Evaluation of physician performance using a concurrent-read artificial intelligence system to support breast ultrasound interpretation

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ABSTRACT
Purpose: The purpose of this study was to compare the diagnostic performance and the interpretation time of breast ultrasound examination between reading without and with the artificial intelligence (AI) system as a concurrent reading aid.

Material and methods: A fully crossed multi-reader and multi-case (MRMC) reader study was conducted. Sixteen participating physicians were recruited and retrospectively interpreted 172 breast ultrasound cases in two reading scenarios, once without and once with the AI system (BU-CAD™, TaiHao Medical Inc.) assistance for concurrent reading. Interpretations of any given case set with and without the AI system were separated by at least 5 weeks. These reading results were compared to the reference standard and the area under the LROC curve (AUCLROC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for performance evaluations. The interpretation time was also compared between the unaided and aided scenarios.

Results: With the help of the AI system, the readers had higher diagnostic performance with an increase in the average AUCLROC from 0.7582 to 0.8294 with statistically significant. The sensitivity, specificity, PPV, and NPV were also improved from 95.77%, 24.07%, 44.18%, and 93.50%–98.17%, 30.67%, 46.91%, and 96.10%, respectively. Of these, the improvement in specificity reached statistical significance. The average interpretation time was significantly reduced by approximately 40% when the readers were assisted by the AI system.

Conclusion: The concurrent-read AI system improves the diagnostic performance in detecting and diagnosing breast lesions on breast ultrasound images. In addition, the interpretation time is effectively reduced for the interpreting physicians.

1. Introduction

The estimated number of new cases of breast cancer is the first of all cancers and breast cancer is the second leading cause of cancer death in women [1]. Mammography is the most common screening tool for breast cancer, which is an effective examination to find breast cancer at an early stage. In general, regular mammography scan is not recommended for young women who do not have a personal history or a strong family history of breast cancer [2,3]. The decision to screen with mammography in young women should be an individual one. Therefore, although breast cancer mortality tends to decline due to early detection and improved treatment, it is not reflected in young women [4].

Breast density is highly associated with the risk of breast cancer. Many researchers [5,6] observed an inverse relationship between patient age and breast density. Women with dense breasts that appear as a solid white area on mammograms are more likely to affect radiologists’ interpretation [7]. Hence, breast ultrasound plays an integral part in breast cancer screening, used primarily as an adjunct to diagnostic...
mammographies, such as in cases of palpable lesions, focal clinical findings (pain, possible infection, nipple-areolar changes, etc.), and equivocal mammographic findings (especially in dense breasts). With the popularization of breast ultrasound use, many technologies in artificial intelligence (AI) assisted detection and diagnosis of breast cancer have been investigated.

Most AI systems focus on computer-assisted detection (CADe) or computer-assisted diagnosis (CADx). CADe has been evaluated to improve reader performance and reduce interpretation time for automated breast ultrasound (ABUS) interpretation [8,9], while CADx has been evaluated to improve accuracy for breast ultrasound assessment and to be comparable to that of experienced readers, based on the reader-identified lesion [10-12].

In this study, we evaluated an innovative computer-assisted detection and diagnosis system (BU-CAD™, TaiHao Medical Inc.) by a fully crossed multi-reader and multi-case (MRMC) reader study. The BU-CAD™ automatically identifies lesions on breast ultrasound images and generates a score of lesion characteristics (SLC) in terms of malignancy or benignity of a lesion, a corresponding breast imaging reporting and data system (BI-RADS) [13] category, and BI-RADS descriptors including shape, orientation, margin, echo pattern, and posterior features. The study compared the reader (radiologists and breast surgeons) performance between interpreting with BU-CAD™ assistance and interpreting with breast ultrasound images alone.

2. Materials and methods

2.1. Data collection

This study was approved by the Institutional Review Board of the Taipei Veterans General Hospital (Taipei, Taiwan) with IRB No. 2019-01-017CC. The requirement to obtain informed consent was waived. All B-mode breast ultrasound images were retrospectively collected at the time of diagnostic sonography or before biopsy. Lesions were identified by breast palpation, mammography, ultrasound, or magnetic resonance imaging (MRI). When the scanning physician performed an ultrasound scan, a lesion was imaged to demonstrate the subtle findings in the perpendicular planes (transverse plus longitudinal or radial plus anti-radial). The images were acquired by the linear transducer with a length of 50 mm for the Philips ultrasound device and 58 mm for the Toshiba/Canon ultrasound device with a minimum 8-MHz acquisition frequency.

Each case consisted of at least two orthogonal projections of a single lesion. In cases where multiple images were present, the two most representative images were selected for use by a senior radiologist with over 30 years of work experience in breast image interpretation. The selection priority was based on (1) the concordance between the image and the clinical report; (2) the images that demonstrate the highest proportion of each lesion; and (3) the highest image quality. A total of 172 B-mode breast ultrasound patient cases (mean age: 54.07 ± 12.01 years; range: 22–77 years) scanned by 11 operators were anonymized for further analysis. Fig. 2 shows the results of the AI analysis of a benign case (fibrocystic change) and a malignant case (invasive ductal carcinoma). Table 1 lists the demographic and clinical characteristics of the cases.

2.2. Demographic and Clinical Characteristics

The 172 patient cases consisted of 65 biopsy-proven malignant, 71 biopsy-proven benign, and 36 benign cases with at least a 2-year follow-up. The distribution of ultrasound scanner models and case characteristics including patient age and lesion size are shown in Table 1 and Fig. 1, respectively. Patients aged 40–70 years account for more than 77% of all patients. Table 2 shows the distribution of cancer types. Among the 65 malignant cases, the invasive ductal carcinoma (IDC) accounts for 80%, and it far outnumbered the ductal carcinoma in situ (DCIS), invasive lobular carcinoma (ILC), and others.

Table 1

| Scanner Model       | Malignant | Benign (Biopsy-Proven, Follow-Up) | All Case |
|---------------------|-----------|-----------------------------------|----------|
| Philips iu22        | 33        | 67 (36, 31)                       | 100      |
| Toshiba Apio 500/Canon Aplio i800 | 32 | 40 (35, 5) | 72 |
| Total               | 65        | 107 (71, 36)                      | 172      |

2.3. Computer-assisted detection and diagnosis system

The computer-assisted detection and diagnosis system used in this study was a medical device software BU-CAD™ (TaiHao Medical Inc.), which had been approved by the U.S. Food and Drug Administration (FDA) in 2021. This system is indicated for breast ultrasound lesion identification and providing diagnostic recommendations. The BU-CAD™ system is an artificial intelligence software application that adopts deep learning neural network techniques and implements instance segmentation [14] for the identification and diagnosis of soft tissue lesion. The CADe functionality identifies regions of interest (automated ROIs) of a single suspicious soft tissue lesion in up to two orthogonal views of breast ultrasound images to assist users in detecting soft tissue lesions. In addition, CADe generates ROI and lesion contour on each breast ultrasound image. The lesion contour in each image will automatically be delineated by the given ROI.

The CADx functionality generates an SLC, and a corresponding BI-RADS [13] category is also presented to respond to clinical practice. The SLC ranging [0, 26], [26, 51], [51, 98], and [98, 100] correspond to BI-RADS Category 2, 3, 4, and 5 respectively by experimental fitting. In addition, lesion morphology by means of BI-RADS lexicon of descriptors including shape, orientation, margin, echo pattern (i.e., internal sono-texture), and posterior features are also provided for the concurrent read. During the reader study, the users were able to replace the automated ROIs with re-delineated rectangular ROIs for analysis by CADx. Only the last analysis results were displayed on the user interface and could be modified by the user. After reading each case, the system automatically recorded the rating results and interpretation time for further analysis. Fig. 2 shows the results of the AI analysis of a benign case (fibrocystic change) and a malignant case (invasive ductal carcinoma).

3. Study design

A fully crossed MRMC reader study was conducted. Sixteen participating physicians were recruited and asked to retrospectively interpret each case under the following two scenarios: (1) reading without BU-CAD™ assistance, and (2) reading with BU-CAD™ assistance. Location-specific receiver operating characteristic (LROC) curves were used to evaluate the diagnostic performance of the readers between the unaided and aided scenarios. In addition, the time spent on the review and interpretation of each case was recorded for analysis.

3.1. Reader recruitment and training

A total of 16 readers were recruited including 14 U.S. board-certified radiologists and 2 breast surgeons from Virginia, Maryland, Pennsylvania, North Carolina, New Hampshire, Ohio, and California. Radiologists’ years of work experience range from 1 to 24 years (average: 10.1 years). Four of the fourteen radiologists had received breast imaging fellowship training. Both board-certified breast surgeons have practiced for more than 30 years. Table 3 lists the specialty, the Mammography Quality Standards Act (MQSA) certification, training of breast imaging fellowship, and years of work experience for each reader.
Table 2
Cancer type distribution of malignant lesions.

| Cancer Type | Percentage | Count |
|-------------|------------|-------|
| DCIS        | 10.77%     | 7     |
| IDC         | 80.00%     | 52    |
| ILC         | 4.62%      | 3     |
| Others*     | 4.62%      | 3     |

* It included two metaplastic carcinoma and one encapsulated papillary carcinoma.

Each study workstation was equipped with the BU-CAD™ system and standard image display functions including ruler, window level/window width, zoom in/out, and pan functions were provided to each reader. In addition, a function key was provided for the study reader to stop the study and shade the screen to measure real interpretation time in case the reader was interrupted.

Training for each reader consisted of two parts: a written guideline and one-on-one instruction. Twenty cases (8 malignant and 12 benign cases in random order) were used for each training session before the study. These training cases were not part of the reader study. All functionalities of the reading tool were demonstrated to the reader, and then the readers used the tools under observation to ensure their competence.

3.2. Study scenario and workflow

One hundred and seventy-two cases were randomized and split into dataset A and dataset B with the same number of cases in each group. Sixteen readers were randomized and split into two groups X and Y with the same number of readers in each group. For each reader, the study was conducted in 2 reading sessions. In the first session, each reader in group X interpreted dataset A in different random order first in the unaided scenario and then interpreted dataset B in different random order in the aided scenario. Each reader in group Y interpreted dataset A in different random order first in the unaided scenario and then interpreted dataset B in different random order in the aided scenario. In the second session, each reader in group X interpreted dataset A in different random order in the aided scenario and then interpreted dataset B in different random order in the unaided scenario. Each reader in group Y interpreted dataset A in different random order first in the unaided scenario and then interpreted dataset B in different random order in the aided scenario. Interpretations of any given case set with and without the AI support were separated by at least five weeks. The study workflow of the two study scenarios is depicted in Fig. 3.

The readers were blinded to any information on the study cases, including previous radiology, histopathology report, and mammographic findings. Each breast ultrasound case was presented with two orthogonal views of a single lesion. In the unaided scenario, each reader scored an SLC on a quasi-continuous scale of 0–100, a BI-RADS final assessment of BI-RADS Category (2, 3, 4A, 4B, 4C, or 5), and a set of BI-RADS descriptors including shape, orientation, margin, echo pattern, and posterior features. In the aided scenario, the parameters including ROI(s) and lesion contour(s) to indicate lesion location, SLC, BI-RADS Category, and BI-RADS descriptors were presented on the system. All these parameters were modifiable by the reader. After review by the reader, the parameters and interpretation time were recorded by the study workstation. The specific reading workflows for the unaided and aided scenarios are shown below.

3.2.1. Unaided reading scenario

1. A breast ultrasound case with two orthogonal views showing the same lesion is presented to the reader.
2. The reader draws an ROI on each of the orthogonal views.
3. The reader assigns an SLC associated with its likelihood of malignancy/benignity (between 0 and 100).
4. The reader selects a BI-RADS Category (2, 3, 4A, 4B, 4C, and 5).
5. The reader selects the options of each BI-RADS descriptor (shape, orientation, margin, internal sonographic pattern, and posterior features).
6. The study workstation records the reader’s assessments.

3.2.2. Aided reading scenario

1. A breast ultrasound case with two orthogonal views showing the same lesion is presented to the reader.
2. The system provides an automated ROI on each image for reference, which is completely changeable if the location of the ROI is unsatisfactory to the reader. In that case, the reader can perform the same operation as in the unaided scenario to create a rectangular ROI to encompass the lesion, including the edges, while minimizing the background.
3. The system outputs an SLC associated with its likelihood of malignancy or benignity (between 0 and 100), a BI-RADS category (i.e., 2, 3, 4A, 4B, 4C, and 5), and BI-RADS descriptors.
4. The reader modifies the SLC value, BI-RADS Category, and BI-RADS descriptors as desired.
5. The study workstation records the reader’s assessments.

4. Evaluation

This study compared the reader’s performance between the unaided and aided scenarios. To avoid the possibility that results were rewarded for malignant cases when the readers delineated the wrong locations of
the lesions, a rating adjustment was performed [15]. For a patient case, the center of the ROI placed by the reader (or by the AI system for standalone performance evaluation) was within the ROI delineated by the expert panel and the overlapped ROI region was more than 50% of the ROI delineated by the expert panel, the rating was considered a true positive determination; otherwise, the rating was considered a false negative determination.

The primary endpoint of this MRMC reader study was to compare the reader’s performance between the unaided and aided reading scenarios. Reader performance was quantified by the area under the LROC curve, which gave a continuous SLC rating score (0–100), but the wrong location for a malignant case was penalized as a false negative. Then, given an adjusted reader SLC, the trapezoidal method [16] was used to obtain the area under the LROC curve. For analysis of readers’ performance, the OR-DBM MRMC-ROC (OR-DBM for short) model was applied using the MRMCaov package (version 2.51) in the R 4.1.2 software [17]. We specified both reader and case as random effects and modality (aided vs. unaided by the AI system) as a fixed effect in the OR-DBM model [18, 19].

Next, we conducted a linear regression analysis of the reader-specific
data \((16 \times 2 = 32)\) to assess the effects of reading type (unaided vs.
aided) and reader characteristics (specialty, breast image fellowship,
and years of work experience) on the AUC of ROC. The \logit
transformations (i.e., \(\log(x / (1 - x))\)) were applied to the AUC of ROC for
making its distribution more symmetric, where “log” was the natural
logarithm. To account for the within-reader correlations in such clus-
tered data, we fitted a linear regression model to the reader-specific data
with the \textit{generalized estimating equations} (GEE) method \cite{20,21}.
Computationally, assuming an \textit{exchangeable} working correlation struc-
ture, we used the \textit{geeglm()} function (with the default robust estimator of
standard error) of the \textit{geepack} package \cite{23-25} to fit a GEE marginal
linear regression model of correlated continuous responses in R. Since
the sample size (i.e., the number of clusters) of 16 was small in this
MRMC study, the robust estimate of standard error would preferably be
obtained by computing the \textit{fully iterated jackknife variance estimator}
(specifying \textit{std.err} = “\textit{fij}” in the \textit{geeglm()} function) in R.
To ensure the analysis quality, the model-fitting techniques for (1)
variable selection, (2) goodness-of-fit (GOF) assessment, and (3)
regression diagnostics and remedies were used in our GEE linear
regression analysis. Specifically, the modern \textit{stepwise variable selection
procedure} (with the iterations between the \textit{forward} and \textit{backward}
steps) was applied to obtain the best candidate final GEE marginal
linear regression model. The available covariates, including the reading type
(unaided vs. aided), reader characteristics (specialty, breast image
fellowship, and years of work experience), and some of their interaction
terms such as specialty \(\times\) reading type, were placed on the variable list
to be selected. The significance levels for entry (SLE) and stay (SLS) were
both set to 0.25 due to the small sample size (i.e., the number of clusters)
of 16 in this MRMC study. Then, with the aid of substantive knowledge,
the best final GEE marginal linear regression model was identified
manually by dropping the covariates with \(p\) value > 0.10 one at a time
until all regression coefficients were significantly or borderline signifi-
cantly different from 0.
The GOF measure, \textit{coefficient of determination} \((R^2)\), was examined to

| Reader | Specialty | MQSA | Received Breast Image Fellowship | Years of Experience as Radiologist/Breast Surgeon |
|--------|-----------|------|---------------------------------|-----------------------------------------------|
| Dr. X01 | Radiologist | Yes | No | 24 |
| Dr. X02 | Radiologist | Yes | Yes | 3 |
| Dr. X03 | Radiologist | Yes | No | 13 |
| Dr. X04 | Radiologist | Yes | No | 14 |
| Dr. X05 | Radiologist | Yes | No | 8 |
| Dr. X06 | Radiologist | Yes | Yes | 5 |
| Dr. X07 | Radiologist | Yes | No | 2 |
| Dr. X08 | Radiologist | Yes | No | 10 |
| Dr. X09 | Radiologist | Yes | Yes | 12 |
| X10 | Radiologist | Yes | No | 11 |
| Dr. X11 | Breast Surgeon | No | No | >30 (breast surgeon) |
| Dr. X12 | Breast Surgeon | No | No | >30 (breast surgeon) |
| Dr. X13 | Radiologist | Yes | No | 21 |
| Dr. X14 | Radiologist | Yes | No | 1 |
| Dr. X15 | Radiologist | Yes | No | 13 |
| Dr. X16 | Radiologist | Yes | No | 5 |

Fig. 3. Study workflow of Two Study Scenarios.
assess the GOF of the fitted GEE marginal linear regression model. Technically, the \( R^2 \) statistic \((0 \leq R^2 \leq 1)\) for a linear regression model is equal to the square of Pearson’s correlation between the observed and predicted response values and indicates how much of the response variability is explained by the covariates included in the linear regression model.

Simple and multiple generalized additive models (GAMs) were fitted to draw the GAM plots for detecting nonlinear effects of continuous covariates and identifying the appropriate cut-off point(s) to discretize continuous covariates, if necessary, during the stepwise variable selection procedure. Computationally, we used the vgam() function with the default values of the smoothing parameters (e.g., \( \lambda, df = 4, spar = 0 \)) for the cubic smoothing splines of the VGAM package to fit the GAMs for our continuous responses, and then used the plotvgam() function of the same package to draw the GAM plots for visualizing the linear or nonlinear effects of continuous covariates in R. Finally, the statistical tools of regression diagnostics for residual analysis, detection of influential cases, and check of multicollinearity were applied to discover any model or data problems. The value of the variance inflation factor (VIF) \( > 10 \) in continuous covariates or \( \geq 2.5 \) in categorical covariates indicates the occurrence of the multicollinearity problem among some of the covariates in the fitted linear regression model, but interaction terms inevitably enlarge VIF values.

Then, we performed secondary analyses of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and interpretation time. Sensitivity, specificity, PPV, and NPV were calculated according to the reference standard and the reader’s rating of the BI-RADS category since the clinical decision threshold for cancer vs. non-cancer is BI-RADS 3 vs. BI-RADS 4A and the BI-RADS fifth edition [13] concluded that patients with Category \( \geq 4A \) lesions are recommended to undergo biopsy, the analysis of sensitivity, specificity, PPV, and NPV are still based on BI-RADS 4A as the cutoff point (i.e., a BI-RADS Category of 4A or higher defines a positive call for cancer diagnosis). To compare the sensitivity, specificity, PPV, and NPV between the aided and unaided reading scenarios, we applied the Mc Nemar’s test to compare two binomial proportions from the pair-matched data of size \( = 16 \) [26].

The interpretation time of each reading was automatically recorded by the study workstation. The research by Hupse et al. [27] appeared to explain the observed variation in the \( AUC_{LROC} \) of the breast surgeon was 1.6741 – 0.1176 = 1.5085. By contrast, in the subgroup of 70 patients \( > 55 \) years, the \( AUC_{LROC} \) also differed significantly from zero between the aided and unaided scenarios (unaided: 0.7282, aided: 0.8132, \( p = 0.0021 \)). Additionally, subgroup analysis based on lesion size was performed. In the subgroup of 43 cases with lesion size less than 1 cm, the \( AUC_{LROC} \) differed significantly from zero between the aided and unaided scenarios (unaided: 0.7998, aided: 0.8428, \( p = 0.0229 \)). In the subgroup of 74 cases with a lesion size between 1 and 2 cm, the \( AUC_{LROC} \) differed significantly from zero between the aided and unaided scenarios (unaided: 0.7438, aided: 0.8111, \( p = 0.0207 \)). In the subgroup of 55 cases with lesion size larger than 2 cm, the \( AUC_{LROC} \) differed marginally significantly from zero between the aided and unaided scenarios (unaided: 0.7588, aided: 0.8092, \( p = 0.0953 \)).

Next, to explain the observed variation in the \( AUC_{LROC} \) among the 16 readers in the unaided and aided scenarios (see Table 4), the results of the GEE marginal linear regression analysis of logit(\( AUC_{LROC} \)) are shown in Table 6. We found that after adjusting for the effects of the other covariates, the mean value of logit(\( AUC_{LROC} \)) increased by 0.7285 in the aided scenario compared to the unaided scenario (\( p < 0.0001 \)), which was the most striking finding in this MRMC study. Specifically, after adjusting for the effects of the other covariates, we learned that:

1. In the unaided scenario, the estimated mean value of logit (\( AUC_{LROC} \)) of the breast surgeon was 1.6741 – 0.7285 = 0.9456, the radiologist without the breast image fellowship was 1.6741 – 0.7285 + 0.1176 = 1.0632, and the radiologist with the breast image fellowship was 1.6741 – 0.7285 + 0.5630 = 1.5080, respectively.

2. By contrast, in the aided scenario, the estimated mean value of logit(\( AUC_{LROC} \)) of all readers was 1.6741, but those with years of work experience \( \leq 1.4 \) years or \( > 12.4 \) years were just 1.6741 – 0.1661 = 1.5080.

It is interesting to see that the readers in the aided scenario can perform as well as the radiologist with the breast image fellowship. The

| Reader | Unaided | Aided | \( p \)-Value |
|--------|---------|-------|-------------|
| Dr. X01 | 0.7487 (0.6699, 0.8275) | 0.8234 (0.7562, 0.8905) | 0.0097 |
| Dr. X02 | 0.8230 (0.7607, 0.8852) | 0.8377 (0.7784, 0.8971) | 0.5401 |
| Dr. X03 | 0.7333 (0.6564, 0.8102) | 0.7925 (0.7250, 0.8600) | 0.0452 |
| Dr. X04 | 0.7815 (0.7101, 0.8527) | 0.8346 (0.7702, 0.8990) | 0.1616 |
| Dr. X05 | 0.7638 (0.6910, 0.8367) | 0.8764 (0.8256, 0.9274) | 0.0002 |
| Dr. X06 | 0.8533 (0.7938, 0.9129) | 0.8777 (0.8262, 0.9293) | 0.3659 |
| Dr. X07 | 0.7907 (0.7199, 0.8615) | 0.8440 (0.7836, 0.9043) | 0.0378 |
| Dr. X08 | 0.7656 (0.6936, 0.8376) | 0.8418 (0.7814, 0.9022) | 0.0099 |
| Dr. X09 | 0.8185 (0.7556, 0.8815) | 0.8238 (0.7626, 0.8850) | 0.8449 |
| Dr. X10 | 0.7421 (0.6678, 0.8164) | 0.8131 (0.7509, 0.8754) | 0.0239 |
| Dr. X11 | 0.7113 (0.6324, 0.7902) | 0.8159 (0.7497, 0.8862) | 0.0086 |
| Dr. X12 | 0.7374 (0.6602, 0.8146) | 0.8306 (0.7690, 0.8922) | 0.0130 |
| Dr. X13 | 0.7248 (0.6439, 0.8057) | 0.8104 (0.7430, 0.8779) | 0.0211 |
| Dr. X14 | 0.7017 (0.6219, 0.7915) | 0.8052 (0.7404, 0.8700) | 0.0242 |
| Dr. X15 | 0.7289 (0.6664, 0.8114) | 0.8250 (0.7648, 0.8852) | 0.0153 |
| Dr. X16 | 0.6972 (0.6174, 0.7770) | 0.8195 (0.7554, 0.8848) | 0.0001 |
| Average | 0.7582 (0.7014, 0.8151) | 0.8294 (0.7777, 0.8813) | <0.0001 |

The difference achieves statistical significance. That is the \( p \)-value calculated from the OR-DBM model is less than or equal to 0.05.
The value of the GOF measure $R^2 = 0.7975$ was quite high, indicating that Pearson’s correlation between the observed and the predicted values of logit(AUCLROC) was $(0.7975)^{1/2} = 0.8930$.

5.2. Reader sensitivity, specificity, PPV, and NPV

In the unaided scenario, the mean ± standard error of sensitivity was 0.9577 ± 0.0250, ranging from 0.8154 to 1, with a median sensitivity of 0.9769. The mean ± standard error of specificity was 0.2407 ± 0.0413, ranging from 0.0187 to 0.6262, with a median specificity of 0.1963. The mean ± standard error of PPV was 0.4418 ± 0.0415, ranging from 0.3824 to 0.5699, with a median PPV of 0.4233. The mean ± standard error of NPV was 0.9350 ± 0.0462, ranging from 0.8462 to 1, with a median NPV of 0.9297.

In the aided scenario, the mean ± standard error of sensitivity was 0.9817 ± 0.0166, ranging from 0.9231 to 1, with a median sensitivity of 0.9846. The mean ± standard error of specificity was 0.3067 ± 0.0446, ranging from 0.0374 to 0.5327, with a median specificity of 0.3037. The mean ± standard error of PPV was 0.4691 ± 0.0425, ranging from 0.3832 to 0.5455, with a median PPV of 0.4660. The mean ± standard error of NPV was 0.9610 ± 0.0332, ranging from 0.8 to 1, with a median NPV of 0.9667. All indicators were improved in the aided scenario (Table 7) and the specificity shows significant a difference between the unaided and aided reading scenarios.

5.3. Interpretation time

A total of 192 outliers were identified in the 5504 readings. The
average interpretation time of each reader and the other sample statistics for all cases are shown in Table 8 and Fig. 6. The average interpretation times of the 16 readers with and without outliers were compared between the aided and unaided scenarios using the paired t-test [28].

In the unaided scenario, the mean (with the 95% CI) ± standard error of interpretation time was 30.15 (9.92, 50.37) ± 10.31 s, ranging from 18.57 to 57.76 s, with a median interpretation time of 30.0 s. In the aided scenario, the mean (with the 95% confidence interval) ± standard error of the interpretation time was 16.87 (2.29, 31.45) ± 7.44 s, ranging from 8.34 to 38.35 s, with a median of interpretation time of 15.09 s. The difference in interpretation time between the aided and unaided scenarios was 11.67 s per reading (40.9% interpretation time reduction).

When the outlier interpretations were excluded, the mean (with the 95% CI) ± standard error of the interpretation time was 18.11 (2.49, 33.72) ± 10.16 s, ranging from 9.16 to 40.94 s, with a median interpretation time of 16.11 s. The difference in interpretation time between the aided and unaided scenarios was 10.31 s, ranging from 17.73 to 28.54 s, with a median of interpretation time of 16.11 s. The difference in interpretation time between the aided and unaided scenarios was 10.31 s, ranging from 17.73 to 28.54 s, with a median of interpretation time of 2.39 s, ranging from 0.85 to 5.47 s, with a median of interpretation time of 1.02 s. The difference in interpretation time between the aided and unaided scenarios was 1.02 s, ranging from 0.85 to 5.47 s, with a median of interpretation time of 1.02 s.

The readers decided to accept or modify the AI-derived results based on the recommendation of the AI system. To investigate the influence of the AI system on the readers, the number of readings that the reader’s BI-RADS category changed after the artificial intelligence system was recommended is listed in Table 9. In this study, the readers increased a total of 37 true positive readings, of which the readers accepted 34 recommendations from the AI system. The net increase in true positive readings was 34. For the 217 increased true negative readings, the readers accepted the 187 readings suggested by the AI system. The net increase in true negative readings was 29. For the 217 increased true negative readings, the readers accepted the 187 readings suggested by the AI system. The net increase in true negative readings was 29.

The clustered data of this MRMC study were analyzed by fitting a multiple marginal linear regression model with the generalized estimating equations (GEE) method (assuming an exchangeable correlation structure) to assess the effects of reading type (unaided vs. aided), reader characteristics (specialty, breast image fellowship, and years of work experience), and some of their interaction terms on the mean value of logit(AUC). The number of clusters (n) was 16 with cluster size of 2, and thus the total number of observations (m) was 32. The coefficient of determination ($R^2$) was 0.7975, quite high, indicating that Pearson’s correlation between the observed and the predicted values of logit (AUC) was (0.7975)$^2 = 0.8930$.

The symbol “×” between two covariates was used to indicate an “interaction” and it can literally be interpreted as “and” for categorical variables in this table.

Since the sample size (i.e., the number of clusters) of 16 was small in this MRMC study, the robust estimate of standard error would preferably be obtained by computing the fully iterated jackknife variance estimator (specifying std.err = “fij” in the geeglm() function) in R.

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Table 6
Marginal linear regression analysis of the logit-transformed AUCLROC over the 16 readers using the generalized estimating equations (GEE) method.$^*$

| Covariate | Regression Coefficient Estimate | Robust Standard Error$^a$ | Wald’s $\chi^2$ Test | p-Value$^b$ |
|-----------|---------------------------------|---------------------------|----------------------|------------|
| Intercept | 1.6741                          | 0.0521                    | 1034.3511            | <0.0001    |
| Scenario: Unaided vs. Aided Radiologist × Fellowship: No × Scenario: Unaided Radiologist × Fellowship: Yes × Scenario: Unaided Years of Experience <1.38 or ≥12.42 × Scenario: Aided | -0.7285 | 0.0660 | 121.8694 | <0.0001 |
|           | 0.1176                          | 0.0442                    | 7.0891               | 0.0078     |
|           | 0.5630                          | 0.0783                    | 51.6320              | <0.0001    |
|           | -0.1661                         | 0.0554                    | 8.9871               | 0.0027     |

$^a$ The clustered data of this MRMC study were analyzed by fitting a multiple marginal linear regression model with the generalized estimating equations (GEE) method (assuming an exchangeable correlation structure) to assess the effects of reading type (unaided vs. aided), reader characteristics (specialty, breast image fellowship, and years of work experience), and some of their interaction terms on the mean value of logit(AUC). The number of clusters (n) = 16 with cluster size of 2, and thus the total number of observations (m) = 32. The coefficient of determination ($R^2$) = 0.7975 was quite high, indicating that Pearson’s correlation between the observed and the predicted values of logit (AUC) was (0.7975)$^2 = 0.8930$.

$^b$ The symbol “×” between two covariates was used to indicate an “interaction” and it can literally be interpreted as “and” for categorical variables in this table.

$^*$ Since the sample size (i.e., the number of clusters) of 16 was small in this MRMC study, the robust estimate of standard error would preferably be obtained by computing the fully iterated jackknife variance estimator (specifying std.err = “fij” in the geeglm() function) in R.

$^1$ The difference achieves statistical significance. That is the p-value calculated from the OR-DBM model is less than or equal to 0.05.

Table 7
Reader sensitivity, specificity, PPV, and NPV.

| Performance Measure | Unaided (95% CI) | Aided (95% CI) | p-Value $^a$ |
|---------------------|------------------|---------------|--------------|
| Sensitivity         | 95.77% (0.9088, 1.0066) | 98.17% (0.9492, 1.043) | 0.2991       |
| Specificity         | 24.07% (0.1597, 0.3217) | 30.67% (0.2193, 0.3940) | 0.0448       |
| PPV                 | 44.18% (0.3606, 0.5231) | 46.91% (0.3858, 0.5523) | 0.0580       |
| NPV                 | 93.50% (0.8445, 1.0255) | 96.10% (0.8959, 1.0261) | 0.0580       |

$^a$ The difference achieves statistical significance. That is the p-value calculated from McNemar’s test is less than or equal to 0.05.

5.4. Influence of AI system on readers

The readers decided to accept or modify the AI-derived results based on comprehensive consideration of their own medical expertise and the recommendation of the AI system. To investigate the influence of the AI system on the readers, the number of readings that the reader’s BI-RADS category changed after the artificial intelligence system was recommended is listed in Table 9. In this study, the readers increased a total of 37 true positive readings, of which the readers accepted 34 recommendations from the AI system. The net increase in true positive readings was 34. For the 217 increased true negative readings, the readers accepted the 187 readings suggested by the AI system. The net increase in true negative readings was 29.

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5.5. Standalone performance of AI system

Of the 172 study cases, six benign cases (including 4 cases not identified by the AI system) and three malignant cases (including 1 case not identified by the AI system) failed to pass the location correctness determination. Therefore, the accuracy of the lesion identification algorithm was 94.77%. Further exploration of these fail-identified cases revealed that they were non-mass lesions that do not have clear boundaries on ultrasound images. Fig. 7 shows one example of benign lesion with a non-mass-like pattern and architectural distortion that the AI system did not identify. Fig. 8 shows an example of malignant lesion with a non-mass-like pattern and microcalcifications. The AI system falsely identified the fatty tissue.

Table 10 lists the system’s standalone performances with and without adjustment for the wrong-location penalty. With adjustment for the wrong location penalty, the AUC under the LROC curve (AUC\textsubscript{LROC}) was 0.8384 with 95% CI = (0.7726, 0.9041). The sensitivity, specificity, PPV, and NPV were 93.85%, 55.14%, 55.96%, and 93.65%, respectively. Without adjustment for wrong-location penalty, the AUC under the ROC curve (AUC\textsubscript{ROC}) was 0.8591 with 95% CI = (0.8028, 0.9155).

### Table 8
The interpretation time for unaided and aided scenarios.

| Sample Statistic | Interpretation Time (Seconds) | Difference, p-Value [*] |
|------------------|------------------------------|-------------------------|
|                  | Unaided Scenario             | Aided Scenario          |                               |
| All Readings     | Mean                          | 30.15                   | 18.11                        | 12.04 (39.9%), p < 0.0001 |
|                  | Standard Error                | 10.31                   | 7.97                         | –                         |
|                  | Median                        | 30.0                    | 16.11                       | –                         |
|                  | Min                           | 18.57                   | 9.16                        | –                         |
|                  | Max                           | 57.76                   | 40.94                       | –                         |
|                  | 95% Lower CI                  | 9.92                    | 2.49                        | 8.87                       |
|                  | 95% Upper CI                  | 50.37                   | 33.72                       | 15.21                       |
| All Readings Exclude Outlier | Mean | 28.54                   | 16.87                       | 11.67 (40.9%), p < 0.0001 |
|                  | Standard Error                | 10.16                   | 7.44                        | –                         |
|                  | Median                        | 28.95                   | 15.09                       | –                         |
|                  | Min                           | 17.73                   | 8.34                        | –                         |
|                  | Max                           | 56.39                   | 38.35                       | –                         |
|                  | 95% Lower CI                  | 8.62                    | 2.29                        | 8.74                       |
|                  | 95% Upper CI                  | 48.46                   | 31.45                       | 14.60                       |

*The p value was obtained from the paired t-test (df = 15).

### Table 9
Reader determination changes after the AI system recommendation.

| AI System Recommendation | Changes in Reader Determination |
|--------------------------|---------------------------------|
|                         | Malignant Lesion | Benign Lesion |
|                         | Incorrect to Correct | Incorrect to Incorrect | Incorrect to Correct | Incorrect to Incorrect |
| No biopsy\(^a\) | 1 | 3 | 187 | 42 |
| Biopsy\(^b\) | 34 | 3 | 21 | 54 |
| Fail-identified | 2 | 2 | 9 | 8 |
| Total | 37 | 8 | 217 | 104 |

\(^a\) The AI system recommended BI-RADS Category 2 or 3.

\(^b\) The AI system recommended BI-RADS Category 4A, 4B, 4C, or 5.

### Table 10
The system’s standalone performances with and without adjustment for the wrong-location penalty.

| Sample Statistic | Interpretation Time (Seconds) | Difference, p-Value [*] |
|------------------|------------------------------|-------------------------|
|                  | Unaided Scenario             | Aided Scenario          |                               |
| All Readings     | Mean                          | 30.15                   | 18.11                        | 12.04 (39.9%), p < 0.0001 |
|                  | Standard Error                | 10.31                   | 7.97                         | –                         |
|                  | Median                        | 30.0                    | 16.11                       | –                         |
|                  | Min                           | 18.57                   | 9.16                        | –                         |
|                  | Max                           | 57.76                   | 40.94                       | –                         |
|                  | 95% Lower CI                  | 9.92                    | 2.49                        | 8.87                       |
|                  | 95% Upper CI                  | 50.37                   | 33.72                       | 15.21                       |
| All Readings Exclude Outlier | Mean | 28.54                   | 16.87                       | 11.67 (40.9%), p < 0.0001 |
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|                  | Median                        | 28.95                   | 15.09                       | –                         |
|                  | Min                           | 17.73                   | 8.34                        | –                         |
|                  | Max                           | 56.39                   | 38.35                       | –                         |
|                  | 95% Lower CI                  | 8.62                    | 2.29                        | 8.74                       |
|                  | 95% Upper CI                  | 48.46                   | 31.45                       | 14.60                       |

*The p value was obtained from the paired t-test (df = 15).
The sensitivity, specificity, PPV, and NPV were 96.92%, 55.14%, 56.76%, and 96.72%, respectively.

6. Discussion

In our study, when assisted by the AI system, readers effectively improved their diagnostic performance with increased average AUC\_LROC that provides an aggregate measure of performance across all possible thresholds. For individual readers, the AUC\_LROC value of each reader is improved, but four readers do not achieve statistical significance. Further analysis revealed that three of the four non-significant improved readers had completed breast imaging fellowship training receiving in-depth training in mammography, tomosynthesis, breast ultrasound, breast MRI for screening and diagnosis, as well as image-guided interventions. Therefore, their unaided AUC\_ROC of 0.8230 (Dr. X02), 0.8533 (Dr. X06), and 0.8185 (Dr. X09) are among the top three of all readers. It is expected that AI support has less improvement for experienced readers, since their diagnostic performances are already relatively high in the unaided scenario.

In the subgroup analyses, the readers improved their diagnostic performance in the age subgroups (age ≤55 years and age >55 years) and the lesion size subgroups (less than 1 cm, between 1 and 2 cm, and larger than 2 cm). Except for the subgroup with lesion sizes larger than 2 cm, the improvements were statistically significant in all subgroups. The readers’ sensitivity, specificity, PPV, and NPV were also improved, especially the specificity, reached a statistically significant improvement. Additionally, the average interpretation time was significantly reduced by approximately 40% when readers were aided by the AI system.

The system’s standalone performance presents the performance evaluations based on the automated ROIs. Due to the performance of automated ROIs that achieved an accuracy of 94.77%, the system standalone performance adjusted for the wrong-location penalty was similar to the unadjusted performances. Both achieved AUC above 0.8 (AUC\_ROC: 0.8591 vs. AUC\_LROC: 0.8384). By comparing the system standalone performance and the unaided reading scenario, it is noted that the AUC\_LROC (0.8384) of the AI system was higher than every reader’s AUC\_LROC value for those without breast imaging fellowship training, with an unaided average AUC\_LROC of 0.7582, ranging from 0.6972 to 0.7815. Their average performance in AUC\_LROC was lifted to 0.8240 by the assistance of the AI system, which was close to the performance of readers with breast imaging fellowship training (AUC\_LROC: 0.8214) in the unaided reading scenario.

Clinically, cancer cell growth and division are cell proliferation activities that are usually accompanied by angiogenesis and infiltration of surrounding tissues [32,33], and thus the variation of the ROIs range

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Table 10

| Statistical Parameter | Without Adjustment for Wrong-Location Penalty | With Adjustment for Wrong-Location Penalty |
|------------------------|-----------------------------------------------|------------------------------------------|
| AUC                    | 0.8591 (AUC\_ROC)                            | 0.8384 (AUC\_LROC)                      |
| Sensitivity            | 96.92%                                        | 93.85%                                   |
| Specificity            | 55.14%                                        | 55.14%                                   |
| PPV                    | 56.76%                                        | 55.96%                                   |
| NPV                    | 96.72%                                        | 93.65%                                   |

The sensitivity, specificity, PPV, and NPV were 96.92%, 55.14%, 56.76%, and 96.72%, respectively.

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Fig. 7. Two Orthogonal Views: A fifty-one-year-old woman had a non-mass benign lesion (white arrow) with architectural distortion in her right breast, which was not identified by the AI system.

Fig. 8. Two Orthogonal Views: A fifty-six-year-old woman had a non-mass malignant lesion (white arrow) with microcalcifications in her left breast. The fatty tissue was falsely identified by the AI system.
delineated by the readers can affect the system analysis results. Most studies [11,12] adopted the original ROIs placed by the original interpreting physician from the data source to reduce the intra-reader variability and focused on the diagnostic results. In our study, although the AI system provided automated ROIs for assisting users in detecting the location of breast soft tissue lesions, the users were still allowed to replace the automated ROIs with re-delineated ROIs for further analysis by the AI system. To evaluate the robustness of the AI system when different rectangular ROIs were drawn around the same lesion, two reproducibility experiments of the same lesion cropped by different rectangular ROIs were conducted. In the first reproducibility experiment, each corner point of an ROI was shifted by randomly changing the horizontal and vertical dimensions up to 20% respectively from the reference standard ROI defined by the expert panel. The experiment was repeated 20 times and the results show that AUCs remained stable between 0.8525 and 0.8682 (Fig. 9). In the second reproducibility experiment, each corner point of the reference standard ROI was altered by systematically shrinking the horizontal and vertical dimensions respectively from 1% to 30%. The results showed that as long as the shrinking percentage of the width and height of the ROIs is within 15%, the AUC remained above 0.8 (Fig. 10).

There are some limitations of this study. First, the fifth edition of BI-RADS concluded that patients with BI-RADS Category ≥ 4A lesions are recommended to undergo biopsy, while most BI-RADS Category 3 lesions that have a probability of malignancy less than 2% are recommended for follow-up instead of biopsy to reduce the number of false-positive biopsies. In this study, not all benign lesions were pathologically proven that exists a slight likelihood of false negatives. Secondly, the retrospectively collected cases were scanned by 11 operators. Although different operators are more compliant with the real clinical scenario, ultrasound is still an operator-dependent imaging technique that would be a variable in imaging quality. Lastly, in clinical practice, the physicians report a breast cancer diagnosis decision by referencing relevant clinical information such as patient age, family medical history, mammography report, and context of patient symptoms. This retrospective reader study only focused on assessing the assistance of the AI system to readers in breast ultrasound image interpretation.

7. Conclusions

In conclusion, radiologists and breast surgeons improved their diagnostic performance in detecting and diagnosing breast lesions on breast ultrasound images with the assistance of the AI system. In particular, the AI system was able to help breast surgeons and radiologists who have no breast imaging fellowship training to improve their diagnostic performance to the level of radiologists specializing in breast imaging those who have received breast imaging fellowship training and read breast images daily. Additionally, the interpretation time was reduced by approximately 40% by the AI system support. However, even if the AI system is helpful in this study, the practical application in a real clinical environment should be further explored.

Declaration of competing interest

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