Diagnostic Performance of Two-dimensional Shear Wave Elastography in Advanced Liver Fibrosis: A Prospective Pathology-based Study

Yao-Kuang Huang
Division of Gastroenterology & Hepatology, Department of Internal Medicine, Taichung Veterans General Hospital

Ren-Ching Wang
Department of Pathology, Taichung Veterans General Hospital,

Sheng-Shun Yang
Division of Gastroenterology & Hepatology, Department of Internal Medicine, Taichung Veterans General Hospital

Shou-Wu Lee
Division of Gastroenterology & Hepatology, Department of Internal Medicine, Taichung Veterans General Hospital

Hsin-Ju Tsai
Division of Gastroenterology & Hepatology, Department of Internal Medicine, Taichung Veterans General Hospital

Teng-Yu Lee (gihepatology@gmail.com)
Division of Gastroenterology & Hepatology, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan

---

Research Article

Keywords: diagnostic performance, two-dimensional Shear-wave Elastography (2D-SWE), Area Under the ROC (AUROC)

Posted Date: December 15th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-122956/v1

Abstract

Studies for evaluating the diagnostic performance of two-dimensional Shear-wave Elastography (2D-SWE) in a patient cohort including various liver disorders, remain limited. We aimed to evaluate the validity of 2D-SWE in the diagnosis of advanced liver fibrosis amongst patients with various liver disorders. In this pathology-based study, patients who underwent a liver biopsy for various benign liver diseases were prospectively recruited during the period between February, 2017 and September, 2020. Data of 2D-SWE, Fibrosis-4 Index (FIB-4), and Aspartate Aminotransferase to Platelet Ratio Index (APRI) were simultaneously collected. The cut-off values for predicting advanced fibrosis, i.e. Metavir fibrosis stage ≥ F3, were determined using Receiver Operating Characteristic (ROC) analysis. The diagnostic performance was evaluated and then compared by Area Under the ROC (AUROC). In total, 95 patients were recruited for study analysis. The diagnostic performance of 2D-SWE was significantly superior to that of both FIB-4 (AUROC: 0.88, 95% confidence interval [CI]: 0.80-0.94; vs 0.72, 95%CI: 0.62-0.81; p=0.001) and APRI (AUROC: 0.88, 95%CI: 80-0.94; vs 0.76, 95%CI: 0.66-0.84; p=0.007). With an optimal cutoff value of 9.3 kPa, the sensitivity and specificity were 90.91% and 76.47%, respectively. In subgroup analysis, the AUROC of 2D-SWE was the highest when compared to that of FIB-4 and APRI in patients with chronic hepatitis B, chronic hepatitis C, fatty liver, and concurrent hepatitis. 2D-SWE can therefore be a valid non-invasive method in the detection of advanced liver fibrosis in various liver diseases.

Introduction

Chronic hepatitis has been estimated to affect at least 325 million people worldwide[1], and can eventually result in advanced fibrosis, liver malignancies, and death. Accurate evaluation regarding the degree of liver fibrosis is therefore essential in the diagnosis and treatment of chronic liver diseases[2, 3]. Early diagnosis of advanced liver fibrosis can be life-saving in patients with chronic liver diseases[4, 5]. However, although a liver biopsy remains the gold standard in the evaluation of liver fibrosis, it is limited by its invasive nature and the possibility of severe complications and/or discomfort[6]. Thus, an effective non-invasive test is highly helpful in clinical practices. However, the diagnostic performance of most commonly used non-invasive tests, such as Aspartate Aminotransferase (AST) to Platelet Ratio Index (APRI) or the Fibrosis-4 Index (FIB-4), are not satisfactory and should be improved.

Although several novel non-invasive tests have been developed in recent years; for example, using serum biomarkers which are directly related to the molecular pathogenesis of liver fibrosis; they are usually only available in certain health care units[7]. In addition, in recent years several ultrasound-based methods have been used for measuring liver stiffness, including Transient Elastography (TE), Acoustic Radiation Force Impulse (ARFI), and two-dimensional Shear Wave Elastography (2D-SWE); however, some disadvantages in each may limit their applications in clinical practice or research. For example, TE, i.e. Fibroscan®, has been proven to offer strong diagnostic performance with an Area Under the Receiver Operating characteristic Curve (AUROC) of 0.8 to 0.9 for the diagnosis of advanced fibrosis in patients with chronic hepatitis C[8]; however, TE requires separate equipment in addition to the sonography probe. Moreover, the

TE measurement may be affected by non-parenchymal structures, such as blood vessels, ligaments, or tumor lesions[9]. ARFI and 2D-SWE are both ultrasound-based methods which could be incorporated into a conventional ultrasound device without additional equipment. However, ARFI has been proved to have lower diagnostic performance in a liver with steatosis[10].

2D-SWE is a novel technique for non-invasive evaluation of liver fibrosis with several advantages. For example, multiple measurements can be performed over a relatively larger field of view, compared to ARFI[11]. In addition, operators can choose a proper area by avoiding non-parenchymal structures[12], and by checking the shear-wave propagation displayed by parallel lines in the selected region. This way, the operator can ensure a higher reliability of the measurement[13]. Although 2D-SWE has also been proved to have a good diagnostic performance for liver diseases[14,15,16], only a few studies have been validated by the reference standard of liver fibrosis, i.e. liver pathology. In addition, data from 2D-SWE applied in a patient cohort with various liver disorders remains limited. The aim of this study was to evaluate the diagnostic performance of 2D-SWE amongst patients with various disorders.

Method

Study design and patient selection

In this prospective trans-sectional study, patients who were scheduled to receive a liver biopsy for the evaluation of benign liver diseases, were recruited in Taichung Veterans General Hospital, a tertiary medical center in central Taiwan, during the period between February, 2017 and February, 2020. Patients with malignant liver tumors were excluded. All patients received a liver biopsy after a 2D-SWE study had been performed on the same day. Liver function-related blood tests, such as bilirubin, albumin, AST, Alanine Aminotransferases (ALT), complete blood count, and Prothrombin Time (PT), were collected within 2 weeks prior to the liver biopsy. This study has been approved by the Institutional Review Board of Taichung Veterans General Hospital (IRB No. CE18315A). All methods of this study were performed in accordance with the Declaration of Helsinki and the relevant guidelines and regulations. The informed consent has been obtained from all the study participants.

Liver biopsy and histopathology

After a 2D-SWE examination, real-time sonography-guided percutaneous liver biopsies were performed at the same site of the 2D-SWE examination, using a 16-gauge core needle. At least one liver tissue fragment at a length ≥ 15 mm was obtained through the right intercostal space. All the liver specimens were reviewed by two independent pathologists, and a consensus for liver fibrosis staging was made by the two pathologists if the fibrosis stages were different. The degree of liver fibrosis was classified according to the Metavir system[17].

2D-shear Wave Elastography

The 2D-SWE measurements were performed using the Aplio 500 Platinum Series ultrasound machine and 6C1 (PVT-375BT) curved array ultrasound transducer (Canon Medical Systems Corporation). All patients fasted for at least 6 hours prior to the examination. The examinations were performed using the right intercostal approach, with patients holding their breath during expiration. Under the view of a sonography, a 2 × 4 cm acquisition box was selected for SWE detection, with a 10-mm diameter circle used to select the Region Of Interest (ROI). The parallel propagation of shear wave contours was observed in the ROIs. The shear wave conduction speed was measured in the selected region and expressed in meters per second (m/s). The Liver Stiffness Measurement (LSM), also known as the elastic modulus, was calculated by the program incorporated in the sonography machine, which was expressed in kilopascal (kPa)[18]. At least 10 measurements were obtained for each patient, and the median of the measurements was calculated[19].

Subgroup analysis

We further analyzed the diagnostic performance of 2D-SWE in subgroups of patients with chronic hepatitis B, chronic hepatitis C, fatty liver disease, and concurrent ALT elevation (defined as ALT > 35 U/L in male patients and ALT > 25 U/L in female patients)[20]. Fatty liver disease was defined as steatosis of more than 5% hepatocytes in the histopathology specimen[21].

Statistical analysis

We presented continuous variables as median values (25–75% Interquartile Range [IQR]) and categorical variables as numbers (percentages). FIB-4 and APRI were calculated according to the formula presented in previous literature[22, 23]. The upper normal limit of AST for calculating APRI was 35 U/L according to the reference range of our hospital. The diagnostic performances of FIB-4, APRI and 2D-SWE were determined according to the results of liver pathology. Metavir fibrosis stage F3 or above was defined as advanced fibrosis. Data were expressed with a Receiver Operating Characteristic (ROC) curve and AUROC. Optimal cutoff values were calculated by the measurement of the highest Youden index. Paired comparison of the AUROC of each method to predict advanced liver fibrosis was performed using the Kruskall-Wallis test. Statistical analysis was performed using SPSS software version 22.0.

Results

Study subjects

As shown in Table 1, 95 patients were recruited in total. Most of the patients were middle-aged, with a median age of 59 years. In the etiology of liver diseases, 53% patients had chronic Hepatitis B Virus (HBV) infection, 38% patients had chronic Hepatitis C Virus (HCV) infection, and 3.2% patients had HBV and HCV coinfection. Approximately 30% of the patients had diabetes mellitus, hypertension, or dyslipidemia. The median levels of AST and ALT in the blood were 47 U/L and 53 U/L, respectively. Around 45% of patients suffered from ALT elevation. The median value of calculated FIB-4 and APRI was

2.38 and 0.91, respectively. In the liver pathology findings, 43.2% of the patients experienced fatty liver disease, with 46.3% patients belonging to advanced fibrosis (Metavir fibrosis F3 or F4).

Table 1
The characteristics of the study subjects

Patient characteristics	**n = 95**
Age, years	59.0 (48.0–67.0)
Gender	
Female	41 (43.2%)
Male	54 (56.8%)
Underlying comorbidities, n (%)	
Chronic HBV infection	50 (52.6%)
Chronic HCV infection	36 (37.9%)
HBV HCV coinfection	3 (3.2%)
Diabetes mellitus	27 (28.4%)
Hypertension	24 (25.3%)
Dyslipidemia	31(32.6%)
Blood test data	
AST, U/L	47.0 (32.0–78.0)
ALT, U/L	53.0 (34.0-116.0)
ALT elevation, n (%)	43 (45.3%)
Bilirubin, mg/dL	0.7 (0.5–0.9)
Platelet, (10^3/mm^3)	149.0 (116.0-208.0)
FIB-4	2.38 (1.39–3.81)
APRI	0.91 (0.52–1.47)
Pathology findings	
Fatty liver disease, n(%)	41 (43.2%)
Metavir fibrosis stage, n (%)	
F0	17 (17.9%)
F1	15 (15.8%)

Note. Continuous data presented as median (IQR); **HBV**: Hepatitis B virus; **HCV**: Hepatitis C virus; **AST**: Aspartate Transaminase; **ALT**: Alanine Transaminase; **FIB-4**: Fibrosis-4 Index; **APRI**: Aspartate Aminotransferase to Platelet Ratio Index; ALT elevation: ALT > 35 and > 25 U/L in male and female patients, respectively

Patient characteristics	n = 95
F2	19 (20.0%)
F3	23 (24.2%)
F4	21 (22.1%)

Note. Continuous data presented as median (IQR); **HBV**: Hepatitis B virus; **HCV**: Hepatitis C virus; **AST**: Aspartate Transaminase; **ALT**: Alanine Transaminase; **FIB-4**: Fibrosis-4 Index; **APRI**: Aspartate Aminotransferase to Platelet Ratio Index; ALT elevation: ALT > 35 and > 25 U/L in male and female patients, respectively

The measurements of 2D-SWE

Figure 1 demonstrates the box-plot diagram for 2D-SWE measurements taken for patients in each fibrosis stage. The median values of liver stiffness measurement from F0 to F4 were 7.0 (25–75% IQR: 6.0-8.5), 7.4 (25–75% IQR: 6.6-9.0), 9.0 (25–75% IQR: 8.0-11.1), 12.1 (25–75% IQR: 10.0-16.4), and 14.5 (25–75% IQR: 12.6–17.1) kPa, respectively. The values in the various fibrosis stages were significantly different ($p < 0.001$).

The diagnostic performance of 2D-SWE

Table 2 demonstrates the diagnostic performance of 2D-SWE, APRI, and FIB-4. With a cutoff value of 9.3 kPa, the AUROC of 2D-SWE (0.88, 95% confidence interval [CI]: 0.80–0.94) was significantly better than that of APRI (0.76, 95% CI: 0.66–0.84; $p = 0.007$) and FIB-4 (0.72, 95% CI: 0.62–0.81; $p = 0.001$) (Fig. 2).

Table 2
The diagnostic performance of various tests in the whole patient cohort

	Cutoff	AUROC	(95% CI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
2D-SWE	9.3	0.88	(0.80–0.94)	90.91	76.47	76.92	90.70
APRI	0.58	0.76	(0.66–0.84)	93.18	52.94	63.08	90.00
FIB-4	2.58	0.72	(0.62–0.81)	63.64	74.51	66.67	69.81

Note. 2D-SWE: Two-Dimensional Shear Wave Elastography; **FIB-4**: Fibrosis-4 Index

APRI: Aspartate Aminotransferase to Platelet Ratio Index; **CI**: Confidence Interval; **AUROC**: Area Under the Receiver Operating characteristic Curve; **PPV**: Positive Predictive Value; **NPV**: Negative Predictive Value

Sensitivity analysis for the patient subgroups

Table 3 shows the diagnostic performance of 2D-SWE, APRI, and FIB-4 in patients with chronic hepatitis B. Although the statistical significance was not reached due to the small sample size in this subgroup, the AUROC of 2D-SWE (0.90, 95% CI: 0.78–0.95) remained the highest when compared to that of APRI (0.86, 95% CI: 0.73–0.94; $p = 0.438$) and FIB-4 (0.78, 95% CI: 0.64–0.89; $p = 0.092$) with a cut off value of 9.3 kPa. The sensitivity and specificity of 2D-SWE were of 81.21% and 89.29%, respectively.

Table 3
The diagnostic performance of various tests in patients with chronic hepatitis B

	Cutoff	AUROC	(95% CI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
2D-SWE	9.3	0.90	(0.78–0.95)	81.82	89.29	85.71	86.21
APRI	0.62	0.86	(0.73–0.94)	95.45	78.57	77.78	95.65
FIB-4	2.22	0.78	(0.64–0.89)	72.73	78.57	72.73	78.57
Note. 2D-SWE: Two-Dimensional Shear Wave Elastography; **FIB-4**: Fibrosis-4 Index							
APRI: Aspartate Aminotransferase to Platelet Ratio Index; **CI**: Confidence Interval; **AUROC**: Area Under the Receiver Operating characteristic Curve; **PPV**: Positive Predictive Value; **NPV**: Negative Predictive Value							

Table 4 shows the diagnostic performance of 2D-SWE, APRI, and FIB-4 in patients with chronic hepatitis C. Although the statistical significance was not reached due to the small sample size in this subgroup, the AUROC of 2D-SWE (0.81, 95% CI: 0.64–0.92) remained the highest when compared to that of APRI (0.64, 95% CI: 0.47–0.80; $p = 0.130$) and FIB-4 (0.66, 95% CI: 0.48–0.81; $p = 0.158$) with a cut off value of 11.1 kPa. The sensitivity and specificity of 2D-SWE were 85.00% and 75.00%, respectively.

Table 4
The diagnostic performance of various tests in patients with chronic hepatitis C

	Cutoff	AUROC	(95% CI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
2D-SWE	11.1	0.81	(0.64–0.92)	80.95	80.00	85.00	75.00
APRI	1.40	0.64	(0.47–0.80)	47.62	80.00	76.92	52.17
FIB-4	3.24	0.66	(0.48–0.81)	61.90	73.33	76.47	57.89
Note. 2D-SWE: Two-Dimensional Shear Wave Elastography; **FIB-4**: Fibrosis-4 Index							
APRI: Aspartate Aminotransferase to Platelet Ratio Index; **CI**: Confidence Interval; **AUROC**: Area Under the Receiver Operating characteristic Curve; **PPV**: Positive Predictive Value; **NPV**: Negative Predictive Value							

Table 5 demonstrates the diagnostic performance of 2D-SWE, APRI, and FIB-4 in patients with fatty liver disease. With a cutoff value of 10.1 kPa, the AUROC of 2D-SWE (0.92, 95% CI: 0.80–0.98) was better than that of APRI (0.79, 95% CI: 0.64–0.90; $p = 0.116$), although not reaching statistical significance due to a relatively small sample size. The AUROC of 2D-SWE was significantly better than FIB-4 (0.76, 95% CI: 0.61–0.88; $p = 0.048$). The sensitivity and specificity of 2D-SWE were 89.47% and 86.47%, respectively.

Table 5
The diagnostic performance of various tests in patients with fatty liver disease

	Cutoff	AUROC	(95% CI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
2D-SWE	10.1	0.92	(0.80–0.98)	85.00	90.48	89.47	86.36
APRI	0.58	0.79	(0.64–0.90)	95.00	57.14	67.86	92.31
FIB-4	2.58	0.76	(0.61–0.88)	60.00	85.71	75.00	68.00

Note. 2D-SWE: Two-Dimensional Shear Wave Elastography; **FIB-4**: Fibrosis-4 Index

APRI: Aspartate Aminotransferase to Platelet Ratio Index; **CI**: Confidence Interval; **AUROC**: Area Under the Receiver Operating characteristic Curve; **PPV**: Positive Predictive Value; **NPV**: Negative Predictive Value

Table 6 demonstrates the diagnostic performance of 2D-SWE, APRI, and FIB-4 in patients with abnormal liver function. With a cutoff value of 10.9 kPa, the AUROC of 2D-SWE (0.87, 95% CI: 0.77–0.93) was significantly better than that of APRI (0.69, 95% CI: 0.57–0.79; $p = 0.004$) or FIB-4 (0.71, 95% CI: 0.59–0.81; $p = 0.009$). The sensitivity and specificity of 2D-SWE were 90.91% and 76.47%, respectively.

Table 6
The diagnostic performance of various tests in patients with abnormal liver function

	Cutoff	AUROC	(95% CI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
2D-SWE	10.9	0.87	(0.77–0.93)	80.00	83.33	84.21	78.95
APRI	0.58	0.69	(0.57–0.79)	95.00	38.89	63.33	87.50
FIB-4	1.51	0.71	(0.59–0.81)	90.00	50.00	66.67	81.82

Note. 2D-SWE: Two-Dimensional Shear Wave Elastography; **FIB-4**: Fibrosis-4 Index

APRI: Aspartate Aminotransferase to Platelet Ratio Index; **CI**: Confidence Interval; **AUROC**: Area Under the Receiver Operating characteristic Curve; **PPV**: Positive Predictive Value; **NPV**: Negative Predictive Value

Discussion

This prospective study clearly presents that 2D-SWE is a useful non-invasive tool for evaluating the degree of liver fibrosis in clinical practices, as well as being more effective in determining advanced fibrosis than either FIB-4 or APRI. In this prospective pathology-based study, all study subjects underwent the liver biopsy and 2D-SWE examination on the same day, so the bias in previous studies of 2D-SWE, such as lacking a pathology standard reference[24] or an up to 24-week interval between liver biopsy and 2D-SWE examination[25], could have been well overcome. Although there are fewer studies of 2D-SWE than there are of other modalities in evaluating liver fibrosis, the results of this study provide solid data that 2D-SWE can be implemented as another non-invasive alternative in clinical practices.

Several non-invasive tests have been used for the evaluation of liver fibrosis; however some disadvantages may limit their applications. Although FIB-4 and APRI have been widely used to predict advanced liver fibrosis because of being non-invasive, cheap, and convenient, the sensitivity and specificity of FIB-4 and APRI have not been satisfactory. Both FIB-4 and APRI were initially established to predict advanced fibrosis in patients with chronic hepatitis C; however in a previous study, the fibrosis status could not be determined in a significant proportion of patients (35.4% in FIB-4 and 49% in APRI)[22, 23]. In a recently published study examining the diagnostic performance of FIB-4 and APRI in cirrhotic patients with chronic hepatitis B, a lower AUROC in FIB-4 (0.75) and APRI (0.65) was also reported[26]. In addition, although TE has been proven to be superior to APRI in the evaluation of liver fibrosis, its measurements were proved to be less reproducible in patients with fatty liver disease, obesity, and ALT elevation[27]. Furthermore, the diagnostic performance of TE has been found to be inferior to that of 2D-SWE in predicting advanced fibrosis in a meta-analysis study[28]. Although ARFI has fewer limitations than TE[29], its accuracy also decreases in patients with fatty liver disease[29, 30]. In this study, the diagnostic performance of 2D-SWE was validated not only within the whole patient cohort experiencing various liver disorders, but also in the individual patient subgroups. 2D-SWE may well be an easy-to-use tool for effectively accessing patients with various liver conditions.

Although there have been several studies in recent years involving 2D-SWE for the purpose of evaluating liver fibrosis, most of them were retrospective studies. The measurement of 2D-SWE and the performing of a liver biopsy were usually not conducted on the same day, with the time interval possibly being up to 12 weeks[31,32]. In this situation, the severity of liver fibrosis may have changed during this period. Importantly, the liver area selected for a 2D-SWE measurement might be different from that chosen for a liver biopsy, with the data taken from the 2D-SWE possibly not being representative of the pathology findings. In this pathology-based prospective study, the data regarding the 2D-SWE measurements and blood tests were collected right before the liver biopsy, with the liver specimens acquired from the area selected for 2D-SWE measurement. The possible bias which occurred in previous 2D-SWE studies has been minimized in this study. In addition, data regarding 2D-SWE in a patient cohort, including various liver disorders, remains limited. Most previous 2D-SWE studies were conducted in East Asian countries, and the reported data basically investigated from patients with chronic HBV infection[14,33]. On the other

hand, studies which have been carried out in Western countries mainly focused on patients with chronic HCV infection[34]. In this study which included patients with various liver disorders, 2D-SWE presented a good diagnostic performance not only in the whole patient cohort, but also in patients with various liver disorders.

Several limitations should be acknowledged in this study. First, the sample size of our study was not large enough to confidently evaluate the accuracy of 2D-SWE in all patient subgroups, such as patients with alcoholic liver disease or autoimmune liver disease. A larger study for investigating other patient subgroups should be conducted in the future. Second, most patients recruited for this study had been infected with HBV and/or HCV, therefore patients without chronic viral hepatitis should be interpreted with caution. For example, although this study demonstrated that the diagnostic performance of 2D-SWE was not interfered in patients with concurrent fatty liver disease, subgroup analysis for patients experiencing purely fatty liver disease could not be conducted due to the small sample size. Although the strong diagnostic performance of 2D-SWE in non-alcoholic liver disease has been reported in a recent small study[35], further validation studies for patients without chronic viral hepatitis should be encouraged. Third, this has been a study conducted in Taiwan, and the data of this study would need to be validated in Western countries.

In conclusion, 2D-SWE can be widely used as an effective non-invasive tool for the diagnosis of advanced liver fibrosis in patients with various liver disorders.

Data Availability

All relevant data has been reported within the manuscript. Further supplementary datasets can be obtained upon written request addressed to the corresponding author.

Declarations

Acknowledgements

This work was supported in part by Taichung Veterans General Hospital (110DHA0500741, 110DHA0500008), Taiwan. The funders had no role in the design and conduct of the study, the collection, analysis, and interpretation of the data, or the preparation, review, or approval of the manuscript. We thank the Biostatistics Task Force of Taichung Veterans General Hospital, Taichung, Taiwan, for their statistical assistance. The interpretations and conclusions contained herein do not represent those of Taichung Veterans General Hospital.

Competing interests

The authors declare no competing interests.

Author contributions

T.Y.L. and Y.K.H.: Study concept and design; T.Y.L. and Y.K.H.: Acquisition and analysis of data; T.Y.L. and Y.K.H.: Manuscript drafting; All authors: Interpretation of data; All authors: Critical revision of the manuscript for important intellectual content; All authors: Final approval of the manuscript; T.Y.L. and Y.S.S.: Administrative, technical, or material support; T.Y.L. and Y.S.S.: Study supervision.

Additional information

Correspondence and requests for material should be addressed to Teng-Yu Lee.

References

1. *World Health Organization Health topics: Hepatitis*. https://www.who.int/health-topics/hepatitis#tab=tab_1.
2. Sarin, S. K. et al. Asian-Pacific clinical practice guidelines on the management of hepatitis 2015 update. *Hepatol Int.* **10**, 1–98. DOI: https://doi.org/10.1007/s12072-015-9675-4 (2016).
3. Omata, M. et al. APASL consensus statements and recommendations for hepatitis C prevention, epidemiology, and laboratory testing. *Hepatol Int.* **10**, 681–701. DOI: https://doi.org/10.1007/s12072-016-9736-3 (2016).
4. European Association for the Study of the Liver. EASL Recommendations on treatment of hepatitis C. *J. Hepatol.* **69**, 461–511. DOI: https://doi.org/10.1016/j.jhep.2018.03.026 (2018).
5. European Association for the Study of the Liver. EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. *J. Hepatol.* **67**, 370–398. DOI: https://doi.org/10.1016/j.jhep.2017.03.021 (2017).
6. Bravo, A. A., Sheth, S. G., Chopra, S. Liver biopsy. *N. Engl. J. Med.*. **344**(**7**), 495–500. DOI: https://doi.org/10.1056/nejm200102153440706 (2001).
7. Chin, J. L., Pavlides, M., Moolla, A., Ryan, J. D. Non-invasive markers of liver fibrosis: Adjuncts or alternatives to liver biopsy? *Front. Pharmacol*. 2016; **7**, 159. DOI: https://doi.org/10.3389/fphar.2016.00159 (2016).
8. Castéra, L. et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. *Gastroenterology.* **128**(**2**), 343–50. DOI: https://doi.org/10.1053/j.gastro.2004.11.018 (2005).
9. D'Onofrio, M. et al. Acoustic Radiation Force Impulse of the liver. *World J Gastroenterol*. 2013 Aug 14; **19**(**30**), 4841–4849. DOI: https://doi.org/10.3748/wjg.v19.i30.4841 (2013).
10. Joo, S. K. et al. Steatosis severity affects the diagnostic performances of noninvasive fibrosis tests in nonalcoholic fatty liver disease. *Liver. Int.* **38**(**2**), 331–341. DOI: https://doi.org/10.1111/liv.13549 (2018).
11. Barr, R. G. et al. Elastography assessment of liver fibrosis: Society of radiologists in ultrasound consensus conference statement. *Radiology.* **276**(**3**), 845–861. DOI: https://doi.org/10.1148/radiol.2015150619 (2015).

12. Bruno, C., Minniti, S., Bucci, A., Mucelli, R. P. ARFI: From basic principles to 3 view *Insights Imaging.* **7**(**5**), 735–746. DOI: https://doi.org/10.1007/s13244-016-0514-5 (2016).
13. Lijima, H. Approaches to the diagnosis of liver fibrosis.
14. https://uk.medical.canon/wp-content/uploads/sites/2/2015/01/Approaches-to-the-Diagnosis-of-Liver-2014-shear-wave.pdf
15. Gao, Y. et al. Liver fibrosis with two-dimensional US Shear-Wave Elastography in participants with chronic hepatitis B: A prospective multicenter study *Radiology.* **289**(**2**), 407–415. DOI: https://doi.org/10.1148/radiol.2018172479 (2018).
16. Abe, T. et al. Accuracy of 2D shear wave elastography in the diagnosis of liver fibrosis in patients with chronic hepatitis C. *J Clin Ultrasound*. **46**(**5**), 319–327. DOI: https://doi.org/10.1002/jcu.22592 (2018).
17. Furlan, A. et al. Comparison of 2D Shear Wave Elastography, Transient Elastography, and MR Elastography for the diagnosis of fibrosis in patients with Nonalcoholic Fatty Livecr Disease. *AJR Am J Roentgenol.* **214**(**1**), W20-W26. DOI: https://doi.org/10.1002/hep.510240201 (2020).
18. Bedossa, P., Poynard, T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. *Hepatology.* **24**, 289–93. DOI: https://doi.org/10.1002/hep.510240201 (1996).
19. Ozturk, A., Grajo, J. R., Dhyani, M., Anthony, B. W., Samir, A. E. Principles of ultrasound elastography *AbdomRadiol (NY)*. **43**(**4**), 773–785. DOI: https://doi.org/10.1007/s0261-018-1475-6 (2018).
20. Chung, M., Baird, G. L., Weiss, K. E., Beland, M. D. 2D shear wave elastography: Measurement acquisition and reliability criteria in noninvasive assessment of liver fibrosis. *AbdomRadiol.* **44**, 3285–329420. DOI: https://doi.org/10.1007/s00261-019-02183-0 (2019).
21. Terrault, N. A. et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 Hepatitis B guidance. *Hepatology.* **67(4**), 1560–1599. DOI: https://doi.org/10.1002/hep.29800 (2018).
22. Chalasani, N. et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. *Hepatology.* **67**(**1**), 328–357. DOI: https://doi.org/10.1002/hep.29367 (2018).
23. Vallet-Pichard, A. et al. FIB-4: An inexpensive and accurate marker of fibrosis in HCV infection, comparison with liver biopsy and fibrotest. *Hepatology.* **46**(**1**), 32–36. DOI: https://doi.org/10.1002/hep.21669 (2007).
24. Wai, C. T. et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology.* **38**(**2**), 518–526. DOI: https://doi.org/10.1053/jhep.2003.50346 (2003).
25. Zeng, J. et al. Comparison of 2-D shear wave elastography and transient elastography for assessing liver fibrosis in chronic hepatitis B. *Ultrasound Med Biol.* **43**(**8**), 1563–1570. DOI: https://doi.org/10.1016/j.ultrasmedbio.2017.03.014 (2017).

26. Herrmann, E. et al. Assessment of Biopsy-Proven Liver Fibrosis by Two-Dimensional Shear Wave Elastography: An Individual Patient Data-Based Meta-Analysis *Hepatology*. **67**(**1**), 260–272. DOI: https://doi.org/10.1002/hep.29179 (2018).
27. Sonneveld, M. J. et al. Optimisation of the use of APRI and FIB-4 to rule out cirrhosis in patients with chronic hepatitis B: Results from the SONIC-B study *Lancet Gastroenterol Hepatol.* **4**(**7**), 538–544. DOI: https://doi.org/10.1016/S2468-1253(19)30087-1 (2019).
28. Oshioka, K., Kawabe, N., Hashimoto, S. Transient elastography: Applications and limitations. *Hepatology Research.* **38**, 1063–1068. DOI: https://doi.org/10.1111/j.1872-034X.2008.00386.x (2008).
29. Xiao, G. Q. et al. Comparison of laboratory tests, ultrasound, or magnetic resonance elastography to detect fibrosis in patients with nonalcoholic fatty liver disease: A meta-analysis. *Hepatology*. **66**(**5**), 1486–1501. DOI: https://doi.org/10.1002/hep.29302 (2017).
30. Bota, S. et al. Meta-analysis: ARFI elastography versus transient elastography for the evaluation of liver fibrosis *Liver Int* **33**(**8**), 1138-47. DOI: https://doi.org/ 10.1111/1754-9485.12482 (2013).
31. Harris, N. et al. Acoustic radiation force impulse accuracy and the impact of steatosis on liver fibrosis staging *J Med Imaging Radiat Oncol*. **60**(**5**), 587–592. DOI: https://doi.org/10.2214/AJR.19.21267 (2016).
32. Furlan, A. et al. Comparison of 2D Shear Wave Elastography, Transient Elastography, and MR Elastography for the Diagnosis of Fibrosis in Patients With Nonalcoholic Fatty Liver Disease AJR Am J Roentgenol. **214**(**1**), W20-W26. DOI: https://doi.org/10.2214/AJR.19.21267 (2020).
33. Yan, Y. et al. Assessment of biopsy proven liver fibrosis by two-dimensional shear wave elastography in patients with primary biliary cholangitis. *Dig Liver Dis.* **52**(**5**), 555–560. DOI: https://doi.org/10.1016/j.dld.2020.02.002 (2020).
34. Zhuang, Y. et al. Two-dimensional Shear-Wave Elastography Performance in the Noninvasive Evaluation of Liver Fibrosis in Patients with Chronic Hepatitis B: Comparison with Serum Fibrosis Indexes. *Radiology*.**283**(**3**), 873–882. DOI: https://doi.org/10.1148/radiol.2016160131 (2017).
35. Ferraioli, G. et al. Accuracy of Real-Time Shear Wave Elastography for Assessing Liver Fibrosis in Chronic Hepatitis C: A Pilot Study *Hepatology.* **56**(**6**), 2125–2133. DOI: https://doi.org/10.1002/hep.25936 (2012).
36. Lee, D. H. et al. Accuracy of Two-Dimensional Shear Wave Elastography and Attenuation Imaging for Evaluation of Patients With Nonalcoholic Steatohepatitis. *Clin Gastroenterol Hepatol.* **S1542-3565**(**20**), 30693–5. DOI: https://doi.org/10.1016/j.cgh.2020.05.034 (2020).

Figures

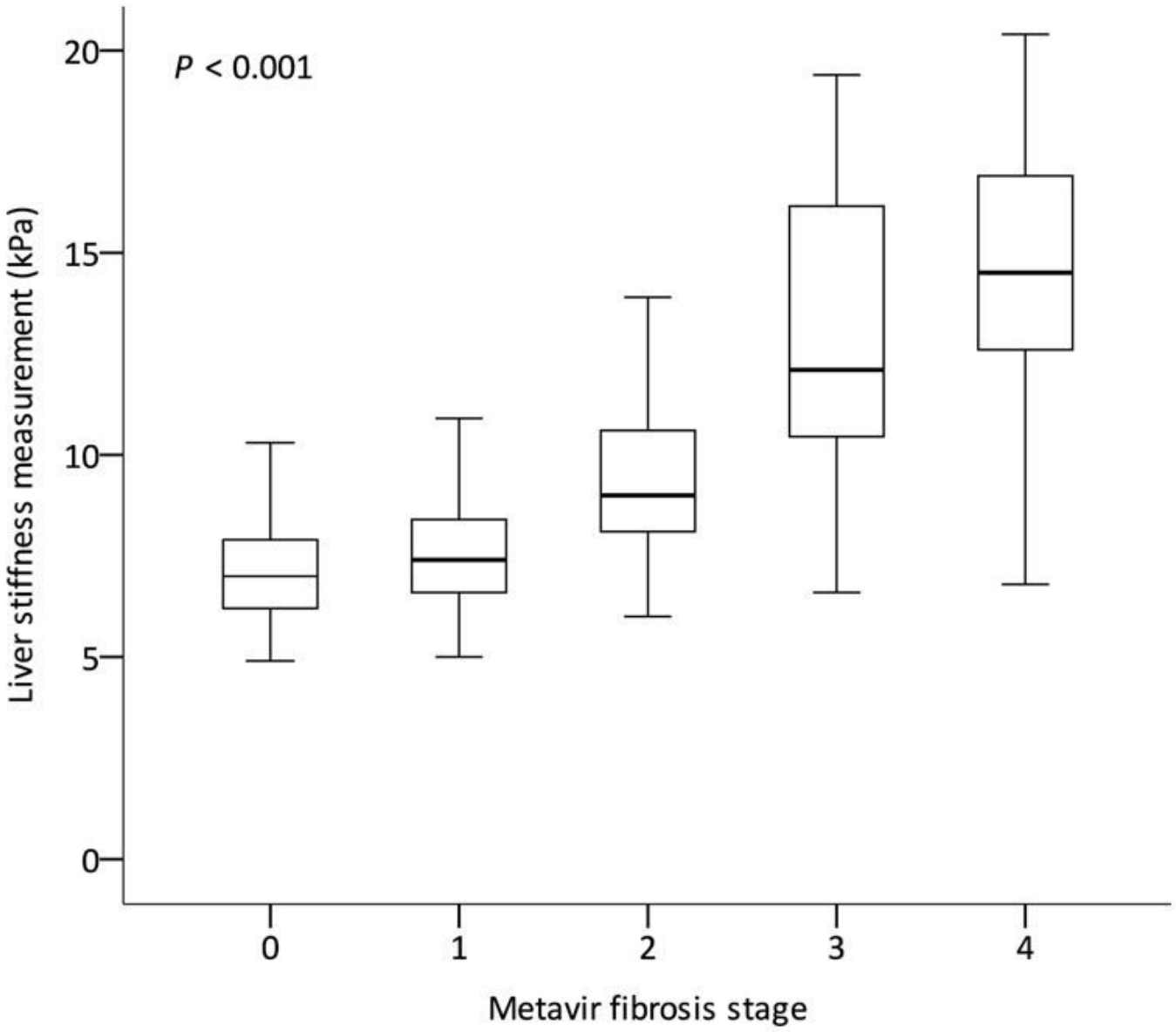

Figure 1

The box-plot diagram of Liver Stiffness Measurement (LSM) of the patients at each fibrosis stage. The bold horizontal lines stand for the median value of LSM in each fibrosis stage. The box stands for the Interquartile Range (IQR) of the LSM. The vertical line between the two short horizontal ones shows the distribution of the LSM.

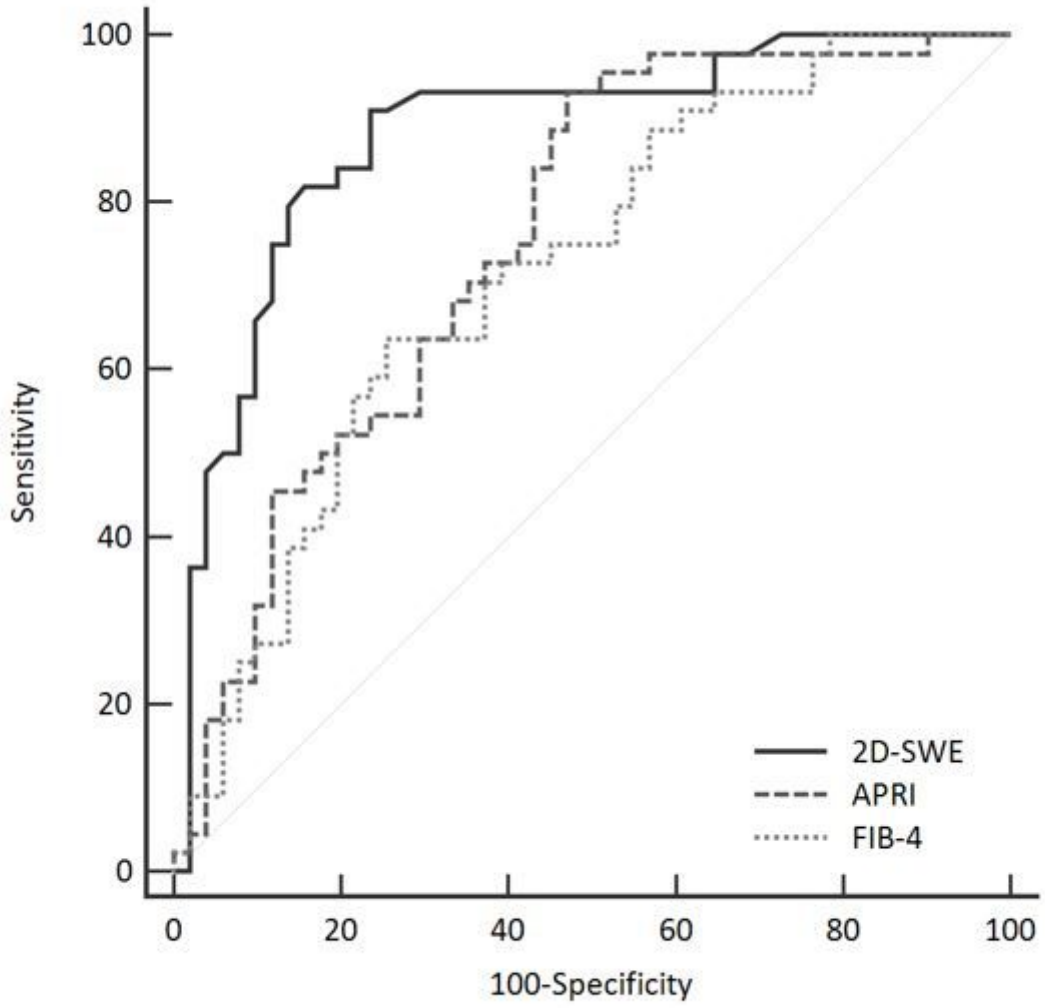

Figure 2

The Receiver Operating Characteristic curves of the different methods for predicting advanced liver fibrosis.