

## Peer Review File

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### Reviewer A

Thank you for your submission. This is a well conducted and written meta-analysis / systematic review of the literature with respect to the combination of SWE and CEUS for breast malignancy differentiation. For the most part, the study is designed correctly with appropriate search terms, inclusion criteria, and quality assessment methods. Additionally, the statistical analysis is appropriate. I have a few comments/questions. First, you used very strict end points for your included papers, specifically path was required. I know that many times, breast biopsy is not performed for nodules that are "probably benign." Instead, these nodules are followed over time. Therefore, many studies will use long term stability as an end-point. Did this lead to many papers being excluded? I also wonder if you can break down the number of times an abstract was rejected for each inclusion criterion. With respect to the SROC, have you considered a hierarchical SROC analysis? Can you comment to that end? Additionally, I think the paper would benefit from more detail with respect to how SWE and CEUS studies were conducted. Specifically, what were the thresholds for SWE or criteria for CEUS that lead to the a decision between benign and malignant across the included studies? How was SWE and CEUS results combined to arrive at the combined decision (ie. was it SWE or CEUS vs SWE and CEUS)? Also, while I am aware of and have used these techniques, many readers are likely to know little about these methods from a technical standpoint. More discussion of what these techniques are and why they would help one detect cancers in the introduction would be helpful. Finally, can you talk a bit about how these techniques may impact BI-RADS? US audiences would likely find that of interest.

Nice job overall.

Reply A: Thank you for your comments. For the examination of nodules, whether it is biopsy, SWE, CEUS, or CEUS combined with SWE, the diagnostic result only corresponds to the examination at that time, and it is an instantaneous result, or rather a short-term result. It is impossible to predict the transformation of nodules over time. Both our article and the included articles have short-term conclusions, so there is no disagreement in this regard, and our conclusions do not involve long-term results. Regarding the breakdown of the number of rejected abstracts based on each inclusion criterion, we did not consider such precision when selecting literature, so we cannot provide this answer at present. Regarding your mention of hierarchical SROC analysis, we do not quite understand the specific layering scheme you mentioned. We have already created their own SROC for SWE, CEUS, and CEUS combined with SWE. I have considered conducting hierarchical SROC for different thresholds, but due to the significant differences in thresholds, grouping cannot be formed, and a large part of the literature has vague descriptions of thresholds, which makes it impossible for us to perform hierarchical SROC for different thresholds.

## **Reviewer B**

Congratulation on extensive work performed. Your review offers a good insight into importance of CEUS and SWE in breast lesion characterization. However, for the purpose of a really insightful review I would ask you to elaborate on SWE and CEUS parameters that were used in the studies you analyzed. It is of the utmost importance for everyday use which parameters should be observed when a breast lesion is examined. For instance, did the studies show that maximum or mean lesion stiffness is more accurate? Is it better to use shear wave speed of propagation or kPa value? Does contrast enhancement pattern contributes more to diagnostic accuracy than does kinetic curve observed? Which parameters should be combined? If you elaborate on abovementioned points, I would be prone to suggest acceptance of your review.

Reply B: Thank you for your comment. The SWE and CEUS parameters you mentioned are very useful for improving the quality of this article. I have added SWE and CEUS parameters in Table 2, such as the frequency of the CEUS Probe, SWE parameters, and judgment threshold. From the included literature, it seems that the use of shear wave kPa values is more common. We have re read all the included literature, and when used in combination, each result is scored. The relative score of the two results is determined based on the pre-set threshold to determine whether they are malignant or benign.

Change in the text: Table 2.

## **Reviewer C**

This appears to be a well thought out study with appropriate study methods and conclusions.

The study is methodically designed, demonstrating a clear and well-structured approach to addressing the research question. The authors' choice of research methods appears to be well-aligned with their objectives. The data analysis is robust, and the results provide valuable insights into the subject matter.

Overall, I find the study to be of high quality, and I believe it would make a valuable addition to the journal's content. I commend the authors for their efforts in conducting this research and presenting it in such a compelling manner.

Reply C: Thank you for your comment. We will work harder to conduct research and hope to achieve more and better results in this field.

## **Reviewer D**

Thank you for your work entitled "Diagnostic performance of contrast-enhanced ultrasound combined with shear wave elastography in differentiating benign from malignant breast lesions: a systematic review and meta-analysis". The authors performed a meta-analysis of studies investigating the performance of CEUS and SWE together. Please find my comments below:

## Introduction

- Second paragraph: "Ultrasonography is the first choice for clinical screening and diagnosis of breast masses". Mamography is the method of choice for screening breast cancer.
- Second paragraph: "...it cannot be relied upon to correctly diagnose and grade tumors". Although the statements in this sentence correctly highlight the drawbacks of US, US is by no means an unreliable tool for diagnosing breast tumors.

Reply 1: We have advised the sentence accordingly.

Change: Second paragraph 1 in the Introduction section.

Methods: OK

## Results:

- Figures 3-6 could be more high resolution graphics.
- It would be very beneficial if the threshold ranges for SWE could be provided within Table 1.

Reply 2: The attachment we uploaded uses a higher resolution for tracking girls, but the resolution automatically decreases when converted to PDF files. You can view the original image file.

We have added the threshold ranges for SWE in Table 2.

## Discussion:

- The first paragraph is just general information and together with the second paragraph could be incorporated into the Introduction section.
- Second paragraph: "...it also has a higher FP rate than does conventional ultrasound". This statement needs a reference.
- Second paragraph: "... deeply in the catheter". Statement unclear. Please explain what "growing deeply in the catheter" means. What is the catheter referring to?
- "2 methods" and "2 techniques" should be written as "two methods" and "two techniques".
- The discussion in general only superficially discusses the study itself. It is mainly made up of general information and re-iteration of the results. What do other meta-analyses report on B-mode US, Doppler (including microvascular imaging), SWE, and CEUS separately? Are there other meta-analyses reporting on the combination of these modalities? How does the combined use of CEUS+SWE stack up against MRI or CE-mamography, for example. You could also discuss the shortcomings of using CEUS and SWE. For example, CEUS needs injection of a contrast agent and is thus more invasive and expensive.

In short, the article needs a deeper discussion section.

Reply 3:

- I have integrated the first paragraph of the discussion into the Introduction section.

- The reference of "...it also has a higher FP rate than does conventional ultrasound" is the 32nd reference.
- I have revised the statement '... deeply in the catcher' in the article, and the phrase 'catheter' is incorrect, I have changed it to 'duct', means 'ductal cancer'.
- I have revised "2 methods" and "2 techniques" to "two methods" and "two techniques".
- At present, we have not found a meta-analysis of B-mode ultrasound, Doppler (including microvascular imaging), SWE, and CEUS combinations in the diagnosis of breast lesions, or the results of the combination compared with CE mammography, so we are unable to conduct relevant discussions. Thank you for your suggestion.