Obesity Surgery (2019) 29:2585–2592
https://doi.org/10.1007/s11695-019-03889-2

ORIGINAL CONTRIBUTIONS

Measurement of Liver Stiffness with 2D-Shear Wave Elastography (2D-SWE) in Bariatric Surgery Candidates Reveals Acceptable Diagnostic Yield Compared to Liver Biopsy

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Published online: 10 May 2019

Abstract

Background Nonalcoholic fatty liver disease (NAFLD) is common among severely obese patients. Two-dimensional shear wave elastography (2D-SWE) has been validated as a noninvasive diagnostic tool for liver stiffness measurement. However, the technical feasibility and accuracy of this method in severely obese patients are still under debate.

Objective We aimed to assess the diagnostic accuracy of 2D-SWE in bariatric surgery candidates in comparison with the gold standard liver biopsy.

Methods Ninety severely obese candidates for bariatric surgery were included. Liver stiffness was measured using 2D-SWE 14 days before liver biopsy. Liver biopsy was taken on the day of surgery. The area under the receiver operating curve (AUROC) was calculated for the staging of liver fibrosis.

Results 2D-SWE was performed in 97.3% of patients successfully. Histologic stages of fibrosis (F0-F4) were detected in 34.2%, 36%, 6.3%, 3.6%, and 0.9% of patients, respectively. The AUROC for 2D-SWE was 0.77 for F1, 0.72 for F2, 0.77 for F3, and 0.70 for F4. In univariate analysis, 2D-SWE values were correlated with BMI, waist circumference, NAFLD activity score (NAS), and steatosis, whereas these components did not affect liver stiffness in multivariate analysis.

Conclusion Two-dimensional shear wave elastography of the liver can be feasible and has good accuracy in severely obese candidates for bariatric surgery. Therefore, 2D-SWE may be a good option for assessing liver fibrosis, especially in the early stages of fibrosis to lessen complications of surgery in this population. However, this method should be applied on a larger scale for late stage of fibrosis.

Keywords Bariatric surgery · Liver stiffness · Severe obesity · Elastography · 2D-SWE

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11695-019-03889-2) contains supplementary material, which is available to authorized users.

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Introduction

Severe obesity (body mass index (BMI) > 40 kg/m^2 or over 35 with a comorbidity) is associated with increased risk for a wide range of liver diseases, from simple steatosis to more serious conditions such as nonalcoholic steatohepatitis (NASH), advanced fibrosis, cirrhosis, and hepatocellular carcinoma. Consequently, with the rising incidence of severe obesity, an increase in the prevalence of nonalcoholic fatty liver disease (NAFLD) is seen [1, 2].

Accordingly, NAFLD-related fibrosis identification is an important aspect of accurate liver evaluation and associated cardiovascular risk assessment. Besides, diagnosis results in management strategies such as weight reduction in obese population which can reduce progression or improve associated risks [3, 4]. Despite the systemic and challenging nature of NAFLD, diagnostic strategies particularly in severe obesity remains demanding.

The gold standard diagnostic test for liver fibrosis is biopsy. However, factors such as high cost, invasiveness of the technique, and small sample size have rendered it less popular [5]. As a result, the current trend favors noninvasive imaging methods including magnetic resonance elastography (MRE), transient elastography (TE), and shear wave elastography (SWE) [6]. The main limitation of MRE is excess weight. Similarly, transient elastography is limited by poor mechanical beam transmission in obese patients and those with ascites [7–9].

Two-dimensional shear wave elastography (2D-SWE) is a novel technique which quantifies the stiffness of hepatic tissue in real time under the guidance of very high frame rate B-mode imaging. However, few studies have assessed the accuracy of 2D-SWE in NAFLD patients. Further research is required in order to better define cutoff values for liver stiffness using this method [10–13].

To the best of our knowledge, there have been no studies on the diagnostic accuracy of 2D-SWE for liver fibrosis in severely obese patients with a high risk for NASH and liver fibrosis. Therefore, we aimed to compare the diagnostic yield of 2D-SWE with liver biopsy in severely obese patients who were candidates for bariatric surgery. In addition, we evaluated the impact of the major components of NAFLD such as BMI, waist circumference, steatosis and the NAFLD activity score (NAS) on liver stiffness.

Material and Methods

Study Population

In this observational study, only those patients with a BMI over 40 kg/m^2 or over 35 with a comorbidity were included. Subjects were selected from the entire pool of patients presenting to the outpatient clinic at Imam Reza Hospital (the largest tertiary academic hospital in northeast Iran) between December 2016 and September 2017. All of the study participants signed informed consent. Also, any medical or psychological contraindication to bariatric surgery was considered a criterion for exclusion of subjects from the study. The criteria of inclusion consisted of no consumption of alcoholic beverages for more than 20 g/day for woman and 30 g/day for men, no chronic use of hepatotoxic medication, and negative HBs Ag and HCV antibody tests. At the end, 90 patients were included. All procedures performed in this study were in accordance with the ethical standards of the institutional and/ or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Two-Dimensional Shear Wave Elastography

Liver stiffness measurement (LSM) was performed 14 days prior to liver biopsy. To perform LSM, 2D-SWE technology was conducted using the Aixplorer ultrasound system (Supersonic Imagine, France) with a convex broadband probe (SC6-1, 1–6 MHz) in accordance with the manufacturer's instructions. Measurements were obtained via the intercostal spaces after a 6-h fasting period with the patients in the dorsal decubitus position and their right arm maximally abducted. The goal was to capture ten successful acquisitions from each patient. Successful LSM was defined as ten valid measurements obtained from each patient. The result of liver stiffness evaluation (LSE) for each patient was reported as the mean (M) of valid measurements in kilopascals (kPa). The operators were blinded to all data and patient diagnoses.

Histologic Analysis of the Liver

Liver biopsies were performed from the left lobe under direct visualization using a 16-gauge Tru-cut needle during bariatric surgery. Indications for biopsy were abnormal liver tests and either ultrasound results suggestive of liver steatosis/ dysmorphism or macroscopically abnormal liver tissue observed by the surgeon, who was blinded to the 2D-SWE reports. Specimens were fixed and embedded in paraffin wax for histological evaluation. They were stained with hematoxylin-eosin-saffron, Masson's trichrome, and picrosirius red. The one pathologist who studied the biopsy samples was also blinded to the study. NASH Clinical Research Network modified Brunt methodology and NASH Activity Score (NAS) were used for staging and grading of NASH, respectively [14]. Scores were given for hepatic fibrosis in five stages from 0 to 4, for steatosis —based on the proportion of liver involved—from 0 to 3 (0, < 5%; 1, 5–33%; 2, 34–66%; 3, > 66%), for lobular inflammation—based on the number of foci per × 20 objective—from 0 to 3 (0, none; 1, 1–2; 2, 2–4; 3, > 4), and for hepatocellular ballooning—based on the number of

ballooned hepatocytes—from 0 to 2 (0, none; 1, few; 2, many). Ultimately, NAS was determined for each patient by adding the scores above. Based on the results, patients were categorized as having no NASH (less than 3 points), borderline NASH (3–4 points), and definite NASH (five or more points). In this study, the patients from the latter two groups were considered as having NASH [14, 15].

Statistical Analysis

Demographic, clinical, and laboratory values were summarized by descriptive statistics, including mean and standard deviation for parametric values, and interquartile range (IQR) and median for nonparametrics. Spearman's rank correlation coefficient was used to determine the correlation between ordinal variables. Quantitative variables were described using frequencies and percentages. Receiver operating characteristic (ROC) curves were applied in order to evaluate the accuracy of LSMs and determine the best cutoff point. Areas under the ROC curves (AUROCs) were assessed through DeLong's method for correlated data [16]. The highest Youden index was used as the optimal cutoff value [17]. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were determined. Statistical analysis was performed using SPSS software version 16 and R. To evaluate the sensitivity and specificity of elastography, which is predicted by covariate variables such as BMI, steatosis, and NAS, we fit a model on each of the variables and elastography. Subsequently, the predicted elastography cutoffs were constructed and AUC was calculated on the elastography and fibrosis stages. The p value for all tests, if applicable, was considered significant at the level of 5%. To calculate the power of the test, we used PASS analysis for the ROC curve. Considering the results of testing AUC = 0.56 vs 0.66, our minimum sample power was 0.82. Therefore, we were able to confirm the sufficiency of our sample size with respect to the acceptable sample power.

Results

Patient Characteristics

One hundred eleven severely obese patients underwent 2D-SWE 2 weeks before bariatric surgery. In three patients, the procedure failed to produce acceptable results due to excessive subcutaneous adipose tissue. Of the remaining 108 subjects, 6 did not consent to liver biopsy, 5 had surgical limitations for biopsy, and 7 had inadequate biopsy samples. Ultimately, 90 patients had both 2D-SWE and liver biopsy (Fig. 1). Among the 90 patients, the mean age was 38.5 ± 11.1 years and the mean BMI was calculated at 45.46 ± 6.26 kg/m^2. More than half (51.9%) had metabolic

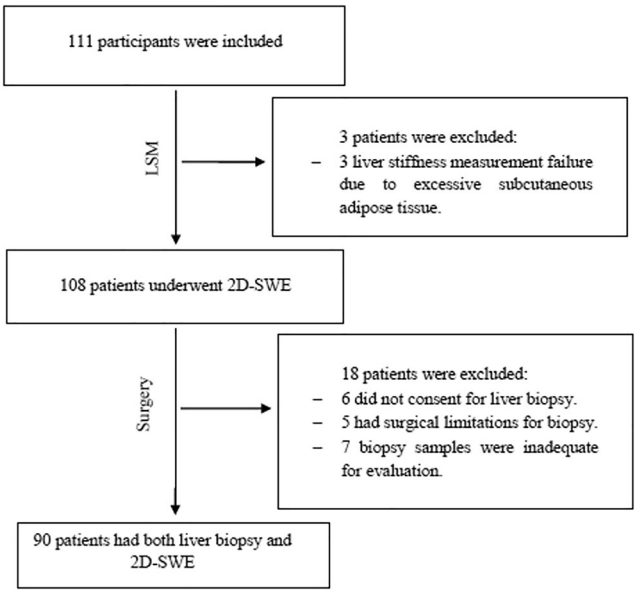


Fig. 1 Flowchart of the study

syndrome on histology; nonadvanced fibrosis (F < 2) and advanced fibrosis (F ≥ 2) were seen in 78 and 12 patients, respectively. Severe steatosis (> 66%) was detected in 8.9% and NASH (borderline and definite NASH) was found in more than half. Patients with fibrosis stage $F \geq 2$ were more likely to have type 2 diabetes ($p < 0.018$), hypertension ($p < 0.047$), higher LSM, NASH, and steatosis (Table 1).

The Relationship Between LSM and Histologic Findings

The measurements obtained via 2D-SWE for each stage of fibrosis are summarized in Table 2. On 2D-SWE, the median LSM increased with the stage of fibrosis (Fig. 2). LSMs determined by 2D-SWE were significantly higher in patients with more severe fibrosis (all p values < 0.05). Spearman's rank correlation coefficient for LSM and fibrosis stage was 0.47 ($p < 0.001$).

Diagnostic Yield of 2D-SWE in Assessing the Stages of Liver Fibrosis

The values 5.85, 6.6, and 6.75 kPa were determined using the ROC curves as optimal cutoff points. The sensitivity, specificity, PPV, and NPV for each NASH CRN-modified BRUNT methodology stage are summarized in Table 3. All specificity and sensitivity values for assessing the stages of fibrosis were ≥ 70%. The NPV for significant fibrosis reached 94%.

Table 1 Patient characteristics based on the stage of liver fibrosis

Variables	Total* ($n = 90$)	Fibrosis stage < 2 ($n = 78$)	Fibrosis stage ≥ 2 ($n = 12$)	p value
Males	18 (20)	16 (20.5)	2 (16.6)	0.753
Age (years)	38.5 ± 11.1	37.94 ± 11.2	42.08 ± 10.36	0.231
BMI (kg/m^2)	45.46 ± 6.26	44.95 ± 5.68	48.7 ± 8.72	0.170
Weight (kg)	121.34 ± 20.32	120.33 ± 20.02	127.7 ± 21.94	0.244
Waist circumference (cm)	133.04 ± 13.6	133.01 ± 13.44	133.27 ± 15.62	0.951
Height (cm)	1.62 ± 8.87	163.36 ± 8.58	160.5 ± 10.56	0.331
Type 2 DM	25 (27.8)	18 (23)	7 (58.3)	0.018
Hypertension	23 (25.6)	17 (21.7)	6 (50)	0.047
Metabolic syndrome	46 (51.1)	37 (47.4)	9 (75)	0.084
Liver stiffness measurement (kPa)	6.1 ± 1.25	5.93 ± 1.1	7.18 ± 1.6	0.001
Fibrosis stage				0.001
0 = No fibrosis	38 (42.2)	38 (48.7)	0	
1 = Zone 3 perivenular or pericellular fibrosis	40 (44.4)	40 (51.3)	0	
2 = Stage 1 plus portal fibrosis	7 (7.77)	0	7 (58.3)	
3 = Bridging fibrosis, focal or extensive	4 (4.44)	0	4 (33.3)	
4 = Residual pericellular fibrosis	1 (1.11)	0	1 (8.3)	
NASH status				0.001
No NASH (0–2)	39 (43.3)	38 (48.7)	1 (8.33)	
Borderline [3, 4]	21 (23.3)	20 (25.6)	1 (8.33)	
Definite NASH [5–8]	30 (33.3)	20 (25.6)	10 (83.33)	
Steatosis status				0.001
S0 = <5%	39 (43.3)	38 (48.7)	1 (8.33)	
S1 = 5–33%	31 (34.4)	27 (34.6)	3 (25)	
S2 = 34–66%	12 (13.3)	9 (11.5)	4 (33.3)	
S3 = > 66%	8 (8.9)	4 (5.12)	4 (33.3)	

BMI body mass index, *DM* diabetes mellitus, *NASH* nonalcoholic steatohepatitis

*Patients who had both liver biopsy and liver stiffness measurement; results are expressed as mean ± standard deviation or number (percentage)

Concordance Rates of 2D-SWE Determined LSMs Compared to Those of the Modified BRUNT Methodology

Table 4 summarizes the concordance rates of the LSMs determined with 2D-SWE compared to the NASH CRN modified BRUNT methodology. Fifty-eight (64.4%) subjects were accurately classified using 2D-SWE. For patients classified in the 0–1 stages of fibrosis, the correctly classified percentage was more than 90 %. However, the percentage of correctly classified patients in F2 and F3 stages was lower (concordance rates < 50%).

Confounding Factors of Liver Stiffness in Patients with NAFLD

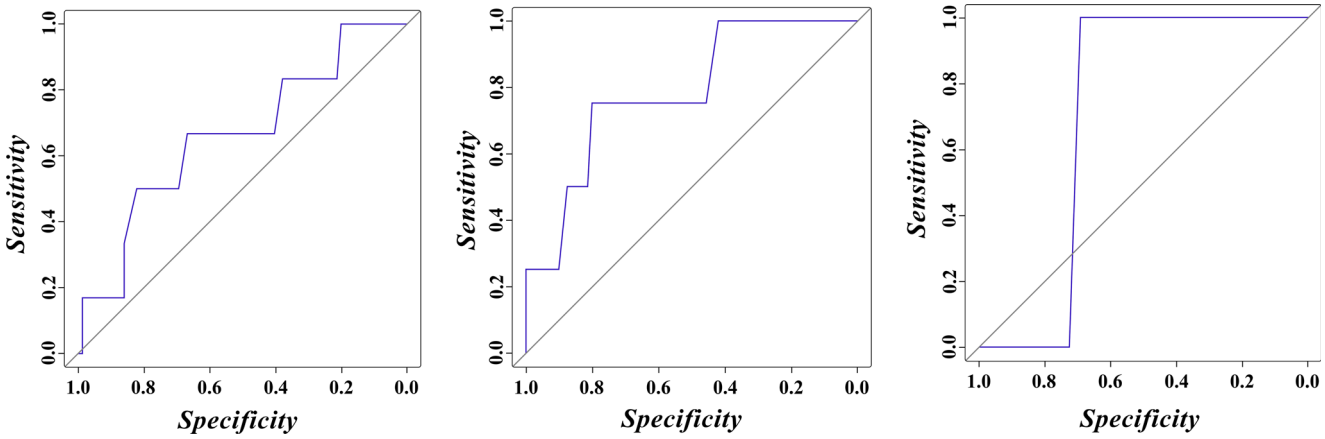
Applying univariate analysis, we calculated the correlation coefficient values for liver stiffness and multiple factors including the stage of fibrosis, gender, BMI, waist circumference, steatosis, NAFLD activity score, age, DM, and HTN

Table 2 Two-dimensional shear wave elastography values according to fibrosis stage (NASH CRN modified Brunt methodology)

Variable	F0	F1	F2	F3	F4	CC*
2D-SWE	5.5 (± 1.4)	6.35 (± 1.52)	7 (± 1.6)	7.25 (± 4.27)	6.8	0.47**

2D-SWE two-dimensional shear wave elastography, *NASH* nonalcoholic steatohepatitis, *CRN* clinical research network, *IQR* interquartile range, *2D-SWE* two-dimensional shear wave elastography, *CC* correlation coefficient. Data are expressed as the median ± (IQR)

*Nonparametric Spearman's correlation coefficient was used; **p value < 0.001)



a Significant fibrosis (F2 or greater) b Severe fibrosis (F3or greater) c Cirrhosis (F4)

Fig. 2 Receiver operating characteristic (ROC) curves for 2D-SWE: significant fibrosis (**a**), severe fibrosis (**b**), and cirrhosis (**c**). Spearman's correlation coefficient for the LSMs and stages of fibrosis was 0.47 ($p < 0.001$)

(Table 5). Based on univariate linear regression, liver steatosis, BMI, NAFLD activity score, and waist circumference can affect 2D-SWE results. In order to reveal the effect of these factors on the accuracy of 2D-SWE independently, we applied a regression model for each factor. Increasing BMI and waist circumference reduced diagnostic accuracy of 2D-SWE (Table 5 and Supplementary Table 5A and 5B). On the other hand, liver steatosis and NAFLD activity score showed enhanced diagnostic accuracy for 2D-SWE in the early stages of fibrosis (F1–F2). However, in severe fibrosis (F3–F4), the accuracy was diminished (Table 5, Supplementary Table 5C and 5D). Finally, multiple linear regression revealed liver fibrosis as the only factor associated with LSM (Table 5).

Discussion

In severely obese patients, the prevalence of nonalcoholic fatty liver disease (NAFLD) is 90% higher than that of the normal population [1]. Therefore, early assessment of liver fibrosis is very important in patients with severe obesity. While many of the common noninvasive diagnostic techniques have been widely tested in general populations with NAFLD, fewer studies have focused on this high-risk obese population [13]. Obesity can result in imaging failure in TE in up to one third of cases. Similarly, in MR elastography, excess weight is a major limitation in device performance. While two-dimensional shear wave elastography may be an alternative to other diagnostic techniques, it is not yet established whether the result are more reliable [18–21]. We evaluated the feasibility and diagnostic accuracy of 2D-SWE for detecting NAFLD in an exclusively obese population.

Indeed, low success rates are considered a major obstacle when performing LSM in NAFLD obese patients. There are few studies covering the knowledge gap about applicability of these tests in the obese. Successful readings may result from optimizing probe position using B-mode ultrasound imaging with 2D-SWE [11]. 2D-SWE success rate in our patients with a mean BMI of 45.35 ± 6.16 kg/m^2 was 97.3% (108 of 111 patients). However, previous studies on other imaging technique have reported a failure rate between 3 and 13% in LSM [6, 18, 19].

Regarding diagnostic accuracy of 2D-SWE for fibrosis grading in severely obese patients, previous data have achieved good diagnostic performance with AUROC values ranging from 0.86 to 0.94 in different etiologies of liver diseases and regardless of the patients' BMI [10, 20, 21]. Studies focusing on NAFLD demonstrated AUROCs of 86%, 89%, and 88% for ≥ F2, ≥ F3

Table 3 Diagnostic performance of 2D-SWE vs fibrosis stage (NASH CRN modified Brunt methodology)

Diagnostic performance	Fibrosis stage	AUC (95%CI)	Best accuracy	Cutoff	Sens	Spec	PPV	NPV
2D-SWE	F ≥ 1	0.77 (0.66–0.87)	72%	5.85	71%	74%	78%	65%
	F ≥ 2	0.72 (0.56–0.89)	71%	6.6	72%	70%	26%	94%
	F ≥ 3	0.77 (0.58–0.96)	75%	6.75	80%	71%	14%	98%
	F = 4	0.70	70%	6.75	100%	70%	3%	100%

2D-SWE two-dimensional shear wave elastography, *NASH* nonalcoholic steatohepatitis, *CRN* clinical research network, *AUC* area under the curve, *Sens* sensitivity, *Spec* specificity, *PPV* positive predictive value, *NPV* negative predictive value

Table 4 Concordance rates of LSMs determined with 2D-SWE compared to the NASH CRN modified BRUNT methodology

Fibrosis stage (NASH CRN modified BRUNT methodology)					
Liver stiffness measurement	F0–F1	F2	F3	F4	Concordance rates (%)
F0–F1, ≤ 6.6 kPa	53	2	1	0	94.6
F2, > 6.6 to ≤ 6.75 kPa	9	2	0	1	16.6
F3–F4, > 6.75	13	3	3	0	15.7
Cumulative concordance rates					42.3

2D-SWE two-dimensional shear wave elastography, *NASH* nonalcoholic steatohepatitis, *CRN* clinical research network;

and F4, respectively [6, 10]. However, we found AUROC of 0.77, 0.72, 0.77, and 0.70 for successive fibrosis stages. This decline in the AUROC may be the result of severe obesity in our study population, since it has been previously shown that thick adipose tissue can interfere with the transmission of ultrasound waves and mechanical beam [22]. Accordingly, the TE AUROC values in studies with overweight/obese patients were in line with those of ours [23, 24].

Moreover, it has been established that optimization of cutoff values would be able to differentiate between liver diseases while using 2D-SWE modality. Recently, a meta-analysis has been published reporting 2D-SWE cutoff values for NAFLD subjects to be in a range from 7.15 to 11 kPa. In this study, based on the analysis of the ROC curves, we obtained these cutoffs for mild (F ≥ 1), significant (F ≥ 2), and severe fibrosis (F ≥ 3) to be 5.85, 6.6, and 6.75 kPa, respectively. While these values may be in a different range from previous reports, it should be noted here that extensive application of such cutoff limits in practice necessitates future large-scale multiethnic studies to optimize these values.

Most of the above discussed imaging techniques have been revealed to have good accuracy at the extremes of fibrosis grades but failed to maintain this level of perform in early and intermediate stages [25]. The diagnostic accuracy of 2D-SWE in different stages of fibrosis has been reported differentially. Some have found it to be more accurate in advanced fibrosis [26–28], while others showed a privilege for this method in mild and intermediate stages [29–31]. We were able to demonstrate the best concordance rate in F0–F1 for 2D-SWE and biopsy, which was almost 95%, highlighting the good diagnostic accuracy of 2D-SWE in early stages. Of note, the clinical significance of this finding would be providing a wider window opportunity for treatment. Also, the lower accuracy in more advanced stages may be reflective of a too low sample size. Therefore, further studies are required to evaluate the accuracy of this method in advanced stages of liver fibrosis.

Table 5 Variables affecting the stiffness of liver tissue

Variable	CC (ρ)	*p* value	Multiple regression (*p* value)
Age	0.02	0.701	0.7
BMI	0.27	0.004	0.7
DM	0.13	0.155	0.9
HTN	− 0.05	0.523	0.3
Metabolic syndrome	0.07	0.411	0.7
Steatosis	0.43	< 0.0001	0.5
NAS	0.46	< 0.0001	0.2
Fibrosis stage	0.49	< 0.0001	< 0.0001
Waist circumference	0.23	0.017	0.4

BMI body mass index, *DM* diabetes mellitus, *HTN* hypertension, *NAS* nonalcoholic fatty liver disease activity score, *CC* correlation coefficient

Spearman's correlation coefficient (ρ) and regression were applied to conduct univariate and multivariate analyses, respectively

Notably, some conditions interfere with liver stiffness measurement by 2D-SWE and TE [6]; however, published data are conflicting with this regard [28, 32–35]. Based on univariate analysis, our study revealed an association between 2D-SWE and factors such as steatosis, NAS, BMI, and waist circumference. Higher BMI and waist circumference decreased the accuracy of 2D-SWE, while liver steatosis and NAS enhanced it in the early stages of fibrosis. Therefore, the accuracy of 2D-SWE will probably be increased if different cutoff values are defined for each grade of NAS and steatosis [24]. Using multivariate analysis, we observed that steatosis and inflammation (indirectly assessed via the NAS score) did not have an effect on LSM result significantly. Interestingly, multivariate analysis revealed LSM to be mainly correlated with the fibrosis stage. This shows that elastography results may not be affected by these confounding factors. These findings are also in line with those of Cassinotto et al. [6]

Specifically, in this study, we focused on a subtype of patients which previously had shown limitations for imaging techniques other than 2D-SWE [7, 24]. In addition, we were able to take large surgical liver biopsies (> 50 mm) instead of small percutaneous samples obtained through the intercostal spaces (< 25 mm). According to the literature, the latter has a 25 % chance of misclassification and a higher rate for complications [36, 37].

It is worth noting that there was a nonuniform distribution of patients across different stages of fibrosis, with more than 95% having fibrosis stages F0–F2. This may be due to the inherent selection bias resulting from recruitment of

consecutive candidates of bariatric surgery rather than a pre-screened cohort from a liver disease setting. This trend was also observed in previous studies with similar recruiting policies [38–41]. Furthermore, bariatric surgery candidates are usually younger than the average of the population and may be more health conscious, thus creating an inevitable selection bias.

Conclusion

Based on liver biopsy, over half of our severely obese patients had NASH and about a quarter had developed advanced fibrosis. Correlation between findings of 2D-SWE and histology was promising, especially in the early stages. However, studies on larger sample sizes are warranted to confirm these results before that 2D-SWE can be used more widely and reliably. Therefore, the application of 2D-SWE could be useful for diagnosis and follow-up of NAFLD in severely obese patients as well as for their peri-surgical risk assessment.

Acknowledgments The results described in this paper formed part of a thesis submitted by the first author for a Ph.D. degree in Nutritional Sciences. The study was supported by the Vice Chancellor for Research at Mashhad University of Medical Sciences.

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Analysis and interpretation Jamialahmadi T, Jabbari Nooghabi M, Doaie S
Data collection Jamialahmadi T, Jangjoo A, Nematy M, Rajabzadeh F, Ghaffarzadegan K, Javid Z
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Final approval Jamialahmadi T, Nematy M, Goshayeshi L, Jangjoo A, Jabbari Nooghabi M, Rezvani R,
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Obtained funding Nematy M
Overall responsibility Rajabzadeh F

Compliance with Ethical Standards

Source of Support This study was supported by the Vice Chancellor for Research of Mashhad University of Medical Sciences (grant number 951586).

Conflict of Interest The authors declare that they have no conflicts of interest.

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