223 to 231.
2. DBT image analysis: The methods do not mention whether the agreement between the radiologists was assessed (e.g., using kappa statistics). This could be an important aspect to include, as it provides insight into the consistency of the image interpretations.		Two junior radiologists (3-5 years' experience) independently reviewed separate patient samples, with each radiologist assigned different sets of images. Since both junior radiologists did not evaluate the same sample, kappa statistics for inter-rater agreement were not applicable. Kappa requires both reviewers to assess the same cases to measure agreement. To ensure consistency and accuracy in the final results, the senior radiologist (PI) conducted the final review of all images and made the ultimate diagnostic judgment.
3. Breast density: The manuscript mentions breast density in the methods and results but does not provide a detailed analysis of how DBT's performance varies across different breast density categories. This is an important aspect since breast density is a known factor that can affect the accuracy of mammographic imaging.		We did consider breast density; however, we encountered a limitation in the distribution of breast density categories. Specifically, we only had data for two density categories: Type B (Scattered areas of fibroglandular density) and Type C (heterogeneously dense, which may obscure small masses). We have included the lack of DBT's performance across different breast density categories in the limitation part of the Discussion section from lines no. 427 to 430.
4. Histopathology: The consensus process between the two pathologists is briefly mentioned but not described in detail. Understanding how discrepancies were resolved is important for assessing the reliability of the histopathology results.		We have now provided a detailed description of the process for resolving discrepancies in histopathology results in the methods section from lines no. 258 to 262.
5. Statistical Analysis: The diagnostic performance of DBT is assessed using a BI-RADS cutoff of category four, but there is no mention of sensitivity, specificity (although the authors presented in table). Other diagnostic accuracy measures (e.g., AUC of ROC curves) can be included if data permit. Calculate the power of the study.		We have now mentioned the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy calculation in the statistical analysis part of methods section from lines no. 272 to 280. We appreciate the reviewer's suggestion to include additional diagnostic accuracy measures, such as the AUC of ROC curves. However, due to the limitations of our data, we were unable to perform these analyses. We agree with the reviewer's suggestion regarding calculation the power. So, we conducted a post-hoc power analysis using a Z score test for proportions based on the sensitivity, which yielded a power of 94.18%, considering a hypothesized sensitivity of 92.9%. We included the result in the statistical analysis part.
6. Line 246 - Is it based on the BI-RADS scale to classify breast density? In the method section, the scale is in		We acknowledge that the classification of breast density in line 246 is based on BI-RADS scale to classify breast density

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numeric 1/2/3/4 but here the author mentions the B/C scale. Need to resolve this discrepancy in text and Table 2. Please calculate the confidence interval for the sensitivity and specificity.	and understand that in the methods section it was not mentioned the BI-RADS categories as A, B, C, and D and instead appeared as numerical values. So, now we have revised the category in methods section appropriately including the type A/B/C/D based on BI-RADS scale from lines no. 247 to 251. We have also made necessary revision in corresponding table 3 (previous table 2).
7. Table 4: I assume the columns are based on histopathology. Please clarify the column heading.	We have revised the table as 2 × 2 table to show the cross-tabulation between the DBT findings and histopathology finding while also incorporating the sensitivity, specificity, Accuracy, PPV and NPV in the right-hand side as per the suggestion of the executive editor. We have also presented the confidence interval for the sensitivity and specificity in the table 5.
Minor comments:	-
8. Introduction: A statement of why macrocalcification is important will strengthen the rational of the study.	We have included a statement highlighting the importance of microcalcification in the introduction section from lines no. 267 to 271.
9. Line 168: Change "having" to "with."	Lines 188 (168): We have changed “having” to “with” to enhance readability.
10. Line 179: Change "went through" to "underwent."	Line 203 (179): We replaced “went through” with “underwent” for more precise language.
11. Line 250: The distribution of the calcifications mostly showed a linear pattern in 14 (40%) patients, followed by a segmental pattern in 10 (28.6%) patients, and a grouped arrangement in 7 (20%) patients	Lines 305 (250): We have revised the sentence to clearly state: “The distribution of the calcifications mostly showed a linear pattern in 14 (40%) patients, followed by a segmental pattern in 10 (28.6%) patients, and a grouped arrangement in 7 (20%) patients.”
12. Line 333: Clarify the pronoun "they" by specifying the subject.	Lines 417 (333): We have clarified the pronoun “they” as “the cysts” to avoid ambiguity.
Reviewer’s recommendation: **Revisions Required**	
Executive Editor’s name: **M Mostafa Zaman** ORCID: **0000-0002-1736-1342**	
1. The short title should be shorter.	We have shortened the short title as “Digital breast tomosynthesis (DBT) is a valid tool to detect malignant breast microcalcification.”
2. Highlights: Drop the third bullet, but add one sentence on the cardinal finding of the study.	We have dropped the third bullet and added one sentence on the cardinal finding of the study in line no. 105.
3. Referencing: All citations should be in superscripts.	We have revised all the citations in superscript.
4. Introduction: Line 159: Sounds like an analysis of correlation coefficient (r), which is not the case. Therefore, revise the sentence.	We have revised the sentence in line no. 176 as follows.
5. Line 167: How the convenience sampling was done. Provide an approximate number of eligible patients who visited the hospital during the study period. This will show how representative your patients were.	We have now included it in the methods section of the manuscript from lines no. 184 to 187.
6. Exclusion: How many subjects were excluded for each of the criteria? What is the meaning of non-cooperative women?	We have now revised the manuscript and have added the number of subjects that were excluded for each criterion in the methods section from lines no. 194 to 197. The term "non-cooperative women" in the exclusion criteria refers to those who did not consent to participate in the study.
7. Your inclusion included breast biopsy, but exclusion included the absence of histopathology. Were these two tests different?	As for inclusion, "breast biopsy" denotes patients who were advised to and agreed to undergo the biopsy procedure as part of their clinical evaluation. Conversely, "absence of

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	histopathology" in the exclusion criteria refers to patients who were not advised to undergo a histopathology test by their clinicians, which meant they did not have this test performed. It wasn't indented to mean two different types of tests, but to address whether the procedures were conducted based on clinical recommendations and patient consent.
8. Line 174 and elsewhere: Avoid using the term cohort to loosely describe a group of people. The cohort has a specific meaning in research (e.g., a cohort study).	We have revised the manuscript to remove or replace the term as appropriate.
9. Line 178: What are those hospital units? Mention those in the parenthesis.	We have included the name of hospital units in parenthesis as follows- "respective units (the Department of Radiology and Imaging, and The Department of Pathology) at BSMMU".
10. Line 203: Who were those two radiologists? Mention the initials of their names if they were the investigators. If not, write their full names and affiliations. Who was the third radiologist? Kindly follow the above comment.	We thank the executive editor for the comment regarding the identity of the radiologist and agree with it. So, we have included the initials of the two junior radiologists in the methods section in line no. 233 also we included the initials in the methods section in lines no. 235.
11. Ethical concerns: There is nothing about ethical issues or concerns. It would help if you described it here. A simple statement about obtaining IRB clearance is not enough.	We have included the ethical concerns in the Methods section from lines no. 197 to 199.
12. Statistical analysis: How did you calculate the sensitivity, specificity, and accuracy? Describe here. What was the threshold value of DBT for which these analyses were done?	We have included the formula for calculating the sensitivity, specificity, and accuracy in the statistical analysis part of the Methods section from lines no. 272 to 280.
13. Results: For the first time, the breast composition type (B, C, etc) appears here. Describe these in the Methods section.	We understand that in the methods section, the BI-RADS category of breast composition was not mentioned as A, B, C, and D and instead appeared as numerical values. So, now we have revised the category in the methods section appropriately including the type A/B/C/D based on the BI-RADS scale from lines no. 247 to 251. We have also made necessary revisions in corresponding table 3 (previous table 2).
14. Discussion: Avoid repeating results here.	We have revised the manuscript and removed the repeating results in the Discussion section.
15. You have made the comparisons elaborately, but the discussion on pathobiology related to pathobiology is missing.	We have included it in the discussion section from lines no. 361 to 371.
16. Biopsies were based on two different methods. It would be best if you discussed its implications for introducing bias. Provide your thoughts on possible results if a single method was used.	We have included it in the discussion section from lines no. 393 to 401.
17. Your subject selection was very restrictive. What if all patients who reported having a breast lump (or other symptoms) could be recruited? Discuss briefly.	We aimed to include all patients presenting with a breast lump or other relevant symptoms, it was necessary to implement certain exclusions for both practical and ethical reasons such as non-cooperative patients, those who did not require a histopathological test, pregnant women etc. These exclusions were made to ensure the safety of the patients and the integrity of the study's results. Though our subject selection was very restrictive due to these criteria, we believe that it did not significantly impact the generalizability of the findings. Several studies in various demographics have revealed the high diagnostic efficacy of DBT in the detection of breast cancer. Thus, we believe the results are still applicable to the intended patient population.

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	We have included this information in the Discussion section from lines no. 422 to 426.
18. Limitations: You have rightly mentioned the problem of convenient samples. However, a single centre and tertiary care hospital setting is not a limitation for such a study. Your predictive values could have been different had it been done in wider categories of hospitals or communities. Please discuss what if it is applied in primary and secondary care hospitals.	We have revised the manuscript and removed the limitation related to the single centre and tertiary care hospital settings. We also acknowledge the comment regarding the potential variation in predictive value when applied across different hospital categories or community settings which are now discussed in the manuscript starting from lines no. 422 to 426.
19. Conclusion: Do you suggest DBT as a screening test at the population level? Discuss for a yes or no answer. Please emphasise that these results will be applicable to a tertiary hospital like BSMMU.	In response, at the moment we do not recommend digital breast tomosynthesis (DBT) as a primary screening test at the population level. The limitations of DBT, such as higher radiation doses, increased procedural time, patient discomfort, lack of availability at local levels currently outweigh its benefits for widespread screening. Ongoing studies are evaluating DBT's effectiveness in population settings, but no clear advantage has been established yet. We have incorporated this discussion into the Conclusion section from lines no. 439 to 443.
20. Table 4: Provide a 2 x 2 table. Then, indicate the sensitivity, specificity and accuracy on the right-hand side. The footnote must have the formula for these calculations.	We have revised the table 5 (previous Table 4) accordingly following the suggestion. We have also removed the previous Table 5, as we have included the diagnostic metrics in the new Table 5 (previous Table 4). We have also included footnote containing the formula for these calculations.
Executive Editor's decision: **Revisions Required**	
ROUND 2	
Executive Editor's name: **M Mostafa Zaman**	
ORCID: **0000-0002-1736-1342**	
Comments sent to author (Date: **14-Sep-24**)	Date: **16-Sep-24**
1. Abstract: State the objective clearly under the Background.	We have now State the objective clearly under the Background of the Abstract from lines no. 72-73.
2. Keywords and Highlights: Avoid acronyms.	We have revised the manuscript by removing acronyms from the Keywords and Highlights sections.
3. Introduction: While it is very informative, it's lengthy. It would be good to make it shorter.	The Introduction section has been shortened from 603 to 498 words. Changes were made in several areas.
4. Ethical concerns/Methods section: Please add a small paragraph on the ethical concerns (although you described them briefly, lines 197-198) about this study and how you have addressed those concerns. Patients have the right to refuse participation. It would be best if you did not label them non-cooperative. This has a negative connotation for patients' respect. Please change it.	We have now added a paragraph to address the ethical concerns in the Methods section from lines no. 194-201 Additionally, we appreciate the reviewer's comment on avoiding negative connotations like labelling patients as "non-cooperative." In response, we have revised the selection criteria by adding "patients who give consent to participate in the study" as an inclusion criterion and removed the exclusion criterion of "non-cooperative patients" to ensure respectful language towards the patients.
5. You had 35 patients. I wonder how your statistical tests had a power of 94%. Please refer to your response to one of the reviewers. Kindly provide an estimation of the sample size or power calculation in the Methods section. Otherwise, the readers might be surprised.	We acknowledge that the manuscript previously reported a statistical power of 94%, but there was an error in the calculation that resulted in an incorrect value. Therefore, we have removed the incorrect statistical power from the manuscript. Instead, we have included the estimation of sample size in the Methods section from Lines 188-193.

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6. Histopathology: Lines 255-256: The editor's point was on using ultrasonography-guided biopsy (n=20) and DBT-guided biopsy (n=15). Although you agreed with the point, your discussion sounds like you have done these two tests for all of the participants. Your claim (very much justified) for the DBT is higher accuracy, which keeps a discussion point open for doing it for all subjects. The reality might be different, which necessitates ultrasonography-guided biopsy. What could be the results had the DBT been used for all 35 subjects? Please tune your discussion on this point.	We understand that confusion may have arisen regarding the use of diagnostic DBT and the different biopsy methods. In this study, we focused on evaluating the accuracy of DBT in detecting malignant microcalcifications, and DBT was used as a diagnostic test for all participants.
7. Statistical analysis has points that were not done. Correct your claims given in line 264. You have explained what 95% CI means. This section needs only what has been done. Please keep the formula for accuracy only. All others are commonly used estimates; their formulae given in the footnote of Table 5 are enough.	We have revised line 267 (264) and removed the points that were not done from the Statistical Analysis part of the Methods section. We have also removed all the commonly used formulas, such as for sensitivity, specificity, PPV and NPV, only retaining the formula for Accuracy in the Statistical Analysis part.
8. Results: The text description should contain the key findings only. Details are already available in the tables, so make it brief.	We have revised the text description in the Results section to make it more concise. The changes are highlighted using track changes in the uploaded manuscript version 1, which we have provided along with this response.
9. Discussion: Lines 330-333 reiterate the objectives. This should reiterate the main findings or the study's selling point.	We have revised the lines no. 318-321 (330-333).
10. Lines 357-383: This paragraph is a very lengthy. Split it into two thematic paragraphs or make it brief if it is based on a single theme. This will improve the readability.	Lines no. 345-371 (357-383), we have revised the manuscript and split the content into two thematic paragraphs.
11. Lines 402-414 contain many results from other studies. The Discussion should focus on the evidence provided by those articles, not just the repetition of their results. In other words, the numbers in the Discussion should be minimal.	In response, we have revised the manuscript to minimize the use of numerical data from other studies in the Discussion section. Lines no. 390-402 (402-414).
12. Conclusion: Your recommendation of using a bigger sample size (no cohort) is not justified because you had a very high power of your tests. See point number 5 above. Kindly make a claim prudently.	We acknowledge that the manuscript previously cited a high statistical power of 94%, but this figure was based on an erroneous calculation. Given the smaller sample size, the study does not possess high statistical power. So, we have retained the recommendation of using a bigger sample size in the Conclusion section, while in the limitation regarding smaller sample size, we added the information about the lack of high statistical power from lines no. 417-419.
13. Footnotes: Provide the date for the funding Memo and a descriptive statement of the ethical clearance. Keep only acronyms specific to this study, such as BI-RADS, FFDM, LCD, and MLO.	We have provided the date for the funding Memo and added a descriptive statement of the ethical clearance from Lines 452-453. We have also removed all the acronyms that are not specific to this study.
14. Tables: Provide full titles that link them to the study title to identify them even if they were misplaced.	We have revised the table titles of the study.

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15. Table 1: Remove age. A text description would suffice. Clump the education and occupation categories to have a meaningful number. Most numbers are very small. Remove the % sign from all cells; the column heading indicates it.	We have removed the age as per the reviewer's suggestion, which is present in the text in the Results section from lines no. 283 to 284.
16. Table 5: The marginal totals do not match; correct the numbers. I suggest removing PPV and NPV. Having so many analyses for such a small number is not wise. It's good that you have given a 95% confidence interval of sensitivity and specificity. Could you add it to accuracy also to synchronise the findings?	We have also removed the PPV and NPV and added a 95% confidence interval for accuracy (0.85 - 0.99) in Table 5 as per the reviewer's suggestion.
Executive Editor's decision: **Revisions Required**	

B. Editorial decision	Date: **17-Sep-24**
Final decision: **Accepted subject to editorial clarifications**	

Editorial Clarifications	
Executive Editor's name: **M Mostafa Zaman**	
ORCID: **0000-0002-1736-1342**	
Comments sent to author (Date: **23-Sep-24**)	Date: **26-Sep-24**
1. I have edited the Abstract, Highlights, Introduction, Tables, and statistical analysis subsection. I found lots of verbosity has been found, which has made the manuscript unnecessarily lengthy. Look at the edited Introduction to see how the length has been reduced without losing any information (see attached file). Therefore, I suggest you do some pruning of the texts to reduce the word count to <3000, if possible 2500.	We would like to thank the Executive Editor for revising the Abstract, Highlights, Introduction, Tables, and the statistical analysis subsection. We appreciate the suggestion regarding the verbosity of the manuscript and agree with it. As such, we have now revised the entire manuscript to reduce the word count of the Main text section from 3150 to 2496 words. We have also done language editing.
2. The references you used for the breast cancer situation in Bangladesh in the first paragraph of the Introduction section. The second reference should credit GLOBOCAN, not WHO. WHO has cited GLOBOCAN on the website you mentioned. The third and fourth references do not have any data on incidence because these are hospital-based cross-sectional studies. Please cite the most appropriate, correct and updated references. Avoid unnecessary citations, if any.	We acknowledge that there may have been some confusion concerning the third and fourth references, as these studies did not directly provide the stated information. These were cited as secondary sources. In response, we have now revised these and other references to ensure that primary sources are cited wherever possible. We have revised some references to provide updated information and removed any unnecessary citations.