Ultrasound in Med. & Biol., Vol. ■■, No. ■■, pp. ■■–■■, 2018

0301-5629/$ - see front matter

https://doi.org/10.1016/j.ultrasmedbio.2018.03.002

● *Original Contribution*

# HEPATIC STEATOSIS ASSESSMENT WITH ULTRASOUND SMALL-WINDOW ENTROPY IMAGING

Zhuhuang Zhou,[*,†] Dar-In Tai,[‡] Yung-Liang Wan,[§,¶,**] Jeng-Hwei Tseng,[§] Yi-Ru Lin,[††] Shuicai Wu,[*] Kuen-Cheh Yang,[‡‡] Yin-Yin Liao,[§§] Chih-Kuang Yeh,[¶¶] and Po-Hsiang Tsui[§,¶,**]

[*] College of Life Science and Bioengineering, Beijing University of Technology, Beijing, China; [†] Faculty of Information Technology, Beijing University of Technology, Beijing, China; [‡] Department of Gastroenterology and Hepatology, Chang Gung Memorial Hospital at Linkou, Chang Gung University, Taoyuan, Taiwan; [§] Department of Medical Imaging and Intervention, Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan; [¶] Department of Medical Imaging and Radiological Sciences, College of Medicine, Chang Gung University, Taoyuan, Taiwan; ** Medical Imaging Research Center, Institute for Radiological Research, Chang Gung University, Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan; [††] Department of Electronic and Computer Engineering, National Taiwan University of Science and Technology, Taipei, Taiwan; [‡‡] Department of Family Medicine, National Taiwan University Hospital, Beihu Branch, Taipei, Taiwan; [§§] Department of Biomedical Engineering, Hungkuang University, Taichung, Taiwan; and [¶¶] Department of Biomedical Engineering and Environmental Sciences, National Tsing Hua University, Hsinchu, Taiwan

(*Received* 25 *September* 2017; *revised* 21 *February* 2018; *in final form* 1 *March* 2018)

**Abstract—Nonalcoholic fatty liver disease is a type of hepatic steatosis that is not only associated with critical metabolic risk factors but can also result in advanced liver diseases. Ultrasound parametric imaging, which is based on statistical models, assesses fatty liver changes, using quantitative visualization of hepatic-steatosis–caused variations in the statistical properties of backscattered signals. One constraint with using statistical models in ultrasound imaging is that ultrasound data must conform to the distribution employed. Small-window entropy imaging was recently proposed as a non–model-based parametric imaging technique with physical meanings of backscattered statistics. In this study, we explored the feasibility of using small-window entropy imaging in the assessment of fatty liver disease and evaluated its performance through comparisons with parametric imaging based on the Nakagami distribution model (currently the most frequently used statistical model). Liver donors (n = 53) and patients (n = 142) were recruited to evaluate hepatic fat fractions (HFFs), using magnetic resonance spectroscopy and to evaluate the stages of fatty liver disease (normal, mild, moderate and severe), using liver biopsy with histopathology. Livers were scanned using a 3-MHz ultrasound to construct B-mode, small-window entropy and Nakagami images to correlate with HFF analyses and fatty liver stages. The diagnostic values of the imaging methods were evaluated using receiver operating characteristic curves. The results demonstrated that the entropy value obtained using small-window entropy imaging correlated well with $\log_{10}$(HFF), with a correlation coefficient $r = 0.74$, which was higher than those obtained for the B-scan and Nakagami images. Moreover, small-window entropy imaging also resulted in the highest area under the receiver operating characteristic curve (0.80 for stages equal to or more severe than mild; 0.90 for equal to or more severe than moderate; 0.89 for severe), which indicated that non–model-based entropy imaging—using the small-window technique—performs more favorably than other techniques in fatty liver assessment. (E-mail: tsuiph@mail.cgu.edu.tw)** 

*Key Words:* **Hepatic steatosis, Fatty liver, Ultrasound, Entropy imaging.**

## INTRODUCTION

Hepatitis steatosis is a condition characterized by the accumulation of fat in hepatocytes and may progress to nonalcoholic steatohepatitis, fibrosis, cirrhosis and even hepatocellular carcinoma (Raff et al. 2015). Nonalcoholic fatty liver disease (NAFLD) is the type of hepatic steatosis that most commonly leads to chronic liver disease (Loomba et al. 2012). In addition, NAFLD is related to metabolic risk factors including cardiovascular disease, obesity, diabetes mellitus and dyslipidemia (Lin et al. 2015). Therefore, early diagnosis and assessment of hepatic

Address correspondence to: Po-Hsiang Tsui, Department of Medical Imaging and Radiological Sciences, Chang Gung University, 259 Wen-Hwa 1st Road, Kwei-Shan, Tao-Yuan, 33302 Taiwan. E-mail: tsuiph@mail.cgu.edu.tw

steatosis are crucial for prompt treatment and for preventing cirrhosis.

Conventionally, liver biopsy is considered the golden standard of fatty liver assessment (Bravo et al. 2001). Liver biopsy may result in sampling errors and have complications such as bleeding (Nalbantoglu and Brunt 2014; Sumida et al. 2014). Because most patients with fatty livers do not have clinical symptoms, performing liver biopsies during routine examination is difficult and unethical. Therefore, using noninvasive imaging techniques to assess fatty livers is of clinical interests. Compared with other methods, ultrasound imaging is widely used as a first screen for liver disease. Ultrasound characterizes liver tissues by transmitting ultrasound waves to the liver; liver parenchyma can thus be modeled as a scattering medium that consists of numerous acoustic scatterers. Various scatterer arrangements or structures result in various acoustic properties, which are used to distinguish tissues. For example, acoustic attenuation (Kanayama et al. 2013; Lu et al. 1999) and the backscatter coefficient (Lu et al. 1999) have been used in liver disease assessment. Microstructure changes within liver parenchyma alter the speckle pattern and image texture of a B-mode image (Berzigotti and Castera 2013; Toyoda et al. 2009). B-mode image texture analyses have also been employed to assess the fat in the liver (Gaitini et al. 2004; Layer et al. 1991). However, texture analysis is typically based on processed grayscale images (not raw data), and the process of tissue characterization is thus system dependent (Chang et al. 2005).

A speckle pattern is formed by ultrasound radiofrequency (RF) backscattered echoes, which are typically considered random signals. Based on signal randomness, analysis of the statistical distribution of backscattered signals may provide clues that are useful in the diagnosis of liver diseases. Acoustic structure quantification (ASQ) is a technique that has recently been employed to characterize liver parenchyma by measuring the difference between backscattered statistics and the Rayleigh distribution. The ASQ technique has been used to assess liver fibrosis (Huang et al. 2015, 2016) and to determine the stage of NAFLD (Karlas et al. 2015; Kuroda et al. 2012; Lee et al. 2017; Shen et al. 2016; Son et al. 2016); however, it was argued that it is an imprecise tool (Krämer et al. 2014). One study suggested using the shape parameter of the Nakagami statistical model to more precisely quantify liver tissue echo amplitude statistics (Tsui et al. 2016a). Several non-Rayleigh statistical models have also been proposed to describe backscattered statistics for ultrasound tissue characterization. The homodyned-K distribution has been recommended as a general model of ultrasound backscattering (Destrempes and Cloutier 2010; Hruska and Oelze 2009). However, considering the analytical complexity of the homodyned-K distribution, the Nakagami distribution—with its useful approximation of backscattered statistics, simplicity and low computational complexity—is the most frequently adopted method for tissue characterization (Mamou and Oelze 2013). Recently, ultrasound Nakagami parametric imaging based on the Nakagami distribution has been systematically validated (Ma et al. 2016; Tsui and Chang 2007; Tsui et al. 2014, 2015; Yu et al. 2015). Several studies have supported the practicality of Nakagami imaging in biologic and medical applications, such as in thermal ablation monitoring (Wang et al. 2013; Zhang et al. 2014, 2017), atherosclerotic plaque characterization (Han et al. 2017) and cataract detection (Caixinha et al. 2014). Nakagami images were also correlated with fatty liver stages in animals (Ho et al. 2013) and humans (Wan et al. 2015).

The Nakagami distribution and imaging technique performs well at tissue characterization; however, a prerequisite for using statistical models describing the statistical properties of echo signals is that the ultrasound backscattered data must conform to the used distribution (Shankar 2006; Smolikova et al. 2004; Tsui et al. 2011; Zhou et al. 2014), which is not always satisfied because of the differing signal detection and processing hardware and software designs among the different ultrasound imaging systems. From this point of view, non-model–based parameters, which can be calculated using any data regardless of the distribution model, have practical application in tissue characterization. Shannon (1948) established information theory and defined entropy (not based on a particular statistical distribution) as a measure of information uncertainty. Hughes pioneered the use of Shannon entropy for analyzing ultrasound signals, indicating that entropy can quantitatively depict changes in the microstructures of scattering media (Hughes 1992, 1993, 1994; Hughes et al. 2007, 2013). In our recent study, we showed that the Shannon entropy is proportional to the Nakagami parameter (Tsui 2015) and demonstrated that ultrasound entropy imaging allows visualization of the changes in signal uncertainty induced by fatty infiltration in the liver (Tsui and Wan 2016b). In particular, small-window entropy imaging was proposed to improve the spatial resolution and suppress boundary artifacts (Tsui et al. 2017a).

In this study, we explored the feasibility of using small-window entropy imaging in ultrasound quantification of hepatic steatosis and to compare the performance of small-window entropy imaging with that of B-mode and Nakagami parametric imaging. Liver donors and patients were recruited and scanned, using ultrasound for parametric imaging and analysis. The stages of hepatic steatosis were identified using hydrogen 1 ($^1$H) proton magnetic resonance (MR) spectroscopy (*i.e.*, $^1$H-MRS) and histologic findings. The clinical results revealed that small-window entropy imaging had superior performance in fatty liver assessment compared with conventional B-mode and