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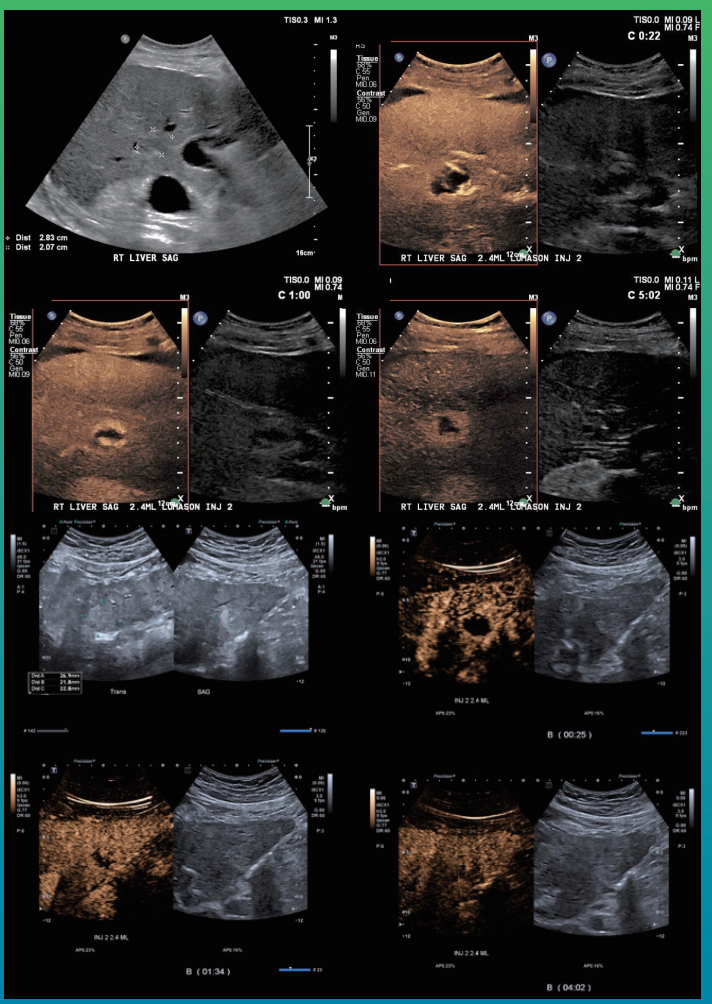

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ORIGINAL RESEARCH

The Value of VTTQ Combined with B-mode US for Distinguishing Benign from Malignant Breast Masses by Comparing with SE: A Clinical Research

Lujing Li, MD [a], Zuofeng Xu, MD [a,*]

[a] Department of Ultrasound, the Seventh Affiliated Hospital of Sun Yat-sen University, Shenzhen, Guangdong, China
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Objective: The purpose of this study was to compare the diagnostic performance of virtual touch tissue quantification (VTTQ) combined with B-mode ultrasonograpgy (US), strain elastography (SE) combined with B-mode US and B-mode US alone in differentiating the properties of breast lesions.

Methods: A retrospective database was queried for 283 healthy subjects and 100 consecutive patients with 130 breast lesions. All the cases were examined by B-mode US, VTTQ and SE. Histological diagnosis was used as the reference standard. The area under the receiver operating curve (AUC) values of each data set was compared.

Results: Twenty-two lesions were determined as malignant and 108 as benign. The best cutoff point of VTTQ was 7.82 m/s. The AUC of B-mode US combined with VTTQ or SE was greater than that of B-mode US alone (0.913 or 0.918 vs. 0.797) (P = 0.007 and 0.012).

Conclusion: Both VTTQ and SE could give help to B-mode US in distinguishing benign from malignant breast lesions about elastography values. There was no difference between them.

Key words: B-mode ultrasonography; Virtual touch tissue quantification; Strain elastography

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Breast cancer is one of the major diseases threatening women's health and has caused a large number of deaths in females. Early detection of breast cancer has moved into the very focus of primary health care. Breast ultrasonography (US) is an invaluable tool for the detection of breast lesions [1-3]. The standardized lexicon for breast US was published in 2013 by the American College of Radiology [4]. The 2013 US Breast Imaging Reporting and Data System (BI-RADS) lexicon was intended to provide a unified language for sonogaphic reporting and research. But there are still a large number of biopsies performed for benign lesions [5-6]. Clearly, there is a great need for development of additional reliable methods to complement the existing diagnostic procedures to avoid unnecessary biopsy.

Ultrasound elastography is the ultrasound-based imaging modality that has gained the interest of researchers in US imaging. Three are three elastography methods: elastography, ARFI (acoustic radiation force impulse) Elastography, and shear wave imaging [7-8]. Gentle repetitive compression is applied to tissue with an ultrasound probe or natural motion with SE. Virtual touch tissue imaging (VTTI) is an ARFI based technique

[*] *Corresponding author: Department of Ultrasound, the Seventh Affiliated Hospital of Sun Yat-sen University, Shenzhen, Guangdong, China*
e-mail: lilujing@mail2.sysu.edu.cn

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and virtual touch tissue quantification (VTTQ) is a shear wave technology.

In this article, we adopted VTTQ to assess normal breast tissue and breast masses. It would be interesting to combine SE or SWE with B-mode US.

Patients and Methods

Patients

Between July 2015 and July 2019, 126 patients underwent B-mode US, VTTQ and SE. Women with a breast mass of at least 5 mm in the longest diameter identified on ultrasound, who required further diagnostic tests for confirmation, were eligible for our study as patients group. Women with large masses (larger than 40 mm) and those who had received neoadjuvant chemotherapy, or who were unwilling or unable to provide informed consent were excluded. 16 patients were excluded due to lack of pathologic results and 10 patients were excluded due to failure of acquirement of exact VTTQ value. B-mode US and VTTQ were also performed on 283 healthy subjects to obtain the VTTQ value of healthy breast parenchyma as control group for the same period. The region of interest (ROI) was placed at depth of 0.5 cm, 1 cm and 1.5 cm, respectively. The inclusion criteria of the healthy subjects were female subjects of at least 18 years of age without a lesion in breast through examining with B-mode US.

This retrospective study was conducted with the approval of the Institutional Review Board of Ethic Committee of our hospital. Written, signed informed consent was obtained from enrolled volunteers and patients.

Instruments and materials

B-mode US, VTTQ and SE studies were performed by a radiologist with 10 years of experience in breast imaging. The investigator was blinded to the pathologic diagnosis and the clinical outcome of the patients. Breast B-mode US was performed using the ACUSON S2000 ultrasound system (Siemens Medical Solutions, Mountain View, CA, USA) equipped with a large format 50mm linear array transducer with a bandwidth of 6-18MHz. VTTQ (Siemens Medical Solutions, Mountain View, CA, USA) was performed using a linear array transducer (9L4, Siemens Medical Solutions, Mountain View, CA, USA) with a bandwidth of 4-9 MHz. SE was obtained using Hitachi HV-900 with a 5-13 MHz linear transducer (Hitachi Medical, Tokyo, Japan).

US technique and pathological diagnosis

The B-mode US scanning was performed first and BI-RADS of 130 solid breast lesions were carefully recorded. The VTTQ module provides measurements of SWV expressed in m/s. Briefly, a 5 × 5 mm ROI was placed in the center of the area of interest and calcification in the ROI was avoided. Each target lesion was measured three times at each site. Mean values of the three measurements were used as the values of the SWV for this evaluation. If X.XX m/s occurred in three consecutive measurements, we replaced X.XX m/s by a value of 9.00 m/s, as previously described [9]. Each lesion was assigned an SE score according to the five-point scoring system proposed by our previous multi-center study [10]. If the entire lesion was shaded in green, it was scored as 1. If the lesion was mostly shaded in green with focal blue spots, it was scored as 2. If the lesion was shaded in green and blue half in half, it was scored as 3. If the entire lesion was shaded in blue or blue in major with a little green, it was scored as 4. If the entire lesion and its surrounding area were blue or blue with a little green, it was scored as 5.

All samples obtained were sent for histological study, and were analyzed by the specialized breast pathologists with at least 15 years of experience.

Statistical analysis

Data were expressed as mean ± standard deviation. The VTTQ values for different depth of ROI of the control group were compared using the Kruskal-Wallis test. The VTTQ values for groups of normal breast tissue, benign and malignant lesions were compared by Kruskal-Wallis test. The best cutoff point for differential diagnosis between benign and malignant lesions was obtained by comparing Youden index (sensitivity + specificity - 1) determined with receiver-operating characteristic (ROC) curve analysis, followed by analysis of the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of diagnosis using the cutoff value. ROC curve analysis was also performed to evaluate the diagnostic performance of B-mode US alone, B-mode US combined with VTTQ and B-mode US combined with SE in distinguishing benign from malignant breast lesions. The differences between the area under ROC curve (AUC) of B-mode US and those of other two sets were compared by using Bonferroni method. The sensitivity, specificity and accuracy of B-mode US were compared with those of the other two data sets by using the McNemar's test. Statistical analyses were performed by Statistical Package for the Social Sciences (SPSS version 13.0 for Windows, Inc., Chicago, IL, USA).

Results

Characteristics of patients and lesions

283 volunteers with normal breast tissue and 100

patients with 130 breast masses were included in our study. The mean age was 46.1 ± 15.6 years, with a range of 18~88 years for control group. The mean age was 37.5 ± 13.3 years, with a range of 18~78 years for patients group. The tumors of patients group varied in size from 5.80 to 37.90 mm (median 15.3 ± 8.3 mm).

VTTQ values of normal breast tissue

The control group consisted of 283 healthy subjects. A total of 283 measurements were successful and returned a numerical value. The mean value of the velocity for ROI depth at 0.5 cm was 2.51 ± 0.64 m/s (range 0.79 - 4.04 m/s). The mean value of the velocity for ROI depth at 1.0 cm was 2.50 ± 0.63 m/s (range 0.82 - 4.05 m/s). The value for ROI depth at 1.5cm was 2.33 ± 0.73 m/s on average (range 0.83-3.86 m/s). There was no statistically significant difference among values at different ROI depths (P = 0.21). An illustration of the VTTQ of normal breast tissue for three depths is shown in Fig. 1.

BI-RADS class of 130 breast lesions

All of 130 lesions were confirmed by pathology (Table 1). Based on histopathologic evaluation, 22 lesions were determined as malignant and 108 lesions as benign. The distribution of benign and malignant lesions for each BI-RADS class was listed in Table 2: (i) 16 lesions, 16 benign (100%) and 0 malignant (0%), were diagnosed as category 2; (ii) 54 lesions, 53 benign (98.1%) and 1 malignant (1.9%), were diagnosed as category 3; (iii) 46 lesions, 39 benign (84.8%) and 7 malignant (15.2%), were diagnosed as category 4; (iv) 14 lesions, 0 benign (0%) and 14 malignant (100%), were diagnosed as category 5.

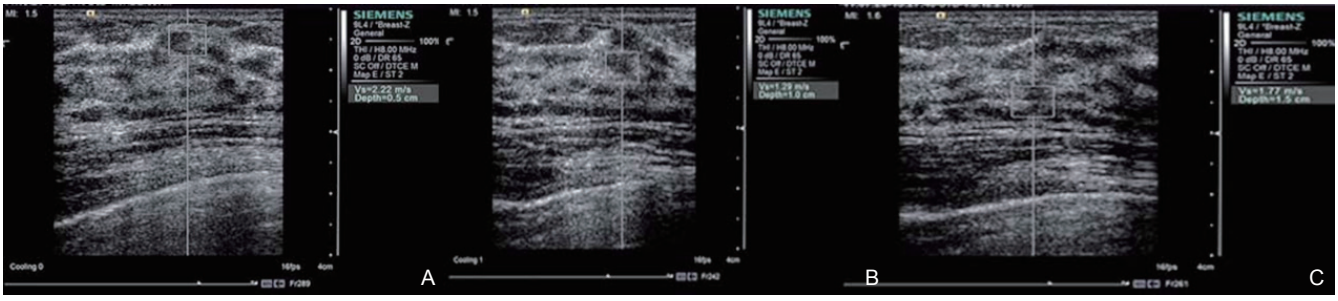

Figure 1 Image of the VTTQ of normal breast tissue for three ROI depths in a 22-year-old woman. (A) The SWV was 2.22 m/s for ROI depth at 0.5 cm.; (B) The SWV was 1.29 m/s for ROI depth at 1.0 cm. (C) The SWV was 1.77 m/s for ROI depth at 1.5 cm.

VTTQ values of breast masses and diagnostic performance of VTTQ

In total, 23 lesions failed to measure SWV in all three consecutive measurements and showed X.XX m/s, including 4 breast masses of benign lesions (3.7%) and 19 breast masses of malignant lesions (86.4%).

The median SWVs of breast lesions were listed in Table 3. The mean SWVs of all benign breast lesions in our study were significantly lower compared with the SWVs measured in invasive ductal carcinoma (8.57 m/s, P < 0.001). The mean SWV of malignant lesions was 8.04 ± 2.50 m/s, while the mean SWV of benign lesions and normal breast tissue was 3.11 ± 1.48 m/s and 2.56 ± 0.62 m/s, respectively. The mean SWV of the malignant lesions was higher than that of the benign lesions and normal breast tissue (P < 0.001). The best diagnostic accuracy was achieved when the cutoff point was set to 7.82 m/s for differentiating malignant lesions from benign ones. The masses with SWV less than 7.82 m/s were designated as benign lesions and the masses with SWVs of higher than 7.82 m/s were designated as malignant lesions. This cutoff point yielded sensitivity of 86.4%, specificity of 96.3% and accuracy of 94.6%.

SE scores of 130 breast lesions

The distribution of benign and malignant lesions for each SE score was listed in Table 4: (i) 59 lesions, 58 benign (98.3%) and 1 malignant (1.7%), were diagnosed as score 1; (ii) 42 lesions, 41 benign (97.6%) and 1 malignant (2.4%), were diagnosed as score 2; (iii) 4 lesions, 3 benign (75.0%) and 1 malignant (25.0%), were diagnosed as score 3; (iv) 19 lesions, 6 benign (31.6%) and 13 malignant (68.4%), were diagnosed as score 4; (v) 6 lesions, 0 benign (0%) and 6 malignant (100%), were diagnosed as score 5.

Combination of B-mode US and VTTQ, B-mode US and SE for distinguishing benign breast lesions from malignant ones

We proposed the revised BI-RADS standards combined with VTTQ or SE results. According to this standard, BI-RADS categories of 2 or 5 kept same without considering VTTQ or SE results. If one lesion was measured with a suspicious SWV (⩾7.82 m/

Table 1 Histological diagnoses of benign and malignant breast lesions in 100 patients with 130 breast lesions

Benign lesions (n =108)		Malignant lesions (n = 22)	
Histopathologic diagnosis	n	Histopathologic diagnosis	n
Fibroadenoma	74	Invasive ductal carcinoma	16
Fibrocystic mastopathy	19	Ductal carcinoma in situ	1
Benign phyllodes tumor	5	Mucinous carcinoma	1
Intraductal papilloma	4	Invasive micropapillary carcinoma	1
Tubular adenoma of breast	4	Malignant phyllodes tumor	1
Hyperplasia	1	Lobular carcinoma in situ	1
Chronic inflammation	1	Neuroendocrine carcinoma	1

Table 2 Distribution of benign and malignant lesions for each BI-RADS class

Lesion type	Class 2	Class 3	Class 4	Class 5	Total
Benign, n	16	53	39	0	108
Malignant, n	0	1	7	14	22
Total	16	54	46	14	130

Table 3 The median SWVs of breast lesions in 100 patients with 130 breast lesions

Benign lesions (n =108)		Malignant lesions (n = 22)	
Histopathologic diagnosis	Median SWVs (m/s)	Histopathologic diagnosis	Median SWVs (m/s)
Fibroadenoma	3.07 ± 1.21	Invasive ductal carcinoma	8.57 ± 1.71
Fibrocystic mastopathy	3.35 ± 2.15	Ductal carcinoma in situ	9.00
Benign phyllodes tumor	2.30 ± 0.33	Mucinous carcinoma	9.00
Intraductal papilloma	4.31 ± 3.16	Invasive micropapillary carcinoma	9.00
Tubular adenoma of breast	2.98 ± 0.69	Malignant phyllodes tumor	0.60
Hyperplasia	2.81	Lobular carcinoma in situ	3.13
Chronic inflammation	1.89	Neuroendocrine carcinoma	9.00

Table 4 Distribution of benign and malignant lesions for each SE score

Lesion type	Score 1	Score 2	Score 3	Score 4	Score 5	Total
Benign, n	58	41	3	6	0	108
Malignant, n	1	1	1	13	6	22
Total	59	42	4	19	6	130

s) or SE score⩾score 3, its corresponding BI-RADS category of 3 would be increased to BI-RADS 4 and its corresponding BI-RADS category of 4 would keep the same. If one lesion was measured with a lower SWV (< 7.82 m/s) or SE score < score 2, its corresponding BI-RADS category of 3 would keep the same and its corresponding BI-RADS category of 4 would be decreased to BI-RADS 3.

Table 5 summarizes the diagnostic performance of the combined sets. There was no statistically significant difference in the sensitivity of B-mode US combined with VTTQ or B-mode US combined with SE and

B-mode US alone (P = 0.607 or 0.953). After addition of VTTQ or SE to B-mode, the AUC for the combined sets (0.913 for VTTQ combined with US and 0.918 for SE combined with US) was significantly higher than that for B-mode US alone (0.797) (P = 0.012 for VTTQ combined with US, P = 0.007 for SE combined with US). There was no significant difference in the AUC between the two combined sets (P = 0.903) (Fig. 2).

Table 5 Comparison of sensitivity, specificity and accuracy of B-mode US, B-mode US combined with VTTQ and B-mode US combined with SE in differentiation between benign and malignant breast lesion

Item	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)
B-mode US	95.5	63.9	69.2	35	98.6
B-mode US combined with VTTQ	86.4	96.3*	94.6*	82.6	97.2
B-mode US combined with SE	90.9	92.6*	92.3*	71.4	98.0

*P < 0.001 versus B-mode US

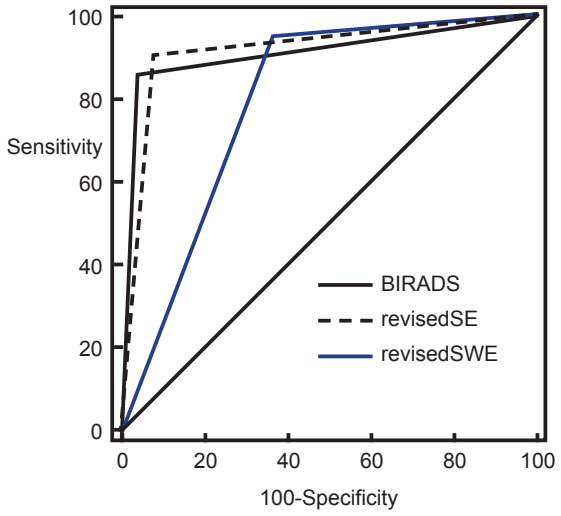

Figure 2 ROC curves for B-mode US, B-mode US combined with VTTQ and B-mode US combined with SE in distinguishing malignant from benign lesions.

False-negative and false-positive diagnosis with B-mode US combined with VTTQ

The false-positive rate was 3.7% (4/108) and the false-negative rate was 13.6% (3/22) for VTTQ combined with B-mode US. The four false-positive benign lesions were one intraductal papilloma and three fibroadenomas. The three false-negative malignant lesions were one malignant phyllodes tumor, one lobular carcinoma in situ and one invasive ductal carcinoma.

False-negative and false-positive diagnosis with B-mode US combined with SE

The false-positive rate was 7.4% (8/108) and the false-negative rate was 9.1% (2/22) for SE combined with B-mode US. The 8 false-positive benign lesions were one intraductal papilloma, two fibrocystic mastopathy and 5 fibroadenomas. The two false-negative malignant lesions were one malignant phyllodes tumor and one lobular carcinoma in situ.

Discussion

The mean SWVs of fibroadenoma, fibrocystic mastopathy, benign phyllodes tumor, intraductal papilloma, tubular adenoma of breast, hyperplasia and chronic inflammation were significantly slower compared with SWV of invasive ductal carcinoma. This result is due to the constitution of pathological tissues. Other researchers also described SWVs of various breast masses. They published initial clinical results using shear wave imaging. They calculated SWV based on single measurements in invasive ductal carcinoma and showed similar results to our fingdings (6.6 m/s) [11]. The results of this study showed that the SWVs of the benign masses were significantly higher than those of normal breast tissue but slower than those of the malignant masses, implying that benign masses tend to be harder than normal breast tissue but softer than malignant masses. As no definite criteria are available for determining whether the internal values or marginal values should be used in clinical practice for distinguishing benign from malignant lesions, different authors used different approaches to perform the measurements. In our study, we did not collect data concerning the external values because we consider that SWVs in the center of the lesion is more accurate than SWVs in the margin. Some researchers assessed the SWV at the margin of the lesion because the failure rate for the measurement of the marginal value was lower than the internal value [12]. The mean SWVs of the malignant lesions and benign lesions (4.49 versus 2.68 m/s) were lower than ours (8.04 versus 3.11 m/s). Some researchers also measured the internal value. The mean SWVs for the malignant and benign masses were 8.38 ± 1.99 m/s and 5.39 ± 2.95 m/s, respectively [13].

Some scholars did not use single approach to perform the measurements. They examined SWVs on average in eight areas of lesions, including central and marginal areas and defined the fastest velocities [14].

During the evaluation of this method, we found that 7.82 m/s was the best cutoff point, with sensitivity of 86.4%, specificity of 96.3%, and accuracy of 94.6%. Sebastian Wojcinski found that the best diagnostic accuracy was achieved when the cutoff point for malignancy was set to > 9.10 m/s, which was higher than ours [13]. The investigators of the Breast Elastography 1 study proposed a cutoff value of 7.3 m/s to upgrade a lesion of BI-RADS 3 to biopsy, which was very close to our results [15]. They placed ROI on the stiffest portion of the lesion (including immediately adjacent tissue). Some scholars found the SWV value of greater than 3.065 m/s was indicative of malignancy [9]. They also suggested repeated non-numeric result X.XX of the SWV measurements as an indicator of malignancy.

Our results suggested that the diagnostic value of B-mode US combined with VTTQ or B-mode US combined with SE was higher than B-mode US alone in the differentiation between benign and malignant breast lesions, which was consistent with previous study [16]. There was no difference between the diagnostic value of B-mode US combined with VTTQ and B-mode US combined with SE. Both of their AUCs were higher than 0.90. Our analysis goal was to develop an algorithm that adds SWV or SE score to B-mode US BI-RADS assessments. Our results showed that addition of SWV or SE score was helpful in the detection of breast lesions. Adding diagnostic data on breast lesion with SE or SWE could improve diagnostic accuracy. However, three malignant lesions were misdiagnosed by B-mode US combined with VTTQ and two malignant lesions could not be diagnosed correctly by B-mode US combined with SE. So the decreasing of BI-RADS should be considered carefully. The reason of misdiagnosis may be that the elastography value of those lesions were quite low so that VTTQ or SE displayed benign signs, including the malignant phyllodes tumor, lobular carcinoma in situ and invasive ductal carcinoma. Furthermore, four benign lesions were misdiagnosed by B-mode US combined with VTTQ and eight benign lesions were misdiagnosed by B-mode US combined with SE. It may be also the result of pathologic characters.

Our results suggested that the ROI depth did not have impact on VTTQ value. Previous study came to the similar conclusion in thyroid tissue [17]. However, different results had been acquired with SE. Researchers had reported that the depth of the breast lesion was the most important factor influencing image quality by SE [18]. It indicated that VTTQ is independent on the depth of ROI and more stable than SE.

Our studies have several limitations. First, the sample size was relatively small. Larger studies including multiple observers would be favorable. Second, sample number of benign and malignant lesions was very different, which might cause the result bias.

Conclusions

In conclusion, consideration of the elastography value of a mass, in addition to standard BI-RADS features, can improve specificity and accuracy of final assessments. If one BI-RADS 3 lesion was measured with a suspicious SWV or SE score, we suggest further verification. If one BI-RADS 4 lesion was measured with a lower SWV or SE score, we suggest 2-3 years follow-up.

Acknowledgment

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Conflict of Interest

The authors have no conflict of interest to declare.

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