RESEARCH ARTICLE

Liver stiffness assessed by transient elastography as a potential indicator of chronic kidney disease in patients with nonalcoholic fatty liver disease

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Background: This study was designed to determine the diagnostic value of liver stiffness measured by transient elastography (TE) in identifying chronic kidney disease (CKD) in individuals with ultrasonography-diagnosed NAFLD.

Methods: A total of 1439 adult patients with ultrasonography-diagnosed NAFLD between October 2015 and August 2017 in China-Japan union hospital of Jilin university were initially eligible. According to the exclusion criteria, 24 patients were excluded, and eventually, a total of 1415 patients were included in the study. The AST/ALT ratio and FIB-4 score were calculated from blood tests, and liver stiffness was measured using TE.

Results: The liver stiffness measured by TE, FIB-4 score, ALT/AST ratio were significantly elevated in CKD patients, compared with those without CKD ($P < 0.001$). The areas under the curve (AUROC) of liver stiffness, FIB-4 score and AST/ALT ratio were 0.694 (0.670-0.718), 0.707 (0.682-0.730), 0.712 (0.688-0.736), showing no statistically significant difference between these three tests. Further, multivariate analysis identified four independent risk factors for CKD: age, diabetes mellitus, serum uric acid, and liver stiffness. Also, the performance of these four independent variables taken together in a logistic regression model for identifying CKD was 0.834 (AUROC; 95%CI: 0.814-0.853), showing a higher diagnostic performance than that of a single application of liver stiffness.

Conclusions: Liver stiffness assessed by TE is a potential indicator for CKD in ultrasonography-diagnosed NAFLD patients. Further, a four-variable model (liver stiffness, age, serum uric acid, and diabetes mellitus) could be a useful tool for identifying subjects at high risk for CKD in NAFLD patients.

KEYWORDS

chronic kidney disease, liver stiffness, nonalcoholic fatty liver disease, transient elastography

1 | INTRODUCTION

NAFLD is the most common liver disease across worldwide, affecting up to 20%-30% of the general population, and is an increasing indicator for liver transplantation in the USA.^{1,2} Nonalcoholic fatty liver disease (NAFLD) is caused by excess fat accumulation in the liver and constitutes a spectrum of conditions, ranging from

simple steatosis to nonalcoholic steatosis hepatitis (NASH), cirrhosis, and even end-stage liver disease. Some studies suggest that NAFLD is not only a disease associated with liver-related mortality and morbidity but also confers a high risk of developing extra-hepatic conditions, such as chronic kidney disease (CKD) and cardiovascular diseases (CVD).³⁻⁶ Notably, CKD as a public health issue, which is associated with substantial morbidity,

mortality, and considerable healthcare costs, is become increasingly common, and the prevalence of CKD is estimated more than 10% in the adult population.

Due to the critical clinical implication, the close relationship of NAFLD with CKD has attracted considerable scientific interest. Accumulating evidence suggests that NAFLD and CKD share multiple common pathogenetic pathways and risk factors (such as insulin resistance, abdominal obesity, and dysglycemia), furtherly supporting the link between NAFLD and CKD. Notably, several studies have argued that the presence of NASH increases the prevalence of CKD, and the severity of liver biopsy-proven NASH histology (fibrosis stage) shows a grading relationship with kidney dysfunction.^{7,8} This association suggested that biopsy-proven liver fibrosis stage in NAFLD patients may have a potential for identifying CKD. Despite the gold standard for hepatic fibrosis assessment, however, liver biopsy is unfeasible in a clinical setting, due to multiple limitations, including sampling variability, rare but fatal complications, and costs. To this end, it is highly desired to develop an invasive and novel method to stage the severity of liver fibrosis.

Against this, numerous invasive methods for staging of liver fibrosis are continually emerging.⁹ Among them, transient elastography (TE), as promising alternatives to liver biopsy, has gained lots of scientific interest. A series of studies have demonstrated that TE has a better performance than serum invasive serum markers for liver fibrosis evaluation, whereas its role in identifying CKD has not yet been established.^{10,11,12-16} Therefore, the aim of this study was (1) to assess the performance of liver stiffness measured by TE, as well as several other noninvasive score indices for identifying CKD, and (2) develop a multiple-variable model for CKD risk assessment among individuals with ultrasonography-diagnosed NAFLD.

2 | MATERIALS AND METHODS

2.1 | Study population

Clinical and demographic characteristics of subjects were collected from the electronic health record in China-Japan union hospital. Adult patients with ultrasonography-diagnosed NAFLD between April 2015 and August 2017 in China-Japan union hospital of Jilin university were initially eligible ($n = 1439$). Exclusion criteria included the following: self-reporting alcohol consumption of more than 30 g or 20 g per day, respectively, for males and females, positivity for hepatitis C virus antibodies or hepatitis B surface antigen, use of hepatotoxic drugs, autoimmune liver diseases, and other chronic hepatic diseases. According to the exclusion criteria, 24 patients were excluded, and eventually, a total of 1415 patients were included in the study.

2.2 | Study size

To calculate the required sample size for the comparison of the area under a ROC curve with a null hypothesis value, the required significance level and power of the test should be taken

into account. Thus, this study was designed to have a power of 90% to test the prespecified hypothesis that the noninvasive methods would have an AUC of 0.85 for the detection of CKD under the null hypothesis, at a one-sided type I error rate of 0.05. Assuming a CKD prevalence of 10%, a sample of 1089 individuals was needed.

2.3 | Clinical and laboratory procedures

Information regarding demographics and lifestyle habits (smoking and drinking history) were retrospectively collected. Liver ultrasonography scanning was performed by the same experienced hepatologists, who was blinded to participants' details. Liver stiffness was measured by TE using Fibroscan (EchoSens, Paris, France) conducted by an independent operator who was blinded to the clinical data of patients. Blood pressure was measured by a digital electronic sphygmomanometer. All serological measurements were made after an overnight fast using standardized methods. The diagnosis of fatty liver was on the basis of the criteria proposed by the Asian Pacific Association for Study of the Liver.¹⁷ Diabetes mellitus was diagnosed according to the American Diabetes Association criteria.¹⁸ Hypertension was defined according to JNC 7 criteria.¹⁹

BMI was calculated by dividing weight in kilograms by height in meters squared. Waist circumference was measured at the level of the umbilicus. Estimated glomerular filtration rate (eGFR) was calculated using the four-variable Modification of Diet in Renal Disease (MDRD) study equation as follows: $eGFR = 175 \times (\text{serum creatinine}^{-1.154}) \times (\text{age}^{-0.203}) \times 1.212 \text{ (if black)} \times 0.742 \text{ (if female)}$. CKD was defined as the presence of $eGFR \leq 60 \text{ mL/min/1.73 m}^2$.²⁰ The FIB-4 score was calculated according to the following formula: $\text{age} \times \text{AST (IU/L)} / \text{platelet count} \times 10^9 / \text{L} \times (\text{ALT (IU/L)})^{0.5}$.²¹ The AST to ALT ratio was calculated as $\text{AST (IU/L)} / \text{ALT (IU/L)}$.²²

2.4 | Statistical analyses

First, the general characteristics of the patients and the clinical and biochemical characteristics were described. Quantitative variables were expressed by mean $\pm$ SD or median (with interquartile range) in the presence of abnormal distribution. Qualitative variables were presented as numbers with percentages. Second, clinical characteristics and laboratory values were compared between those with and without CKD. Student's *t* test, Fisher's exact test or chi-square test was adopted for between-group comparisons.

Third, receiver operating characteristic (ROC) curves analysis was used to assess the performance of each of the noninvasive methods (FIB-4 score, AST/ALT ratio, liver stiffness). The optimal cutoff values for each biomarker were calculated by maximizing the sum of sensitivity + specificity. Fourth, a logistic regression model was established to evaluate the AUROC of the independent predictors of incident CKD taken together. In detail, the logistic regression model generates *c*-statistics, which could be used to calculate the probability of incident CKD for each patient with NAFLD, using the following equation: $\text{probability} = 1 / (1 + \exp(-c))$. The performance of single use of FIB-4 score,

AST/ALT ratio, liver stiffness, and multivariate model for assessing the risk of CKD were compared using the comparison of the AUROCs. All statistical analyses were performed using MedCalc and R package for windows.

3 | RESULTS

3.1 | Patient characteristics

A total of 1439 patients were initially eligible. Twenty-four patients were excluded according to the exclusion criteria for a total of 1415 patients for inclusion in the study (Figure 1). The prevalence of CKD did not differ among the 1415 eligible but excluded patients for whom data collection could not be sufficiently obtained and all the patients ($n = 1439$) of whom data reviewed (136 [9.6%] vs 139 [9.7%], $P > 0.05$). The demographic, clinical characteristics of the studied population are summarized in Table 1. The mean age for the entire cohort was 52.1 ± 4.9 years. There were 787 (55.6%) men. The main characteristics were as follows: CKD in 136 patients (9.6%); current smokers in 141 patients (10%); diabetes mellitus in

234 patients (16.5%); obesity in 275 patients (19.4%); hypertension in 466 patients (32.9%).

3.2 | Univariate analysis of the association of noninvasive staging of liver fibrosis with prevalent CKD in patients with NAFLD

The patients with CKD were older than those without CKD (55.7 ± 4.7 vs 51.7 ± 4.8 , $P < 0.001$) and had higher levels of BMI, AST, ALT, serum uric acid ($P < 0.001$). They also had a higher prevalence of diabetes mellitus (25% vs 15.6%, $P < 0.01$). The FIB-4 score, ALT/AST ratio, and liver stiffness were significantly elevated in subjects with CKD, compared with those without CKD ($P < 0.001$), independently of the presence of diabetes mellitus (Table 2, Figure 2). The difference in systolic blood pressure (SBP) showed a strong tendency toward statistical significance ($P = 0.051$) between patients with or without CKD. There were no significant differences in gender, waist circumference, current smokers, diastolic blood pressure (DBP), GGT, PLT, TG, and LDL between these two groups.

FIGURE 1 Study flow diagram

TABLE 1 Demographic and laboratory characteristics of all NAFLD patients

Characteristic	Total (n = 1415)
Age(years)	52.1 ± 4.9
Gender (male, %)	787 (55.6%)
BMI	25 ± 2.9
Waist circumference (cm)	85.1 ± 6.7
DM (n, %)	234 (16.5%)
Current smoker (n, %)	141 (10%)
SBP (mmHg)	127.8 ± 12.7
DBP (mmHg)	79.6 ± 11.8
AST (UL/L)	22.7 ± 8.8
ALT (IU/L)	27 ± 8.2
GGT (IU/L)	34.4 ± 11
PLT (×10 ⁹ /L)	232.4 ± 54
TG (mmol/L)	1.59 ± 0.69
HDL (mmol/L)	1.41 ± 0.34
LDL (mmol/L)	3.26 ± 0.39
Serum uric acid (μmol/L)	255.6 ± 86.7
ALT/AST ratio	0.83 (0.58-1.17)
FIB-4 score	1.01 (0.66-1.45)
Liver stiffness	5.8 (4.2-7.6)
eGFR (mL/min per 1.73 m ²)	85.7 ± 12.0
CKD no. (%)	136 (9.6%)

BMI, body mass index; DM, diabetes mellitus; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; PLT, platelet; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated GFR; CKD, chronic kidney disease.

TABLE 2 Comparison between NAFLD patients with and without CKD

	CKD		P value
	No	Yes	
Age (years)	51.7 ± 4.8	55.6 ± 4.7	<0.001*
Gender (male, %)	706 (55.2%)	81 (59.6%)	0.378
BMI	25 ± 3	25.1 ± 2.8	0.680
Waist circumference (cm)	85.1 ± 6.6	84.9 ± 7.1	0.808
DM (n, %)	200 (15.6%)	34 (25%)	0.008*
Current smoker (n, %)	127 (9.9%)	14 (10.3%)	N.S.
SBP (mmHg)	127.6 ± 12.6	129.9 ± 13	0.055
DBP (mmHg)	79.6 ± 11.8	80.2 ± 11.7	0.511
AST (IU/L)	22 ± 8.6	28.9 ± 8.4	<0.001*
ALT (IU/L)	27.3 ± 8.2	24.3 ± 7.4	<0.001*
GGT (IU/L)	34.3 ± 11	35.1 ± 11.8	0.450
PLT (×10 ⁹ /L)	232 ± 53.8	236.3 ± 55.9	0.403
TG (mmol/L)	1.58 ± 0.69	1.62 ± 0.71	0.537
HDL (mmol/L)	1.41 ± 0.34	1.42 ± 0.33	0.660
LDL (mmol/L)	3.27 ± 0.4	3.23 ± 0.38	0.296
Serum uric acid (μmol/L)	249.1 ± 84.2	316.2 ± 86.7	<0.001*
ALT/AST ratio	0.81 (0.57-1.11)	1.23 (0.83-1.74)	<0.001*
FIB-4	0.97 (0.64-1.37)	1.47 (1.08-1.99)	<0.001*
Liver stiffness	5.7 (4.1-7.4)	7.6 (6-9.025)	<0.001*
eGFR	89.4 ± 4.1	49.6 ± 3.0	<0.001*

BMI, body mass index; DM, diabetes mellitus; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; PLT, platelet; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

*Statistically significant difference.

3.3 | Performance of noninvasive staging of liver fibrosis for identifying CKD in patients with NAFLD

To evaluate and compare the diagnostic accuracy of noninvasive tests, we used ROC curves. The area under the ROC curve (AUROC) of liver stiffness measured by TE, FIB-4 score, and AST/ALT ratio was 0.694 (0.670-0.718), 0.707 (0.682-0.730), 0.712 (0.688, 0.736), with no statistically significant difference between these three tests ($P < 0.05$) (Figure 3). The sensitivity, specificity, positive predictive values (PPVs), and negative predictive values (NPVs) of each noninvasive method using cutoffs given by the Youden index are shown in Table 3.

3.4 | Multivariate analysis of the association of noninvasive staging of liver fibrosis with prevalent CKD in patients with NAFLD

Multivariate analysis using logistic model identified four independent indicators of CKD (Table 4): age (OR = 1.19; 95%CI: 1.14-1.24; $P < 0.05$), diabetes mellitus (OR = 1.88; 95%CI: 1.16-3.02; $P < 0.05$), serum uric acid (OR = 1.01; 95%CI: 1.00-1.014; $P < 0.05$),

FIGURE 2 Boxplots depicting liver fibrosis score in NAFLD patients with or without CKD using three invasive methods (AST/ALT Ratio, FIB-4 Score, and liver stiffness). The horizontal line inside each box represents the median. The horizontal lines above and below each box encompass the interquartile range (from 25th to 75th percentile), and the vertical lines from the ends of the box encompass the adjacent values (upper: 75th percentile + 1.5 times the interquartile range, lower 25th percentile–1.5 times the interquartile range)

liver stiffness (OR = 1.31; 95%CI: 1.21-1.43; $P < 0.05$). The diagnostic performance of these four variables taken together in this logistic regression model for identifying CKD was 0.834 (AUROC; 95%CI: 0.814-0.853). It was significantly better than the diagnostic performance of liver stiffness (AUROC = 0.694), FIB-4 score (AUROC = 0.707) and AST/ALT ratio (AUROC = 0.712) for identifying CKD among patients with NAFLD ($P < 0.05$) (Figure 4). The 4-variable model estimate was: $c = 0.17 \times \text{age} + 0.63 \times \text{diabetes mellitus (1 or 0)} + 0.01 \times \text{serum uric acid} + 0.27 \times \text{liver stiffness} - 19.13$.

4 | DISCUSSION

The major finding of this study was that NAFLD patients with a higher value of liver stiffness have an increased risk of chronic kidney

FIGURE 3 Comparison of ROC curves of AST/ALT Ratio, FIB-4 Score and liver stiffness for the detection of CKD in NAFLD patients. (A) AST/ALT Ratio, (B) FIB-4 Score, (C) liver stiffness, (D) Comparison between AST/ALT Ratio, FIB-4 Score, and liver stiffness. The diagonal line represents detection achieved by chance alone (AUROC = 0.50); the ideal AUROC is 1.00

TABLE 3 Multivariate analysis of factors associated with chronic kidney disease in patients with NAFLD

Variables	Comparison	Multivariate analysis on the risk of CKD		
		OR	95% CI OR	P value
Age	Per unit increase	1.19	1.14-1.24	<0.05*
Diabetes mellitus	Yes vs No	1.88	1.16-3.02	<0.05*
Serum uric acid	Per unit increase	1.01	1.008-1.013	<0.05*
Liver stiffness	Per unit increase	1.31	1.21-1.43	<0.05*

*Statistically significant difference.

TABLE 4 Comparison of diagnostic performance of each test for the identification of chronic kidney disease in NAFLD patients

Index test	AUROC (95%CI)	Cutoff	Sens (%)	Spec (%)	PPV(%)	NPV(%)
Liver stiffness	0.694(0.670-0.718)	7.2	58.09	74.28	19.4	94.3
FIB-4	0.707(0.682-0.730)	1.23	68.38	67.55	18.3	95.3
AST/ALT ratio	0.712 (0.688-0.736)	1.02	65.44	70.45	19.1	95.0
4-variable model	0.834 (0.814-0.853)	-2.07	72.06	81.31	29.1	96.5

disease. The diagnostic performance (AUROC) of liver stiffness was 0.694 (0.670-0.718). Moreover, we developed a multiple-variable model (age, the status of diabetes, serum uric acid, liver stiffness value) for identifying CKD in NAFLD patients, showing a higher diagnostic performance (AUROC: 0.834; 95%CI: 0.814-0.853). The diagnostic performance of these 4-variable model was significantly better than that of a single use of liver stiffness (AUROC = 0.694), FIB-4 score (AUROC = 0.707), and AST/ALT ratio (AUROC = 0.712) ($P < 0.05$).

These studies confirm and extend a recent work by Xu et al, showing that several noninvasive fibrosis scores (FIB-4 score, AST/ALT ratio) were associated with prevalent CKD, and those with higher noninvasive fibrosis score have an elevated CKD risk.¹⁵ Similarly, Sesti et al reported that advanced fibrosis was related to CKD risk in Caucasian populations with ultrasonography-diagnosed NAFLD. However, the finding above only evaluated the diagnostic performance of the single use of noninvasive serum indices, and the putative role of transient elastography in identifying CKD has not

FIGURE 4 Comparison of ROC curves of a four-variable model (liver stiffness, age, serum uric acid, and diabetes status), AST/ALT Ratio, FIB-4 Score and liver stiffness for the detection of CKD in NAFLD patients. (A) four-variable model, (B) Comparison between the four-variable model, AST/ALT Ratio, FIB-4 Score, and liver stiffness. The diagonal line represents detection achieved by chance alone (AUROC = 0.50); the ideal AUROC is 1.00

yet been established among subjects with NAFLD. Notably, whether the combination of these noninvasive methods would provide higher accuracy than a single use of each for identifying CKD was also undetermined. With more risk factors identified for CKD, there is a need for the establishment of a novel model comprises multiple biomarkers for better risk evaluation.²³

Our finding firstly demonstrated that liver stiffness assessed by transient elastography could be a potential indicator of the CKD risk, and proposed a 4-variable model for CKD risk assessment. The best predictive value of four variable model for CKD given by Youden index was -2.07, with PPV and NPV of 29.1%, 96.5%.

The underlying mechanisms potentially responsible for the association of NAFLD with CKD remain unclear. A large number of studies indicate that NAFLD and CKD share multiple common underlying metabolic risk factors. Many risk factors for NAFLD may also promote the development and progress of CKD.^{24,25} What is more, there is growing evidence suggesting that NAFLD, particularly its advanced form (NASH) implies the pathogenesis of kidney damage and increases the CKD risk, independently of traditional risk factors such as obesity, diabetes mellitus.²⁶ Liver steatosis in NAFLD patients could induce hepatokine secretion and subsequently downstream biological consequences. That is, some pathogenic inflammatory mediators from the steatotic liver, including C-reactive protein (CRP), elevated reactive oxygen species, TNF- α , TGF- β , and other proinflammatory cytokines, may be involved in the pathogenesis of CKD.^{27,28} Likewise, in a large cohort of individuals with type 2 diabetes, patients with chronic B virus infection had an increased risk of ESRD, compared with those who were not infected with HBV.²⁹ This finding was consistent with the hypothesis that liver inflammation in NAFLD may have the potential to be involved in the pathogenesis of CKD.³⁰

Also, insulin resistance has been shown to be a contributor to the progression of kidney disease. In NAFLD patients, insulin resistance activates the sympathetic nervous system, sodium retention, and downregulation of the natriuretic peptide system, leading to impaired renal hemodynamics, making insulin resistance a potential mechanistic link between NAFLD and CKD.^{1,31} Additionally, atherosclerotic dyslipidemia in NAFLD has attracted considerable scientific interest.

Atherogenic dyslipidemia is common in NAFLD, which potentially increases the risk of atherosclerotic vascular that is associated with renal endothelial dysfunction and renovascular damage.³²

Given the cross-sectional design of the present study, whether there is a causal relationship between NAFLD and CKD has not yet been determined. However, in this study, after we adjusted for multiple potential confounding factors (age, serum uric acid, diabetes, liver stiffness), the positive relationship between NAFLD and CKD remain exists. This association might at least imply that CKD is not only a complication of the shared metabolic risk factors but CKD itself as a consequence induced by NAFLD. Furtherly, consistent with our finding, several prospective studies suggest that ultrasound-diagnosed NAFLD is an independent predictor of prevalent CKD.^{28,33}

This study has some limitations. Firstly, the causality of the association between NAFLD and CKD could not be established, as this design of this study is cross-sectional. Secondly, the eGFR calculated by the 4-variable MDRD study equation as an indirect measured GFR was used to diagnose CKD. Although the possibility of underestimates renal function in obese subjects, the MDRD study equation has been a well-accepted means to estimate kidney function in epidemiologic studies.^{20,34,35} Thirdly, the NAFLD was only diagnosed with ultrasonography but was not confirmed by liver biopsy. Nevertheless, it is not appropriate to perform liver biopsy in all NAFLD patients, particularly in a large sample of epidemiologic studies.^{36,37}

Despite these limitations, this study has several strengths. First, this study has a relatively large sample size, ensuring enough power for detecting the potential role of noninvasive methods for identifying CKD. Second, a multivariate logistic analysis was used to adjust for multiple potential confounders. Third, this study adopts a one-gates design, thus avoiding selection bias.

5 | CONCLUSION

Our results suggest that liver stiffness is a potential indicator for CKD in ultrasonography-diagnosed NAFLD patients. Age, serum uric

acid, and the presence of diabetes are also independent risk factors of CKD in subjects with NAFLD. Moreover, a 4-variable model (liver stiffness, age, serum uric acid, and diabetes status) could be a useful tool for identifying subjects at high risk for CKD in NAFLD. Patients with NAFLD should be closely monitored for the development and progression of incident CKD. Further prospective studies are warranted to establish the causal relationship between the severity of NAFLD and CKD.

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CONFLICT OF INTEREST

The authors have declared no conflict of interest.

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