Diagnostic value of the vascular index measured by superb microvascular imaging for evaluating breast tumors: a meta-analysis

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Abstract

Aim: This meta-analysis aims to assess the accuracy of superb microvascular imaging (SMI) using the vascular index (VI) in the diagnosis of breast tumors. Material and methods: PubMed, Web of Science, Embase, Cochrane Library and Scopus were searched for relevant literature by two researchers until March 14, 2023. The Stata Version 16.0 software was utilized to compute the pooled values for sensitivity (Sen), specificity (Spe), positive likelihood ratio (PLR), negative likelihood ratio (NLR) and diagnostic odd ratios (DOR). Heterogeneity among the included literature was assessed using the I2 statistic and Q test. Conducting influence analysis was used to ensure the robustness of the pooled conclusions and the Deeks’ funnel plot asymmetry test to assess publication bias. We also performed the summary receiver operating characteristic (SROC) curve. Results: Six studies included 1200 breast lesions. The ultimate results in the VI of SMI are as follows: The pooled Sen was 0.80 (95% confidence interval(CI), 0.75–0.85), the pooled Spe was 0.68 (95% CI 0.63–0.74), the pooled PLR was 2.54 (95% CI 2.07–3.12), the pooled NLR was 0.29 (95% CI 0.22–0.38), the pooled DOR was 8.91 (95% CI 5.62–14.13), and the area under the SROC (AUC) was 0.81. Conclusion: The application of SMI using VI may have the potential to benefit the patients and represents a valuable quantitative parameter of SMI for the diagnosis of breast neoplasms.

Keywords: breast neoplasms; superb microvascular imaging; vascular index; meta-analysis

Introduction

In the recent years, the incidence of breast cancer has reflected a slight but steady increase and breast cancer is the leading cause of cancer death among women aged 20-49 years [1]. The key in reducing mortality and improving the therapeutic effect of breast cancer is to diagnose it early, an aim which is currently under major research in clinical trials [2]. In breast cancer tissue, owing to the increased metabolic demand of the tumor and a higher vascularization required, the over-expression of vascular endothelial growth factor (VEGF) leads to an imbalance between pro- and anti-angiogenic factors [3]. The tumor microvessel density is associated with pathological grades of breast carcinomas, metastasis and prognosis [4]. Microvascular density (MVD) in pathology serves as the gold standard for evaluating tumor angiogenesis from a pathological perspective, but the pathology sampling is invasive and malignant tumors have the potential for needle metastasis [5]. Therefore, alternative methods for accurate and non-invasive medical imaging indicators have become a topical area of research in the early detection of breast tumors.

The commonly utilized imaging modalities, namely mammography and conventional ultrasound, are limited in accurately differentiating between malignant and benign lesions. Meanwhile, magnetic resonance imaging (MRI), an alternative imaging technique, is not extensively accessible due to its high cost [6].

Some ultrasound techniques capable of detecting blood flow can provide information to identify the character of breast tumors but each has specific limitations.
Color Doppler flow imaging (CDFI) technology is based on progressive scanning of a focused beam, limiting the number of image frames accessible for Doppler processing and then limiting the Doppler sensitivity of vessel detection as a result of its low frame rate. Furthermore, the performance of CDFI is hampered by tissue clutter caused by tissue motion, as the Doppler signal generated by tissue motion is similar to the low-velocity flow components. CDFI typically uses a temporal-domain wall filter to remove clutter, and vessels with blood flow velocities below the tissue rejection threshold, namely microvessels, are filtered out and cannot be detected [7]. Power Doppler (PD) has been likened to conventional angiography due to its relative angle independence, but an ultrasound machine for PD requires an accurate calibrate when the flow rate is low, improving diagnostic quality by minimizing artifacts [8]. Contrast-enhanced ultrasound (CEUS) is a purely blood-based imaging technique that uses contrast agents to strengthen the contrast between blood vessels and surrounding tissues, thus showing microcirculation perfusion and anatomical-morphological features of the lesions and surrounding tissue in real-time, which has huge advantages and is widely used in the differentiation of benign and malignant lesions [9]. The primary constraint associated with CEUS is its inability to comprehensively capture the imaging characteristics of larger breast lesions within a single plane, particularly in cases where patients present with multifocal breast cancers that do not grow on the same plane. Superb microvascular imaging (SMI) is an emerging ultrasound imaging technique that overcomes the limitations of conventional Doppler ultrasound and has several advantages: low-velocity flow visualization, minimal motion artifacts, high frame rates and high resolution of images without using intravenous contrast [10-11].

SMI not only analyses clutter motion but also detects and removes tissue movement to reveal authentic blood flow by using a new adaptive algorithm. With little angular dependence, clutter, or overflow at smaller scales, SMI provides a more complete and accurate branching of blood vessels than CDFI [12]. Vascular index (VI), defined as the ratio of Doppler signal pixels to pixels in the total lesion, is a reliable quantitative parameter of SMI [13]. Currently, VI measured by SMI is used for imaging of the breast, liver, testis and lymph nodes [14-17]. However, the qualitative parameters of SMI may be affected by operator experience and are widely used to differentiate malignant from benign breast masses, whereas VI has been rarely studied [18]. Therefore, the objective of this study is to evaluate the diagnostic value of VI measured by SMI in differentiating breast masses.

Methods

Literature search strategy

Electronic databases, including PubMed, Web of Science, Embase, Cochrane Library and Scopus were searched from the commencement of the databases to March 14, 2023. The search strategy for PubMed is shown in Table I. Additionally, we used the Medical Subject Headings (MeSH) terms and free words for the same search strategy across other databases. Moreover, we carried out a manual review of the relevant articles’ references. The selected articles were meticulously checked and managed by EndNote X9.

Inclusion and exclusion criteria

Only studies meeting the following criteria were considered for inclusion in this meta-analysis: (1) the study evaluated the VI’s diagnostic utility of SMI for patients with breast lesions; (2) all breast lesions were histologically confirmed; (3) literature could directly or indirectly adequate true positive (TP), false positive (FP), false negative (FN), and true negative (TN) values. Meanwhile, the exclusion criteria were as follows: (1) systematic reviews, meta-analysis, and conference reports; (2) repeated publication; (3) studies restricted to specific breast neoplasms, such as intraductal breast lesions; (4) insufficient data of VI.

Literature screening

Two authors independently extracted the following data from the included studies using Microsoft Excel spreadsheets: first author’s name, year of publication, study design, ultrasonic diagnostic apparatus, country, sample size, patient age, scale, cut off value and rates of four times (2 x 2) tables (TP, FP, FN, TN).

Quality assessment

Quality assessment of the studies was performed independently by two authors based on the revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool [19]. The risk of bias and the applicability of included literature were rated as high risk(−), low risk(+), or unclear risk(?). The results of the quality summary were shown both in tabular and graphic formats. The dis-

Table I. The search strategy of PubMed

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<th>Search terms</th>
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agreements between the two authors were resolved after consultation and discussion.

**Statistical analysis**

Meta-Disc version 1.4 software (Universidad Complutense, Madrid, Spain) and Stata Version 16.0 software (Stata Corp, College Station, TX, USA) were used for statistical analysis. The pooled effect quantity, sensitivity (Sen), specificity (Spe), positive likelihood ratio (PLR), negative likelihood ratio (NLR) and diagnostic odd ratios (DOR) with corresponding 95% confidence intervals (CI), was obtained. In addition, the diagnostic capability was evaluated by drawing the summary receiver operating characteristic (SROC). A larger area under the curve (AUC) often indicated higher diagnostic accuracy. The heterogeneity test was performed using I². The threshold effect is determined by observing whether the p value of the Spearman correlation coefficient between Sen logarithms and (1 − Spe) logarithms was more significant than 0.05 by Meta-Disc version 1.4 software. In the included literature, p<0.05 for the Q test or I² values >50% suggested high heterogeneity; p=0.1 for the Q test or I² values <25% suggested low heterogeneity; and 25% ≤ I² values ≤ 50% suggested moderate heterogeneity [20]. If the heterogeneity is high, the random-effects model is used for meta-analysis. Publication bias detection was appraised using Deek’s funnel plots. p value<0.05 denoted statistical significance.

**Results**

**Studies search results**

Figure 1 is the flow chart showing the literature selection process. A total of 122 articles were retrieved after the preliminary search. Based on the inclusion and exclusion criteria, 61 duplicate studies were excluded. After reading the title and abstract, 45 studies were deemed unrelated and excluded. 16 studies were downloaded and read for the full text. 3 studies about conference reports, reviews or meta-analyses were removed. 4 studies were deemed ineligible for inclusion in the analysis due to the absence of VI data or the inability to extract adequate data from fourfold (2×2) tables. We also found some of the studies by the equivalent authors from identical institutions, and 3 studies were judged to be excluded after reading. Ultimately, 6 studies were included.

**Basic characteristics of included studies**

The meta-analysis included 1200 breast lesions. All 6 included articles were English publications that included 4 prospective [5,14,18,23], and 2 retrospective studies [21-22]. We summarized the studies’ basic information in Table II. Two studies’ instruments are Aplio 800, and the remaining studies’ instruments are both Aplio 500.

There are three studies from Korea, two from China, and one from Turkey.

**Quality Assessment of Included Studies**

The results of the quality assessment according to the QUADAS-2 tool are shown in figure 2 and 3. Among the
studies included, two out of six studies had a high risk concerning the flow and timing domain. Two studies had unclear risks concerning the patient selection domain, and four studies had unclear risks of index test bias. Additionally, two studies had unclear applicability of index test concerns. Notably, none of the studies exhibited high risks of bias or applicability concerns in the reference standard.

Quantitative data synthesis

Firstly, Meta-Disc version 1.4 software was used to analyze the threshold effect, the spearman correlation coefficient between Sen logarithms and \((1 - \text{Spe})\) logarithms was \(-0.771\) (\(p=0.072 >0.05\)), which means there was no threshold effect. Stata16.0 software was used to perform the publication bias test, and we found the \(p=0.54 \) (\(p<0.05\)) in VI of SMI (fig 4), and the results suggested no significant influence of publication bias of included studies. The Cochran - Q test of the Spe and NLR showed that there was only slightly high heterogeneity caused by the non-threshold effect. We did not perform meta-regression analysis and subgroup analyses, but we made an influence analysis to show the relative stability of our study. Because of the high heterogeneity, the data of the VI was pooled by the random effects model.

Diagnostic accuracy assessment

As shown in figure 5 and 7, The pooled Sen, Spe, PLR and NLR for VI of SMI in the detection of breast malignant lesions were \(0.80\) (95%CI \(0.75–0.85\)), \(0.68\) (95%CI \(0.63–0.74\)), \(2.54\) (95%CI \(2.07–3.12\)) and \(0.29\) (95%CI \(0.22–0.38\)), respectively. There was slight high heterogeneity of VI in Spe (I²=57.67%, \(p=0.04\)) and NLR (I²=50.13%, \(p=0.07\)), whereas the heterogeneity in Sen (I²=30.17%, \(p=0.21\)) and PLR (I²=18.44%, \(p=0.04\)) was moderate and low, respectively. The AUC was 0.81 and the pooled DOR was 8.91 (95%CI 5.62–14.13) (fig 6, fig 8). In addition, the result of influence analysis showed the relative stability of the pooled conclusion of VI in our study (fig 9).

Table II. Baseline information of included studies

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<td>23.5</td>
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<td>NA</td>
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<tr>
<td>Patient age (year)</td>
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<td>46.1</td>
<td>54.1</td>
<td>50.5</td>
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<td>Velocity Scale (cm/s)</td>
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<td>70</td>
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</tr>
</tbody>
</table>

NA, not available; VI, vascular index; TP, true positive; FP, false positive; FN, false negative; TN, true negative.

Fig 3. Risk of bias and applicability concerns graph.
Discussion

In our current study, 6 articles with 1200 breast lesions were selected to analyze the diagnostic value of VI measured by SMI in differentiating benign and malignant lesions. Since high heterogeneity of Spe was observed in the results, the random-effects model was applied in our analysis. In this quantitative parameter of SMI, the pooled Sen and Spe were 0.80 (95%CI, 0.75–0.85) and 0.68 (95%CI 0.63–0.74), respectively. The relevant AUC was 0.81, AUC<0.9, but AUC>0.7, indicating that VI has a moderate efficiency in the diagnosis value of breast neoplasms. Therefore, VI was demonstrated to be an available quantitative parameter of SMI for differentiating benign and malignant breast masses.

The American College of Radiology has put forth the Breast Imaging Reporting and Data System (BI-RADS) as a way to standardize breast imaging and assess breast lesions. Fewer angiogenic features are included in BI-RADS, but as tumor angiogenesis plays an important role in breast cancer growth and metastasis, the vascular features are essential to distinguish malignant from benign tumors [24]. Some breast carcinomas are evaluated as BI-RADS category 3 by conventional ultrasound in early stages, which can lead to missed diagnoses and reduced overall survival [25]. However, SMI with the ability to detect microfluidic features may reduce this issue occurrence. SMI which has no ionizing radiation and is inexpensive allows the detection of very subtle and slow

![Fig 4. Publication bias in the VI. ESS: effective sample size.](image)

![Fig 5. Coupled forest plot for pooled sensitivity and specificity. CI, confidence interval.](image)
flow signals. In addition, it does not require the usage of contrast agents and can eliminate unnecessary biopsies, contributing to reduce healthcare costs stemming from extraneous tests and inappropriate treatment [26].

The primary SMI parameters for assessing breast masses include alder classification (AC), penetrating vessels (PV), vascular architecture (VA), and VI, with VI being a quantitative parameter while the remaining three parameters are qualitative. A higher AC, PV, VA, and VI are indicative of an increased risk of malignancy. Discrepancies are present regarding the optimal diagnostic threshold for SMI based on AC, as some studies suggest grade 3 while others suggest grade 2 [27-28]. This has led to the studies’ findings being different. In addition, although the presence of PV is a specific sign of malignancy, it may have limited value in differentiating malignant lesions. A study reported that PV was detected in 50% of benign lesions by SMI, implying the diagnostic value of the PV parameters is modest [29]. The VA of malignant lesions which mostly appeared root hair-like or crab claw-like patterns differed from those in benign lesions [30]. However, Certain hypervascular benign tumors, including intraductal papilloma, can display overlapping vascular distribution characteristics with malignant lesions. When accompanied with atypical hyperplasia, the high expression of growth factors such as VEGF also allows it to cross-alias with the VA manifestations of malignant masses [21]. In contrast to the qualitative parameters of breast tumors, VI which is a quantitative measure, can provide more objective information about the tumor vessels within the lesion and thus show a sig-
significant difference between benign and malignant breast tumors, suggesting that it can be used to differentiate between breast masses [22]. Park et al have confirmed that VI is the parameter that shows the largest number of downgraded masses without missing cancer in the effect on BI-RADS category 4A class quality downgrading [5]. Moreover, a study of 225 cases of invasive breast cancer found that VI reflects histologic vascular changes in invasive breast cancer and correlates to some extent with the molecular subtype of invasive breast cancer [13]. The diagnostic value of VI measured by SMI in the diagnosis of breast masses cannot be ignored.

In SMI, the VI measurement can be performed in two ways: by manually drawing a free-hand region of interest (ROI) around the lesion or by using the “box” ROI with a function built into the software. A recent study reported that the Sen was 89% for both types, the Specificity for box ROI and free-hand ROI was 56% and 49%, respectively [31]. We found that almost all of the literature used the free-hand ROI and the studies we included were measured by this method as well. The VI between benign lesions and malignant lesions may be overlapped. Some benign lesions such as fibroadenoma, adenomas and intraductal papillomas, show abundant vascularity, while certain cancers with sclerotic tumor stroma may appear to lack internal vascularity on the instrument [14]. The utilization of combined qualitative and quantitative indicators of SMI offers improved accuracy in the diagnostic processes for determining both the status of benignity and malignancy in breast masses.

Our study is the first meta-analysis that concretely analyses the value of VI measured by SMI in diagnosing breast lesions. Lacking significant publication bias increases the credibility of the results and the influence analysis showed the relative stability of the pooled conclusion in our meta-analysis. However, there are some limitations to our study. The 6 studies included in our study have some heterogeneity after analysis, which might affect the reliability of the study conclusions to a certain extent. It was taken into account that data incompleteness may have been influenced by studies sourced from other databases. Additionally, the six studies included were all from Asia, which affects the reliability of our findings for use across all continents.

In conclusion, the VI of SMI, as a highly reproducible quantitative parameter of tumor blood flow, can provide additional objective information to distinguish malignant from benign breast lesions. Adding VI of SMI to conventional ultrasound examinations may avoid unnecessary biopsies.

Conflict of interest: none

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