Prospective analysis of breast masses using the combined score for quantitative ultrasonography parameters

Eun Ji Lee & Yun-Woo Chang

To investigate the diagnostic value of combined SWE, SMI, and B-mode US scores for distinguishing between benign and malignant masses. A total of 450 breast masses that underwent US-guided core needle biopsies were prospectively enrolled. The breast masses were assessed based on the BI-RADS and quantitative SWE and SMI parameters. The SWEmax, SWEratio, and SMIv1 cutoff value were determined using Youden’s index by comparison to the pathological results. The BI-RADS categories were scored on a scale from 1 to 5, and SWEmax, SWEratio, and SMIv1 were dichotomized based on each cutoff values (0 or 1). The combined scores (1 to 8) were calculated as the sum of the BI-RADS score and the quantitative scores and compared to the pathologic results using AUROC analysis. The cutoff values were 52.25 kPa for SWEmax, 5.03 for SWEratio, and 2.15% for SMIv1. In AUROC, the combined scores showed significantly better diagnostic performance compared to BI-RADS alone (p < 0.001). The combined score showed significantly increased than BI-RADS alone in specificity (p < 0.001) and accuracy (p < 0.001), but a sensitivity decreased without significance (p = 0.082). When a combined score cutoff value of 4 was used, the false negative rate was 2.7%. Using the combined score, 76.4% of the C4a lesions were considered benign also pathologically diagnosed as benign. The combined scores showed improved diagnostic performance in differentiating between benign and malignant breast masses, which could be helpful for determining a breast biopsy eligibility.

Abbreviations

SWE Shear wave elastography
SWEmax Maximum elasticity of shear wave elastography
SWEratio Elasticity ratio between the lesion and subcutaneous fat tissue
SMI Superb microvascular image
SMIVI Vascular index of superb microvascular image
US Ultrasonography
BI-RADS Breast imaging reporting and data system
ROI Region of interest
AUROC Area under the receiver operating characteristics curve
PPV Positive predictive value
NPV Negative predictive value
DCIS Ductal carcinoma in situ
IDC Infiltrative ductal carcinoma
ILC Infiltrative lobular carcinoma

The evaluation of breast masses on ultrasonography (US) is based on B-mode US, and breast masses are categorized according to the Breast Imaging Reporting and Database System (BI-RADS)¹. Although B-mode US based on the BI-RADS assessment category has a high sensitivity in differentiating benign from malignant breast masses, the relatively wide range and low specificity results in a high false positive rate, leading to unnecessary biopsies²–⁴. In addition to B-mode US, supplementary techniques have been developed to compensate for the low specificity of B-mode US by adding information on tissue elasticity and vascularity. Shear wave elastography...
(SWE) is a technique that evaluates tissue stiffness by inducing a push pulse into the tissue and measuring the speed of the propagating shear waves within the tissue. Superb microvascular imaging (SMI) is a new technique that can separate and detect slow blood flow signals, which are removed along with overlaying tissue motion artifacts in conventional Doppler imaging. A recent meta-analysis of 21 studies on supersonic shear imaging reported that the combination of SWE and the B-mode significantly increased the pooled specificity from 0.61 to 0.85 compared to B-mode alone for evaluating breast masses, resulting in better diagnostic performance. This suggests that adding SWE to B-mode US may be a clinically acceptable practice. A few studies reported that when combined with elastography, BI-RADS category 4a lesions were downgraded and category 3 lesions were upgraded. In addition, there are increasing reports that the combined use of SMI to B-mode US could improve diagnostic performance compared to B-mode alone by increasing in specificity. Lee et al. reported that combining all quantitative values for SWEmax, SWEratio and SMIVI with B-mode US improved the diagnostic performance in differentiating between benign and malignant lesions compared to B-mode alone. The purpose of this study was to investigate the diagnostic value of the combined use of B-mode US with the quantitative SWE and SMI parameters for differentiating between benign and malignant breast masses in prospectively enrolled patients using a combined scoring system that was easy to apply.

Materials and methods

Study participants. This prospective study was approved by our Institutional Review Board for Ethical Issues in Clinical Research (Soonchunhyang University Seoul Hospital Institutional review board No. 2019-05-013) and complied with the Declaration of Helsinki. The written informed consent was obtained from all participants before examination. From July 2019 to February 2021, adult women older than 19 years who received US-guided core needle biopsies and breast US including B-mode US, shear wave elastography (SWE), and superb microvascular imaging (SMI) were enrolled in the study. The B-mode US, SWE and SMI examinations were performed on the same day as the biopsy or one month prior to the biopsy. A total of 408 patients were enrolled. Those with non-mass lesions (n = 2) and borderline pathology including borderline phyllodes tumor (n = 2) and atypical ductal hyperplasia (n = 4) were excluded. In 47 patients, fifty lesions of multiple core biopsies were included. Finally, a total of 450 lesions of 401 patients were analyzed (Fig. 1). All participants were women and the mean age was 45.8 ± 12.1 years (range, 20–84 years).

Ultrasonography examination. All US examinations were performed by one of two board-certificated radiologists who had 19 and 4 years of experience in breast imaging and both had 2 years of experience in SWE and SMI. Breast US examinations were performed using the US equipment of the same model of US systems.
Image analysis. The selection of the representative images of breast US data including B-mode and quantitative SWE parameters (SWEmax, and SWEratio) and SMI (SMIVI) was performed by the radiologist who performed the breast US. All breast lesions were assessed by BI-RADS based on B-mode US and classified as category C3 (probably benign: 2% likelihood of malignancy or less), C4a (low suspicion of malignancy: greater than 2% to 10% likelihood of malignancy), C4b (moderate suspicion of malignancy: greater than 10% to 50% likelihood of malignancy), C4c (high suspicion of malignancy: greater than 50% to 95% likelihood of malignancy), and C5 (highly suggest of malignancy: 95% or greater likelihood of malignancy). Assessment category 3 (probably benign) suggests a likelihood of malignancy with the defined < 2% for which short-interval (6-month) follow-up sonography and then periodic sonographic surveillance may represent appropriate management. Category 4 (suspicious abnormality) is reserved for finding that does not have the classic appearance of malignancy but is sufficiently suspicious to justify a recommendation for biopsy. The ceiling for C3 assessment is a 2% likelihood of malignancy, and the floor for category 5 assessment is 95%, so category 4 assessment covers the wide range of likelihood of malignancy in between. Thus, almost all recommendations for breast interventional procedures will come from assessments category 4 or 5.

Regarding B-mode US analysis, BI-RADS category C3 masses were considered benign, and BI-RADS category C4a and higher masses were considered a positive result for malignancy.

To analyze the diagnostic performance of the combined B-mode US and SWE and SMI quantitative parameters, the combined score was used. For B-mode US, the BI-RADS categories were scored on a scale of 1 to 5 (C3: 1, C4a: 2, C4b: 3, C4c: 4, and C5: 5). For SWE and SMI, the SWEmax, SWEratio, and SMIVI cutoff values were determined using the Youden index by comparison to the pathological results, and each value was scored as 0 when less than the cutoff value, and 1 for higher than the cutoff value. The combined score was calculated as the sum of the BI-RADS score and each quantitative parameter score, ranging from 1 to 8.

Statistical analysis. The pathologic results from the US-guided core needle biopsy were used as the reference standard for direct comparison with quantitative parameters of the mass. The SWEmax, SWEratio, and SMIVI cutoff values used to optimally differentiate between benign and malignant masses were determined by a receiver operating characteristic (ROC) curve analysis using Youden's index. B-mode BI-RADS category and combined scores were compared to the pathology results. For the statistical analysis of the diagnostic performance of BI-RADS alone, the BI-RADS categories were divided into two groups; those with negative results were classified as C3 and those with positive results were C4a and above. The diagnostic performance of B-mode US alone based on BI-RADS assessment, combined BI-RADS, and all quantitative SWE and SMI parameter scores were determined by area under the ROC (AUROC) curve analysis. The AUROC values, sensitivity, specificity, accuracy, PPV, and NPV were compared to BI-RADS alone and combined score. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM Corp.) and Rex 3.1.2 version (rexsoft.org). P-values of less than 0.05 were considered statistically significant.

Image evaluation in validation cohort. From March 2021 to April 2022, the combination score 4 was applied as a cut value to 524 masses of 461 patients who performed sonography-guided core needle biopsy in the same institution. The accuracy was analyzed with the pathology as the gold standard. App participants were women and the mean age was 46.1 ± 11.23 years (range, 20–87 years).

Results
Diagnostic performance of quantitative parameters. Of all lesions, 334 (74.2%) were benign and 116 (25.8%) were malignant. The mean size of the breast masses was 1.18 ± 0.8 cm for the benign lesions and 1.67 ± 1.06 cm for the malignant lesions. The diagnostic performance of SWE and SMI quantitative parameters for distinguishing between benign and malignant breast masses is summarized in Table 1. The optimal cutoff
values were 52.25 kPa for SWEmax, 5.03 for SWEratio, and 2.15% for SMIVI, with AUROC values of 0.881, 0.850, and 0.817, respectively.

**Comparison of diagnostic performance between BI-RADS alone and combined scores.** When the combined scores were compared to B-mode only, the combined scores showed significantly higher AUROC values than BI-RADS alone (0.947 vs. 0.663, p < 0.001). Although the cut-off value of the combined score was 3.5, the cut-off value 4 was applied using round-off. The combined scores with a cutoff value of 4 showed significantly better diagnostic performance compared to BI-RADS only (Fig. 2). Compared to BI-RADS alone, the combined scores showed significant increases in specificity (36.8% vs. 86.5%, p < 0.001), accuracy (52.0% vs. 87.3%, p < 0.001), and PPV (34.5% vs. 69.8%, p < 0.001) with no statistically significant loss of sensitivity (95.7% vs. 89.7%, p = 0.085) (Table 2, Fig. 3).

**Analysis of BI-RADS category and combined score according to pathology.** There were 12 malignant cases with combined scores of 1 to 3, representing false negative rate of 2.7% (12/450). Among the two cases of C3 lesions, one case of malignant phyllodes tumor showed a combined score of 3, which was over the SWEmax and SWEratio cutoff values and less than the SMIVI cutoff value. The other C3 lesion showed all quantitative parameters less than the cutoff value but was pathologically diagnosed as invasive ductal carcinoma with necrosis. The 10 cases of false negative C4a with combined scores below 4 were DCIS (n = 5), IDC grade I (n = 4) and ILC (n = 1), with a mean size of 0.68 cm (Fig. 4). Of the 123 cases of C3 lesions considered benign by a combined score of 1 to 3, two cases were pathologically malignant, and false negative rate of C3 lesion were 1.6% (2/123). Among 104 malignant cases with combined scores of over 4, three cases were categorized as C3, but the combined score was 4 because all quantitative parameters were above the cutoff values. The pathologically diagnoses were lymphoma (n = 1), DCIS (n = 1), and IDC (n = 1). Forty-five lesions (10.0%, 45/450) were false positive which were pathologically benign but showed combined scores over 4 including two C3 lesions and 43 lesions.

| Variables   | Cut off* | Sensitivity (%) | Specificity (%) | Accuracy (%) | PPV (%) | NPV (%) | AUROC (95% CI) |
|-------------|----------|-----------------|-----------------|--------------|---------|---------|----------------|
| SWEmax (kPa) | 52.25    | 79.3 (91/116)   | 90.1 (305/338)  | 87.3 (396/454) | 73.6 (91/124) | 92.6 (305/330) | 0.881 (0.843–0.921) |
| SWEratio (%) | 5.03     | 82.8 (96/116)   | 80.8 (272/338)  | 81.3 (368/454) | 60.0 (96/162) | 93.1 (272/292) | 0.850 (0.811–0.884) |
| SMIVI (%)    | 2.15     | 85.3 (99/116)   | 68.3 (229/338)  | 72.7 (328/454) | 48.3 (99/208) | 93.1 (229/246) | 0.817 (0.790–0.851) |

*The optimal cut off values for SWEmax, SWEratio and SMIVI were determined based on the Youden's index.
In this prospective study, we evaluated the diagnostic performance of combined scores divided as the sum of the BI-RADS score and the quantitative value scores. All parameters were scored as BI-RADS categories C3 to C5 using one to five points to reflect the weight of each category, and each quantitative value was dichotomized based on each cutoff value. The combined scores showed significant better diagnostic performance with 86.5% specificity and 87.3% accuracy without a statistically significant loss of sensitivity compared to B-mode US alone. According to a meta-analysis study of adding SWE to B-mode US for the detection of breast cancer, SWE with B-mode US significantly improved specificity in differentiating between benign and malignant lesions and reduces the unnecessary biopsies of the patient having benign lesions. A study on the combined use of the SMI vascular index and B-mode US, a recently introduced quantitative parameter, also showed improved diagnostic performance in distinguishing benign and malignant breast lesions compared to B-mode alone, without a significant change in sensitivity.

In our study, the SWE cutoff value was 52.25 kPa for SWEmax, 5.03 for SWEratio, and 2.15% for SMIVI, which were within the previously reported ranges. However, a previous reported retrospective study showed cutoff values of 86.45 kPa for SWEmax, 3.57 for SWEratio, and 3.35% for SMIVI, which were different ranges than in this study. The difference in cutoff values in this study was likely related to the fact that large numbers of patients who underwent a core needle biopsy were prospectively enrolled and had a relatively high percentage of C4a lesions (48.0%, 216/450), and many of these lesions were benign (89.4%, 193/216). There is no standardization of cutoff value for SWE, and the cutoff values in previous studies varied over a wide range of 45.1–124.9 kPa for Emax and 3.56–5.14 for SWEratio. The previously reported cutoff values of SMIVI ranged from 2.95 to 8.9%, which were within the previously reported ranges. However, a previous reported retrospective study showed cutoff values of 86.45 kPa for SWEmax, 3.57 for SWEratio, and 3.35% for SMIVI, which were different ranges than in this study. The difference in cutoff values in this study was likely related to the fact that large numbers of patients who underwent a core needle biopsy were prospectively enrolled and had a relatively high percentage of C4a lesions (48.0%, 216/450), and many of these lesions were benign (89.4%, 193/216). There is no standardization of cutoff value for SWE, and the cutoff values in previous studies varied over a wide range of 45.1–124.9 kPa for Emax and 3.56–5.14 for SWEratio. The previously reported cutoff values of SMIVI ranged from 2.95 to 8.9%, and were not measured in real-time US in most of the studies because the SMIVI measurements were obtained using post-processing software of the acquired images. The relatively wide range of cutoff values is probably due to the characteristics of breast lesions such as lesion size, the histological malignancy type, overlapping features between benign and malignant lesions. There is also probably related with various study populations, US equipment and methodology of measurement in the reported studies.

The benefit of reducing unnecessary biopsies by adding the SWE or SMI quantitative parameters must be supported by a sufficiently low false-negative rate. According to a previous study, when SWE was combined with B-mode US, the frequency of unnecessary biopsies decreased by 71.3%, and the false-negative rate was low at 2.7% (range, 0–9.4%). A review of previous studies, found that applying lower cutoff values such as < 40 kPa might be an important strategy to decrease the prevalence of false-negative cases. When down-grading BI-RADS C4a lesions to C3, the false negative rate was 6.6% when an Emax cutoff of 87.5 kPa was used, but the false negative rate decreased to 0% when an Emax cutoff of 50 kPa was used. Studies using Emax cutoff of 145.9 kPa reported high false negative rates of 8.0–9.4%. In our study, when the combined score was used, the frequency of unnecessary biopsies decreased by 76.4% (165/216), and the false-negative rate was low at 2.7% (12/450). Relatively low elasticity values in SWE were seen in soft malignant lesions such as DCIS, low-grade IDC, lobular carcinoma, mucinous carcinoma and lymphoma, small-sized malignancies, and lesion located in deep portion. Some benign lesions, such as fat necrosis and mastitis, have relatively high elasticity values. Of the 12 false negative cases in our study population, 10 cases were category 4a and the pathologic

### Table 2. Comparison of diagnostic performance between BI-RADS alone and combined BI-RADS, SWEmax, SWEratio and SMIVI scores. Significant values are in bold. To calculate the combination score, BI-RADS categories were scored 1 to 5 (C3: 1, C4a: 2, C4b: 3, C4c: 4, and C5: 5) and quantitative parameters of SWE and SMI were scored 0 or 1 according to each cutoff value and ranged from 1 to 8 score. Diagnostic performances of B-mode alone and combined score were compared. PPV: Positive predictive value, NPV: Negative predictive value, AUROC: Area under the receiver operating characteristics curve, CI: Confidence interval.

| Variables | Cut off | Sensitivity (%) | Specificity (%) | Accuracy (%) | PPV (%) | NPV (%) | AUROC (95% CI) |
|-----------|---------|----------------|----------------|--------------|---------|---------|----------------|
| BI-RADS (C3–C5) | 4a | 95.7 (111/116) | 36.8 (123/334) | 52.0 (234/450) | 34.5 (111/322) | 96.1 (123/128) | 0.663 (0.635–0.694) |
| | 3.5 | 89.7 (104/116) | 86.5 (289/334) | 87.3 (393/450) | 69.8 (104/149) | 96.0 (289/301) | 0.947 (0.922–0.968) |
| | 4 | 89.7 (104/116) | 86.5 (289/334) | 87.3 (393/450) | 69.8 (104/149) | 96.0 (289/301) | 0.877 (0.852–0.905) |

**Validation analysis of combined score according to pathology.** Of all validation lesions, 423 (80.7%) were benign and 101 (19.3%) were malignant. The mean size of the breast masses were 1.17 ± 0.7 cm for the benign lesions and 1.70 ± 1.06 cm for the malignant lesions. When the cut-off value 4 was applied for validation patients, the accuracy was 91.4% (88.7–93.7, 95% confidence interval) (Table 2).

**Discussion**

In this prospective study, we evaluated the diagnostic performance of combined scores divided as the sum of the BI-RADS score and the quantitative value scores. All parameters were scored as BI-RADS categories C3 to C5 using one to five points to reflect the weight of each category, and each quantitative value was dichotomized based on each cutoff value. The combined scores showed significant better diagnostic performance with 86.5% specificity and 87.3% accuracy without a statistically significant loss of sensitivity compared to B-mode US alone.
results were DCIS (n = 5), IDC grade I (n = 4) and ILC (n = 1), with a mean lesion size of 0.68 cm, consistent with previous studies. Of the C3 cases, 1.1% (5/450) were upgraded by a combined score of 4 or more, suggesting malignant potential. Three cases were malignancies such as lymphoma, DCIS, and IDC, and two cases were benign fibrocystic change.

For the appropriate clinical application of SWE and SMI quantitative parameters, radiologists should evaluate and monitor the optimal cutoff value for each institution because the type of equipment used, the experience of...
Figure 4. DCIS in a 50-year-old female patient. (A) B-mode ultrasound showed a 0.6 m-sized, mass categorized as C4a. (B) The lesion had soft elasticity measured below the cutoff values as SWEmax 13.0 kPa and SWEratio 1.54. (C) The SMI vascular index was measured at 7.1%, over the cutoff value. The combined score was 3, representing a benign lesion, but the pathologic diagnosis was DCIS, intermediate.
In conclusion, combined B-mode US and SWEmax, SWERatio, and SMIVI quantitative parameter scores improved the diagnostic performance in differentiating between benign and malignant breast masses. Combined scoring could be helpful in determining the need for a breast biopsy if applied carefully.

Table 3. Comparison of BI-RADS category and combined score between benign and malignant masses according to pathology. Values are presented as number (%). IDP: intraductal papilloma, PASH: pseudoangiomatous stromal hyperplasia, DCIS: ductal carcinoma in situ, IDC: infiltrative ductal carcinoma, ILC: infiltrative lobular carcinoma. BI-RADS category 3: C3, category 4a:C4a, category 4b: C4b, category 5:C5.
Figure 5. A 32-year-old female patient with fibroadenoma. (A) B-mode ultrasound showed a 0.6 cm-sized, mass categorized as C4a. (B) The SWEmax and SWE ratio were below the cutoff value as as SWEmax 6.4 kPa and SWEratio 2.42. (C) The vascular index of the SMI was 0%. The combined score was 2, indicating that the lesion was considered benign lesion. The pathologic diagnosis was fibroadenoma.
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**Author contributions**

E.J.L. and Y.-W.C. patients enroll and analysis and wrote the main manuscript text and prepared figures. Y.-W.C. reviewed and approved the manuscript. These authors contributed equally to this work as co-first author.

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**Competing interests**

The authors declare no competing interests.

**Additional information**

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