A multi-parametric model for progression of metabolic dysfunction-associated steatohepatitis (MASH) in humans

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***Abstract*— Multiparametric analysis of quantitative ultrasound parameters was previously shown to improve assessment of metabolic dysfunction-associated fatty liver diseases (MAFLD). In this study, we aim to develop a multiparametric model for metabolic dysfunction-associated steatohepatitis (MASH), which contains more complex disease progression as an advanced version of MAFLD.**

We extracted quantitative ultrasound parameters, including H-scan frequency, Burr distribution λ and b, B-mode intensity, and shear wave speed (SWS). The parameters were categorized and displayed in multiparametric space. Support vector machine (SVM) was used to produce hyperplanes to differentiate MASH stages. Gaussian mixture model (GMM) was used to identify the centroids of the MASH stages. The centroids of MASH stages 0, 2, and 4 were then used to find early and late stage MASH progression vectors.

To evaluate the multiparametric model, we performed an *in vivo* human study. 39 patients were enrolled and unterwent clinical tests, such as biopsy, blood biochemistry, metabolomics test (OWLiver), and ultrasound B-mode and shear wave elastography (SWE). A clinician confirmed MASH stages based on the clinical test results (M0: no disease; M1: steatosis; M2: steatohepatitis; M3: steatohepatitis with fibrosis; M4: steatohepatitis with cirrhosis).

Complex disease progression was not well characterized by individual parameters, but the multiparametric model captured the trajectory of MASH progression. SVM classification resulted in 87.0% and 76.8% accuracy for training and testing, respectively. SVM and GMM produced a consistent trajectory in the multiparametric space. In conclusion, our multiparametric model was able to track nonlinear MASH progression trajectory accurately.

Keywords*— *MASH, Multiparametric analysis, Quantitative ultrasound, Tissue characterization, H-scan

I. Introduction

Quantitative ultrasound (QUS) approaches improve diagnostic performance over traditional B-mode imaging by enhancing the qualitative nature and morphological features from the B-mode images with quantitative information about local tissue. This has lead to the development of a variety of QUS parameters for metabolic dysfunction-associated fatty liver diseases (MAFLD) [1]. These MAFLD-associated QUS parameters have been shown to be accurate alternatives to MRI-estimated proton density fat fraction (MRI-PDFF) [2]. However, to apply QUS approaches effectively in the clinic, clinicians need to incorporate information from multiple QUS measures linked to different underlying disease properties. Multiparametric analysis is particularly attractive because it can simplify diagnostics by integrating information from multiple parameters. A multiparametric approach has previously been verified with MAFLD, yielding a single output parameter incorporating multiple input parameters, which showed higher correlation MRI-PDFF compared to all individual parameters and thus enabled improved hepatic steatosis identification [3-5]. Multiparametric models have also been applied to simple liver disease models, such as classification of normal/fibrosis/fat/inflammation [6, 7] and classification of normal/steatosis/fibrosis/tumor [8].

Metabolic dysfunction-associated steatohepatitis (MASH) is a more advanced disease stage of MAFLD and shows more complex disease progression containing a complicated mixture of inflammation, steatosis, fibrosis, and cirrhosis. Detecting this complicated progression using a single QUS parameter is challenging because the underlying disease processes map to different ultrasonic properties or a single quantitative US measure can be correlated with more than one of these processes. Thus, it is difficult to monitor progression of MASH accurately using a linear regression model. This study aims to find a MASH trajectory in multiparametric space where multiple independent quantitative US measures contribute to detecting specific MASH progression stages.

II. Methods

A. Study design

This study was approved by the Institutional Review Board at Galdakao-Usansolo Hospital (Biocruces Bizkaia Health Institute, Bilbao, Spain) and performed under the

requirements of informed consent from the enrolled patients. A total of 39 patients were enrolled at Galdakao-Usansolo, who were suspected of MAFLD. The patients underwent clinical tests and imaging. The clinical tests include blood biochemistry, and metabolomics/lipidomics test (OWLiver), while the ultrasound exams included FibroScan (measuring CAP and KPA) and GE ultrasound-guided attenuation parameter (UGAP). Biopsy was available for suspicious liver cancer patients. Ultrasound scanning was performed through B-mode imaging and shear wave elastography (SWE) with a LOGIQ E10 (GE Healthcare, Wauwatosa, WI, USA) ultrasound scanner. The radiofrequency (RF) data was saved along with the B-mode image and shear wave speed (SWS). According to the test and imaging results, a clinician confirmed MASH staging as M0: no disease; M1: steatosis; M2: steatohepatitis; M3: steatohepatitis with fibrosis; and M4: steatohepatitis with cirrhosis.

We developed a multiparametric model to identify MASH conditions, as shown in Fig. 1. The model used MASH stages and quantitative ultrasound parameters as ground truth and inputs, respectively.

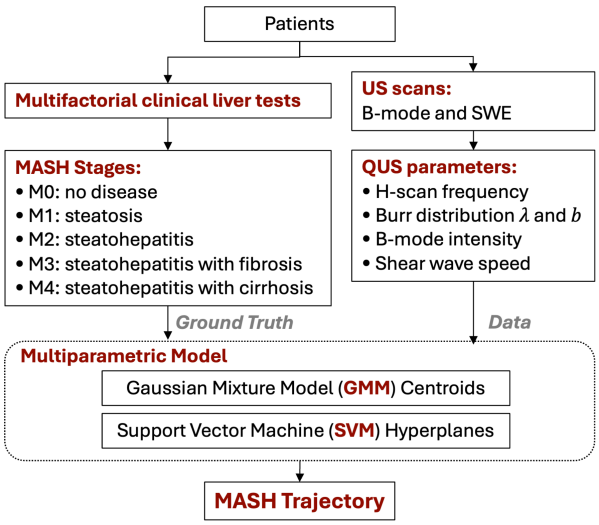

Fig. 1. Study design

B. *Quantitative Ultrasound*

1) ***H-scan frequency:*** H-scan is a matched filter analysis to characterize tissue signatures [9]. The saved RF data were attenuation-corrected to compensate for the frequency downshift due to attenuation. The attenuation-corrected RF data were convolved with 256 Gaussian functions with different peak frequencies as a matched filter bank. For each pixel, there are 256 convolution intensities from the filters. The frequency for any given pixel was chosen as the frequency that maximized the convolution intensity.

2) ***Burr distribution parameters (Burr λ and b):*** We obtained envelope data from the saved RF data. The histogram of envelope data is governed by Burr distribution with two parameters λ and b [10]. Curve fitting was utilized to fit the envelope data to a Burr distribution in order to extract the Burr parameters λ and b. λ is related to echogenicity, which is a scale factor of Burr distribution increasing with speckle echo amplitude. b is related to distribution of the histogram.

3) ***B-mode amplitude:*** We simply measured echo amplitude from envelope data, where the pixel-wise amplitudes were averaged in an region of interest (ROI).

4) ***SWS:*** GE SWE measured SWS, wehre the averaged measurement in an ROI was provided from SWE.

C. *Multiparametric Model*

The parameters are classified into 3 categories based on the measured properties. H-scan measures morphological structure changes which can be found in histology images [6, 11]. Shear wave measures stiffness of medium. B-mode intensity and Burr λ measures echogenicity. Support vector machine (SVM) was used to find hyperplanes that followed a MASH stage trajectory. To further specify the trajectory, a Gaussian mixture model (GMM) was applied to each stage to define a centroid. According to the definition of MASH stages, the main changes between M0 and M2 are from steatosis progression, and later stage changes (M2 – M4) are mainly from fibrosis progression. Thus, the model should show different directional trajectories in multiparametric space. We found the early and later stage MASH progression vectors using the GMM centroids of MASH stages 0, 2, and 4.

III. Results

Fig. 2 demonstrates that the H-scan frequency, SWS, and echo amplitude showed significant correlations with earlier (M0-2), later (M2-4), and overall (M0-4) MASH progressions, respectively. It could indicate that H-scan and SWS are the most sensitive to detect early and later stage changes from steatosis and fibrosis progression, respectively.

Fig. 3 shows the results of multiparametric analysis. The 3 axes represent frequency, SWS, and echo amplitude. Each data point indicates measures from each patient. Due to complicated combinations of multiple diseases, clusters for the stages overlapped each other, rarely showing trajectories only from the clusters. This is in contrast to prior simple steatosis models in animals, where clusters from normal to later stages showed a clear progression trajectory [11]. By connecting centroids from MASH 0 to MASH 2, we obtained

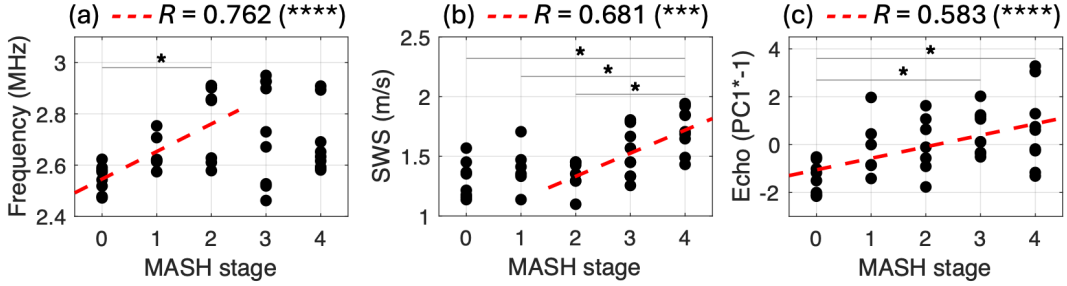

Fig. 2. Individual parameter category measures. The following notations are used for the statistics: ns (no significance) $p > 0.05$; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; and **** $p < 0.0001$.

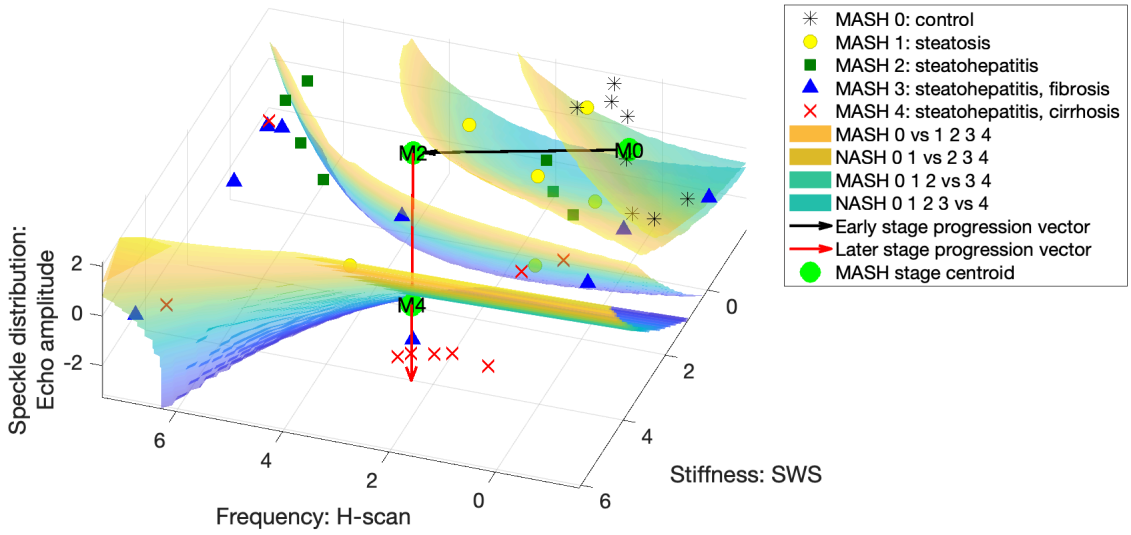

Fig. 3. MASH progression trajectory obtained from multiparametric analysis.

an early stage progression vector, while connecting centroids from MASH 2 and MASH 4 shows the late stage progression vector. The SVM hyperplanes, MASH centroids of M0/2/4, and early/later vectors showed consistent MASH progression trajectories. Although the individual measurements in Fig. 2 mostly overlapped between the stages, the multiparametric approach improved classification compared to the individual parameters: 87.0% and 76.8% accuracy for training and testing, respectively, according to leave-one-out validation. Therefore, our findings demonstrated the potential of a multiparametric US approach to enable non-invasive MASH staging in clinics.

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