

# 学位論文の要旨

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学位論文名      Combinational Elastography for Assessment of Liver Fibrosis in Patients With Liver Injury

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## 論文内容の要旨

### INTRODUCTION

Liver fibrosis is closely associated with the prognosis of chronic liver disease, and its evaluation is important for determining the risk of development of hepatocellular carcinoma. Although an ultrasound-guided liver biopsy procedure is widely accepted as the gold standard method for liver injury diagnosis, it is invasive and can cause fatal complications such as bleeding. Therefore, it is considered important to establish an effective non-invasive method for evaluating liver fibrosis. Elastography was initially developed in 1992 as a non-invasive method for determining liver fibrosis. Two modes are currently available, shear wave imaging and strain imaging, each of which has different characteristics. Point shear wave elastography (pSWE), a type of shear wave imaging, is integrated into conventional ultrasound devices as an acoustic radiation force for quantification of imaging elastography. Another imaging method, real-time strain elastography (RTE) provides 2-D visualization of strain induced by internal heartbeat and vibration of the inferior vena cava. Combinational elastography, which utilizes the characteristics of both SWE and RTE, is currently considered to be applicable for evaluation of chronic liver disease. However, little is known regarding its utility for evaluation of liver fibrosis in NAFLD patients. The purpose of this prospective study was to investigate combinational elastography and its utility for pSWE and RTE in patients with liver injury, including NAFLD cases. Furthermore, in order to increase the accuracy of the evaluation, a liver biopsy was performed in

the same area at the same time as combinational elastography.

### **MATERIALS AND METHODDS**

From April 2017 to March 2020, consecutive patients scheduled for an ultrasound-guided liver biopsy examination as part of routine clinical care and able to undergo an ultrasound combinational elastography examination at the same time were included. Clinical data were collected at the time of the elastography examination, including age, gender, weight, height, and cause of chronic liver disease. Blood samples were taken after an overnight fast on the same day as the liver biopsy. FIB4 index and serum level of type IV collagen 7S (T4c7s) were determined as markers for assessing fibrosis. Measurement of pSWE and RTE were performed after an overnight fast using an ultrasound device (ARIETTA S70; Hitachi, Tokyo, Japan). Then, in the same area where Vs and LFI were measured, a liver biopsy was performed with a 16-gauge cutting biopsy needle. Obtained liver biopsy specimens were all examined by pathologists who were blinded to individual patient characteristics. NAFLD was diagnosed using the Matteoni classification. In the NAFLD patients, liver histology findings were examined based on the Brunt classification and NAFLD activity (NAS) scoring. In the non-NAFLD patients, fibrosis stage and hepatitis grade were assessed using the Metavir scoring system, while steatosis and ballooning grades were assessed by NAS score. The study protocol was approved by the Research Ethics Committee of Shimane University and written informed consent was obtained from all subjects.

### **RESULTS AND DISCUSSION.**

A total of 113 patients with liver injury underwent routine laboratory tests and a liver biopsy. After excluding 17 with poor quality Vs or LFI results, 96 were included in this study. In all patients, multivariate analysis results revealed that Vs was positively correlated with fibrosis stage ( $p<0.01$ ) and hepatitis grade ( $p<0.01$ ), while LFI showed a positive correlation with fibrosis stage ( $p<0.01$ ) and steatosis grade ( $p<0.05$ ). The findings clearly revealed a positive correlation of liver fibrosis stage with Vs ( $p<0.01$ ) and LFI ( $p<0.01$ ) in all of the enrolled patients, indicating the usefulness of combination elastography for evaluation of liver fibrosis in those with liver injury.

Few reports have presented results of combinational elastography performed for examinations of patients with liver injury and it remains unknown whether this method is appropriate for assessment of liver fibrosis in those with NAFLD. Thus, the present enrolled cohort was divided into the NAFLD and non-NAFLD patients, then comparative analysis between the groups was done in order to examine whether pSWE and RTE are useful for liver

fibrosis assessment. Correlations of elastography type with histological parameters in the NAFLD and non-NAFLD patients were examined. Multivariate analysis revealed that fibrosis stage was significantly correlated with Vs in both groups (NAFLD,  $p < 0.05$ ; non-NAFLD,  $p < 0.01$ ). On the other hand, fibrosis stage was correlated with LFI only in the non-NAFLD patients ( $p < 0.05$ ). Furthermore, hepatitis grade was found to be correlated with Vs in the non-NAFLD patients ( $p < 0.01$ ), while steatosis grade was correlated with LFI in the NAFLD patients ( $p < 0.05$ ). The results revealed its utility for assessment of liver fibrosis in patients with liver injury by use of Vs shown by pSWE and LFI shown by RTE results. In a comparison of NAFLD and non-NAFLD patients, there was no correlation of LFI with liver fibrosis stage in the NAFLD patients, indicating that the usefulness of RTE was relatively low in those cases. Even though the average liver fibrosis stage in the NAFLD patients enrolled in the present study was relatively low, pSWE was shown to have significant utility for assessment of liver fibrosis even in those cases. Interestingly, the distance from the body surface to the liver ( $1.8 \pm 0.5$  cm, mean  $\pm$  SD) had a correlation with Vs, suggesting that a thick subcutaneous fat deposition might influence the results of pSWE used for evaluating liver fibrosis in obese patients, including those with NAFLD. Also, since RTE visualizes strain induced by internal heartbeat and vibration of the inferior vena cava, as shown in images of the liver, it is considered that the presence of steatosis may reduce liver deformation, which might explain why RTE was found to be less useful in the present patients with NAFLD.

### **CONCLUSION**

This is the first known study to investigate the usefulness of combinational elastography for evaluating liver fibrosis in patients with NAFLD. The results revealed that combinational elastography had significant utility for examinations of the enrolled cohort, though RTE was found to be less useful as compared to pSWE for evaluation of liver fibrosis in patients with NAFLD. Additional investigations are needed to refine the statistical methods used for assessments performed with combinational elastography in patients with liver injury, including NAFLD.