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Dear Editors,

Dear Reviewers,

We want to thank the Editors and Reviewers for their time evaluating our Mini Review on the ability of different shear wave elastography methods to predict the presence of esophageal varices. While transient elastography is well validated for the non-invasive detection of esophageal varices, especially in combination with platelet count, there are fewer data on the diagnostic validity of ultrasound-based elastography methods and MRE.

We are delighted that our Mini Review has been accepted for publication and will gladly adapt the manuscript based on the recommendations provided by the Reviewers.

Please find below a point-by-point response to the Reviewer's comments.

Reviewer 1 – Anonymous

1. **In this review, the authors summarize current knowledge on non-invasive elastography-based methods for the detection of EV and VNT and its implications in daily clinical practice. They reviewed the literatures on vibration-controlled or transient elastography (TE), point shear-wave-elastography (pSWE), two dimensional shear wave elastography (2D-SWE) and magnetic resonance elastography (MRE). Although there are a lot of literatures on TE, there are fewer on pSWE, 2D-SWE and MRE. The figures are beautiful and comprehensive.**

We appreciate Reviewer 1's kind words.

2. **Major comment #1. The high variance of results (cut-offs, PPV and NPV values) reported in the literature on TE may be attributed to the ambiguous correlation of liver stiffness and the presence of varices. The presence of varices may be relied on the factors other than liver stiffness, such as causes of liver diseases and presence of other collateral routes. The authors should discuss these possibilities.**

We thank Reviewer #2 for raising this very important point. We have added the following part to our discussion section to clarify the ambiguous correlation of liver stiffness with the presence of varices as follows:

"Moreover, presence of esophageal varices may be relied on cofounding factors, other than liver stiffness. Most recently, patients with large or even small portosystemic shunting were found to have an increased prevelance of esophageal varices[1], and although grade of portosystemic shunting was related to liver dysfunction, varices might be missed by transient elastography in those cases. Interestingly patients with preserved liver function (defined as MELD 6-9 or Child Pugh Stage A) and portosystemic shunting showed higher HVPG values and were found with significantly more portal hypertension related complications such as bleeding or ascites than in those without shunting[1], and this emphasizes even more that especially in those patients, where LSM might be low, esophageal varices might be missed. Furthermore, in the era of successful and highly efficient treatment of hepatitis C, nowadays quite a lot of cirrhotic patients present without the initial trigger for their underlying liver disease and it has been shown that directly acting antivirals significantly lower portal pressure[2]. Concerning this matter, no study has up to date evaluated applicability of transient elastography based methods to predict esophageal varices in this cohort, and therefore it is not known whether published cut-offs work in this large subgroup of patients."

3. **Minor comment #1. Page 6, lines 2-5. The exploration volume of TE is 3cm2**

We added the exploration area/ROI of TE to the manuscript on page 6.

Reviewer 2 – Anonymous

1. **Authors reviewed articles about LSM for predicting EV or VNT. Authors concluded that combination LSM and platelet decrease is recommended to rule out VNTs and SSM is a promising modality for screening EV/VNTs. This review is well-written and informative for clinicians. LSM using shear-wave is known to be influenced by inflammation or congestion. Authors should discuss about it. Especially the effect of congestion might be considered in SSM.**

We want to thank Reviewer 2 for his/her comments. In order to clarify the effect of inflammation and congestion on liver and spleen stiffness, we have added the following part to the discussion-section of our review:

"Nevertheless there are some potential limiting factors that may hamper interpretation of results irrespective of operators experience and elastography method. It is known that in states of chronic inflammation such as viral hepatitis[3, 4],autoimmune hepatitis[5] and alcoholic steatohepatitis[6] and in cases of acute liver damage[7] liver stiffness can be false positively increased. Furthermore increased LSM has also been described due to mechanical cholestasis[8]. Lastly hepatic congestion due congestive heart failure[9, 10] and Budd-Chiari syndrome[11, 12] thus generally speaking through increased venous pressure[13] is also known to increase elastography-based LSM values[14]. In a recent review by Lemmer et al. [14] non-invasive methods to diagnose fibrosis in patients with congestive hepatopathy were discussed and conclusions were quite disillusioning since only very limited data exists. In a

study that evaluated LSM in 32 patients with valvular heart disease that underwent valve operation, LSM was found to be consistently higher than in the control group, even though none of the participants were found with evidence of underlying chronic liver disease[15]. Furthermore LSM at baseline was significantly positively correlated with NT-proBNP, and central venous pressure during the operation and negatively with left ventricular ejection fraction[15]. 90 days after surgery LSM values significantly decreased compared to 7 days after surgery (8.4 kPa vs. 6.0 kPa, p=0.026). On the other hand a study evaluating MRE-LSM and -SSM in congestive hepatopathy found promising results and reported significant correlation of LSM (r=0.74, p=0.02) and SSM (r=0.97, p=0.002) with fibrosis stage, although liver biopsy results were only available in 8 patients[16]. Therefore, given the potential pitfalls, we suggest that irrespective of the elastography method used, clinical signs of chronic liver disease, laboratory data and other co-morbidities should always be taken into account when performing LSM or SSM respectively."

Best regards,

Dr. med. univ. Rafael Paternostro

Assoc.Prof. Priv.Doz. Dr. Thomas Reiberger

Dr. med. univ. Theresa Bucsics

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