Author’s response to reviews

Title: Diagnostic effect of shear wave elastography imaging for differentiation of malignant liver lesions: a meta-analysis

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Author’s response to reviews:

Dear editor and reviewers:

Thanks for providing these comments to help us polish our meta-analysis. We have carefully addressed these issues in our manuscript and responded point-by-point. All response is attached in this review letter.

Best wishes

Fankun Meng
Cheng-Hao Tseng (Reviewer 1)

1. There is already one similar meta-analysis about this issue with similar result (Med Ultrason 2017, Vol. 19, no. 1, 16-22). Of course, the current article included more literatures. Perhaps, Pro.Hu could cite this paper, even talking about additional information from the current article is better.

Thanks for your valuable suggestions.

We have carefully read this meta-analysis (Med Ultrason 2017, Vol. 19, no. 1, 16-22) and cited it in our manuscript, moreover we made corresponding comments on the differences between our meta-analysis and this article. We have added “Another meta-analysis (46) discussing the efficiency of SWE imaging for detecting malignant lesions of the liver also showed good results, with sensitivity, specificity and AUC of 0.82, 0.80 and 0.87, respectively; however, the 9 studies included were all to evaluate the diagnostic performance of pSWE while 2D-SWE studies were not included in this meta-analysis.” in line 3, page 11. We compared the two elastography methods in subgroup analysis, which demonstrates 2D-SWE is slightly better than pSWE with regard to sensitivity.


Thanks for your careful review. The reasons lie in follows:


This study which recruited 197 patients included hepatocellular carcinoma (HCC), metastasis, hemangiomas, and focal nodular hyperplasia (FNH). The stiffness of liver lesions and the ratio (lesion to background liver) was calculated. In the results section of the article, the performance of SWE imaging for differentiation of HCC and metastasis was analyzed. But this article did not provide adequate data to evaluate the performance of SWE imaging for differentiation of malignant and benign liver lesions, so it was excluded from our meta-analysis.

(2) Eur J Radiol. 2015 Nov;84(11):2059-64

This article which recruited 56 patients with 76 liver lesions included focal nodular hyperplasia (FNH) and hepatocellular adenoma (HA). FNH and HA are two main types of benign hepatocellular tumors, although the majority of HA at the risk of the possible development of hepatocellular carcinoma. The aim of this study was to assess whether the elasticity
characteristics of FNH and HA are significantly different. This article did not provide adequate data to evaluate the performance of SWE imaging for differentiation of malignant and benign liver lesions and does not meet our inclusion criteria, so it was not included in our meta-analysis.

(3) Ultrasound Med Biol. 2016 Sep;42(9):2156-66

This study met our inclusion criteria, so we included this article in our meta-analysis. (line 23, page 18) (Table 1, Ref. 31)

3. For table 1: It's better to provide the reference number for each article. That would be easier for readers to check.

Thanks for your valuable suggestions.

We have added reference number for each article in table 1 and supplementary table 1 to help reviewers and readers to check. (see Table 1 and Supplementary table 1)

Atsushi Nakajima (Reviewer 2)

Major 1. Whether is there an appropriate size?

Thanks for your comment.

In general, focal liver lesion (FLL) clearly visualized at gray scale ultrasound with size ≥ 1.0 cm; and the region of interest (ROI) of pSWE defined by a box with fixed dimension of 1.0 cm × 0.5 cm. Thus in order to differentiate benign and malignant liver lesions, the diameter of the lesion should be at least 1 cm.

We have added “Fourth, original studies included in our meta-analysis did not provide size-stratified subgroup analysis results which in turn make it hard to identify appropriate size of lesion to do SWE imaging. Future studies are needed to do subgroup analysis according to tumor size to investigate the proper size.” in limitations section (Line 44, Page 12).

In supplementary table 1, we have clearly stated the mean size and/or the range of focal liver lesions in each article. The all nodules in ten included studies are ≥ 1cm (Shuang-Ming et al, 2011; Yu et al, 2011; Kim et al, 2013; Park et al, 2013; Zhang et al, 2014; Guo et al, 2015; Wu et al, 2016; Dong et al, 2017; Wen-Shuo et al, 2016; Gerber et al, 2017). Only three studies included nodules smaller than 1cm (Cho et al, 2010; Davies et al, 2011; Grgurevic et al, 2018).
Major 2. They had better discuss the effect of differentiation of the malignant liver lesions, especially hepatocellular carcinoma. How about the effect of capsule formation and fatty degeneration.

Thank you for your comment.

We think capsule formation and fatty degeneration might effect the results of SWE imaging, but the relationship is not clear according to current research. The reasons lie in follows:

(1) In most original studies, researches did not investigate the direct relationship between capsule formation and SWE imaging. Thus it is hard to say whether capsule formation is related to SWE measurement in our meta-analysis. In majority studies, focal liver lesions (FLLs) localized at least 1.5 cm under Glisson’s capsule to avoid reverberation artifacts, and the region of interest (ROI) did not include any vessels, biliary structures, or capsules. In some studies, the SWE measurements were made on the identified FLL as well as on background liver parenchyma in an area > 2 cm from the tumor (at the same depth) in considering of the performance of differential diagnosis by SWV ratio (FLL to surrounding liver parenchyma).

There was a significant relationship between the ultrasonic signs of hepatic capsular retraction syndrome, irregular shape, unclear boundary, and the malignant lesions. And mass effect, hypoechoic halo and marginal vascular sign were independent predictive factors of malignant liver lesions in conventional ultrasound. Thus it is of significance for clinicians to make comprehensive diagnosis by considering SWE imaging and conventional US characteristics as well.

(2) FLLs with more fibrous tissue are potentially stiffer, and FLLs with more fatty degeneration tend to be softer. When fatty degeneration is present inside the FLLs, the local stiffness of the lesion would decrease. SWE is a useful adjunctive tool for differential diagnosis the two main types of benign hepatocellular tumors, focal nodular hyperplasia (FNH) and hepatocellular adenoma (HA), because there is a significant difference in stiffness between FNH and HA. The decrease of HA stiffness is mainly attributed to the occurrence of fatty degeneration, and the elevation in FNH stiffness is mostly attributed to the presence of that fibrous septa and central scar. (Eur J Radiol. 2015 Nov;84(11):2059-64; J Ultrasound Med. 2013 Jan;32(1):121-130). There is no direct relationship between fatty degeneration and tumor type according current evidences. More studies are needed to investigate this issue.
Liver steatosis causes attenuation of the ARFI pulse and can lead to more variability in the measurements, although theoretically it should not affect the shear wave speed (SWS). According to liver ultrasound elastography: an update to the world federation for ultrasound in medicine and biology guidelines and recommendations (Ultrasound Med Biol. 2018 Dec; 44(12): 2419-40): The impact of hepatic steatosis on liver stiffness is uncertain. Clinicians should exercise caution when interpreting liver stiffness results in patients with severe steatosis and obesity.

Minor 1. The article which showed the difference between malignant or benign liver lesions and background liver is few.

Thank you for your comment.

After systematic retrieval, we have identified 6 studies related to this issue but only 4 studies provided adequate data to evaluate the performance of SWE imaging for differentiation of malignant and benign liver lesions (Davies et al, 2011; Guo et al, 2015; Lu et al, 2015; Dong et al, 2017). Our meta-analysis performed a separate analysis to evaluate the accuracy of SWV ratio (lesion to background liver) for the differentiation of benign and malignant liver lesions, and found that the cut-off value of the SWV/elasticity in FLLs showed superior performance compared to the cut-off value of the SWV ratio, with an AUROC of 0.89 vs. 0.78 (See Line 25, Page 11).

The remaining 2 articles did not meet our inclusion criteria.


This article which recruited 197 patients included hepatocellular carcinoma (HCC), metastasis, hemangiomas, and focal nodular hyperplasia. The stiffness of liver lesions and the ratio (lesion to background liver) was calculated. The results of this study showed that HCC was significantly softer than its surrounding liver parenchyma regardless the cirrhosis status of the surrounding liver. However, the stiffness values for the other examined FLLs were comparable to their surrounding liver parenchyma. Stiffness ratio was superior to stiffness value in discrimination of HCC from metastasis. However, this article did not provide adequate data to evaluate the performance of SWE imaging for differentiation of malignant and benign liver lesions, so it was not included in our meta-analysis.

(2) European Radiology. 2013 Apr; 23(4):1138-1149
This article which recruited 108 patients with 161 FLLs included haemangioma, adenoma, focal nodular hyperplasia (FNH), focal fatty sparing, scar, hepatocellular carcinoma (HCC), cholangiocarcinoma and metastasis. The stiffness of liver lesions and the ratio (lesion to surrounding liver) was calculated. The results of this study showed that SWE imaging could be useful in differentiating FNHs and adenomas, or HCC and cholangiocarcinoma. The ratio of lesion stiffness relative to the surrounding liver was less than 1 for 17 (65%) of the HCCs. However, this article did not provide adequate data to evaluate the performance of SWE imaging for differentiation of malignant and benign liver lesions, so it was not included in our meta-analysis.

Ming-Jen Chen (Reviewer 3)

1. In the selection criteria, there is a diversity of reference standard and unclear study designs of included studies might contribute clinical heterogeneities and the authors did not take it seriously.

Thank you for providing valuable suggestions. The issue you raised is crucial and does exist in clinical setting.

(1) In real-world setting, the final diagnosis of liver lesions was obtained by histologic examination after surgical resection or sonographically guided biopsy; or clinical imaging examination and follow-up. Clinical and imaging examinations included the history of chronic hepatic disease, α-fetoprotein measurement, contrast-enhanced CT, MRI, CEUS and digital subtraction angiography (DSA). Clinical imaging diagnosis were established on the basis of characteristic patterns on more than 1 diagnostic test (eg. CT and MRI) according to the American Association for the Study of Liver Disease (AASLD) recommendation (Hepatology. 2018 Jan; 67(1):358-80) and the ACG Clinical Guideline (Am J Gastroenterol. 2014 Sep; 109(9):1328-47).

One of the inclusion criteria for our meta-analysis was as follow : used an appropriate reference standard for the diagnosis, such as cytology/histology acquired by biopsy or surgical specimens, or clinical imaging findings (CEUS or computed tomography/magnetic resonance imaging [CT/MRI]) with reference to two previous meta-analytical studies (Med Ultrason 2017, Vol. 19, no. 1, 16-22) (Eur Radiol 2012, Vol. 22, no. 12, 2298-805). In original studies, they did not compare sensitivity and specificity stratified by different reference standards, which make it hard for us to tell the difference in our meta-analysis.
In Table 1, we have clearly stated the reference standard used in each article. Indeed, the homogeneity for reference standard is low, with 3 articles (Kapoor et al, 2011; Lu et al, 2015; Dong et al, 2017) using histopathology as the reference standard; 9 articles (Cho et al, 2010; Davies et al, 2011; Shuang-Ming et al, 2011; Yu et al, 2011; Kim et al, 2013; Park et al, 2013; Guo et al, 2015; Wu et al, 2016; Grgurevic et al, 2018) using histopathology and/or CT/MRI as the reference standard; 1 article (Wen-Shuo et al, 2016) using histopathology and/or CEUS as the reference standard; 1 article (Gerber et al, 2017) using histopathology and/or CT/MRI/CEUS as the reference standard; 1 article (Zhang et al, 2014) using histopathology and/or CT/MRI/DSA as the reference standard.

(2) All of the 15 included studies were prospective in design (See line 9, page 7). The type of study design was shown in the second column of supplementary table 1.

2. The baseline adjacent liver stiffness might interfere with the SWE of the tumors, and the authors did not deal with the data seriously. Moreover, the diagnostic flow and timing are unclear.

Thanks for your careful review.

(1) We do agree that for the differential diagnosis of FLLs, the underlying background of liver fibrosis should not be overlooked. Some studies proposed that hepatocellular carcinoma (HCC) generally appeared relatively softer than the surrounding liver tissue and the stiffness of HCC decreased with increasing hepatic parenchymal fibrosis grade, whereas metastasis, hemangioma and focal nodular hyperplasia (FNH) generally appeared harder than the adjacent liver parenchyma (Phys Med Biol. 2008 Jan; 53(1):279-93; Phys Med Biol. 2012 Aug; 57(8):2273-86; World J Gastroenterol. 2013 Feb; 19(2):219-26; Med Oncol. 2015 Mar; 32(3):68). Since metastasis, hemangioma and FNH were encountered in patients without underlying chronic liver disease in most situations, the SWV (shear wave elastography) seemed to be consistently higher than those of background liver. On the contrary, HCC were always encountered in patients with underlying chronic liver disease, and exhibited a relatively uniform and soft interior when compared with the stiff and heterogeneous surrounding parenchyma. Additionally, the SWV for cholangiocarcinoma (CCC) appeared higher than those of their surrounding liver parenchyma because it is rich in fibrotic tissue instead of vessels, thus CCC is comparatively the hardest liver lesion.

Some studies evaluated the diagnostic accuracy of stiffness ratio (lesion to background liver) in the characterization of different focal liver lesions (FLLs). After systematic retrieval, we have
found four studies related to this issue and provided adequate data to evaluate the performance of SWE imaging for differentiation of malignant and benign liver lesions (Davies et al, 2011; Guo et al, 2015; Lu et al, 2015; Dong et al, 2017). Our meta-analysis performed a separate analysis to evaluate the accuracy of SWV ratio (lesion to background liver) for the differentiation of benign and malignant liver lesions, and found that the cut-off value of the SWV/elasticity in FLLs showed superior performance compared to the cut-off value of the SWV ratio, with an AUROC of 0.89 vs. 0.78 (Line 25, Page 11). In this regard, more studies are needed to explore potential relationship between the stiffness of the liver lesion and baseline adjacent liver.

(2) The results of the quality assessment of the included studies are presented in the form of picture (Fig. 2). In order to demonstrate the specific results of the specific quality assessment of each literature included, we add table 2 in the supplemental materials (line52, page7, see Supplementary Table 2 for details). The flow and timing was shown in the fifth column of supplementary table 2. We have added “The time interval between SWE imaging and the reference standard was not described in 3 studies (19, 20, 31).” in quality assessment section (Line 3, Page 8).

3. The quality review of the studies is poorly conducted with hidden information including the judgement of the degree of risk of bias. Besides, there is a high portion of the measurement failure among the included studies (from 1.2% to 26.3%), it is not appropriate to pool the summarize effects without taking in consideration of high attrition rate. It might not be able to pool the biased data and give a simple conclusion. Moreover, the final the application might be an overstatement.

Thanks for your pertinent suggestions.

(1) The quality assessment was performed in accordance with the QUADAS-2 criteria, in this article, the results of the quality assessment of the included studies are presented in the form of picture (Fig. 2). In order to demonstrate the specific results of the specific quality assessment of each literature included, we added table 2 in the supplemental materials (line52, page7, see Supplementary Table 2 for details). We added citations in the section “Quality assessment of the included studies” respectively (Line54, Page7; Line58, Page7; Line60, Page7).

(2) We do agree that the rate of measurement failure might impact our results, thus we added a subgroup analysis to investigate whether attrition rate is related to sensitivity and specificity of SWE imaging in differentiation of benign and malignant liver lesions. Our results showed that attrition rate is related to the sensitivity and specificity, we have added “The sensitivity and the specificity of high attrition rate (≥10%) was higher than low attrition rate (<10%) (82% vs. 80%, P <0.01 ; 81% vs. 78%, P <0.05).” in Line 17, Page 9. (See table 2 and
supplementary figure 1). Moreover we have added “Finally, there is a high potion of the measurement failure among the included studies (from 1.2% to 26.3%), the diversity of attrition rate may be related to the patient inclusion criteria of the original studies and the proficiency of the operator. In general, patients with FLLs in the right liver lobe and a proximal edge located < 7 cm from the body’s surface would be easily detected; and patients with successful measurement had a lower body mass index (BMI) as compared to patients in which SWE measurement failed.” in technical limitation section (Line 9, Page 12). We also made corresponding modifications in the section “Statistical analysis” (line 60, page 5), the section “Results” (line 3, page 9) (line 7, page 9), and the section “Discussion” (line 56, page 11) (Line 25, Page 12).

(3) We agree that several potential limitations existed in our meta-analysis. Currently, the use of SWE imaging for characterization of FLLs remains investigational. It is of significance for clinicians and researchers to conservatively interpret our results, and need to make comprehensive diagnosis by considering conventional ultrasound characteristics and clinical features as well.