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ARTICLE

Advanced liver fibrosis measured by transient elastography predicts chronic kidney disease development in individuals with non-alcoholic fatty liver disease

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Abstract

Aims/hypothesis Non-alcoholic fatty liver disease (NAFLD) and chronic kidney disease (CKD) are progressive chronic conditions that share important cardiometabolic risk factors and pathogenic mechanisms. We investigated the association between liver fibrosis measured by transient elastography (TE) and the risk of incident CKD in individuals with NAFLD.

Methods A total of 5983 participants with NAFLD (defined as controlled attenuation parameter >222 dB/m) but without CKD who underwent TE between March 2012 and August 2018 were selected. The primary outcome was incident CKD, defined as the occurrence of eGFR <60 ml min^{-1} [1.73 m]$^{-2}$ or proteinuria (≥1+ on dipstick test) on two consecutive measurements during follow-up. The secondary outcome was a 25% decline in eGFR measured on two consecutive visits.

Results The mean age was 51.8 years and 3756 (62.8%) participants were male. During 17,801 person-years of follow-up (mean follow-up of 3.0 years), 62 participants (1.0%) developed incident CKD. When stratified into TE-defined fibrosis stages (F0–F4), multivariable Cox models revealed that risk of incident CKD was 5.40-fold (95% CI 2.46, 11.84; $p < 0.001$) higher in the F3/F4 group (≥9.5 kPa) than in the F0 group (<5.5 kPa). During 17,577 person-years of follow-up (mean follow-up of 3.0 years), 201 participants (3.4%) experienced the secondary outcome, for which the F3/F4 group had a 3.22-fold higher risk (95% CI 1.96, 5.28; $p < 0.001$) than the F0 group.

Conclusions/interpretation In this large cohort of individuals with NAFLD but without baseline CKD, advanced liver fibrosis measured by TE was significantly associated with a higher risk of incident CKD.

Keywords Chronic kidney disease · Liver fibrosis · Non-alcoholic fatty liver disease · Transient elastography

Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CAP	Controlled attenuated parameter
CKD	Chronic kidney disease
ESKD	End-stage kidney disease
FAST	FibroScan-AST
GGT	γ-Glutamyltransferase
LS	Liver stiffness
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
TE	Transient elastography
YUHS	Yonsei University Health System

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Introduction

Non-alcoholic fatty liver disease (NAFLD), the most common type of chronic liver disease affecting up to 25–30% of the general population, is characterised by a wide spectrum of

Research in context

What is already known about this subject?

- Non-alcoholic fatty liver disease (NAFLD) and chronic kidney disease (CKD) are progressive chronic conditions that share important cardiometabolic risk factors and pathogenic mechanisms
- Little is known about how varying degrees of steatotic and fibrotic burdens affect the development of CKD in individuals with NAFLD

What is the key question?

- Does advanced liver fibrosis measured by transient elastography (TE) predict CKD development in individuals with NAFLD?

What are the new findings?

- Advanced liver fibrosis measured by TE was significantly associated with a higher risk of incident CKD and kidney function decline

How might this impact on clinical practice in the foreseeable future?

- TE for the measurement of fibrotic burden of the liver may be a useful tool in identifying individuals with NAFLD at a high risk of developing adverse long-term kidney outcomes

liver injury, ranging from simple steatosis (accumulation of more than 5% of triacylglycerols without evidence of hepatocellular injury) to non-alcoholic steatohepatitis (NASH), advanced liver fibrosis and cirrhosis [1–4]. NAFLD is a multisystem disease and is significantly associated with an increased risk of CVD, chronic kidney disease (CKD) and extrahepatic malignancies [5, 6].

CKD is a major global public health problem that affects around 10–15% of the world's adult population. Due to its association with CVD, end-stage kidney disease (ESKD) and death, identifying the causes and risk factors for CKD is an important public health concern to reduce the global burden of CKD [7, 8]. Because of the increasing prevalence of lifestyle-associated diseases such as hypertension, diabetes, obesity and NAFLD, the prevalence of CKD is expected to continually increase [9].

Since both NAFLD and CKD are progressive chronic conditions that share important cardiometabolic risk factors and pathogenic mechanisms, there is a growing body of epidemiological evidence that suggests a strong causal association between NAFLD and CKD, independent of the presence of potential confounding comorbid diseases such as hypertension, diabetes and obesity [10–15]. In an Italian cohort study of diabetic individuals with preserved kidney function at baseline, Targher et al. showed that NAFLD was associated with an increased risk of incident CKD, independent of traditional risk factors such as age, sex, BP and BMI [16]. Although many cross-sectional and cohort studies have revealed similar findings [17–24], given that NAFLD is a disease characterised by a wide spectrum of liver injury, little is known about how varying degrees of steatotic and fibrotic burdens, in particular those obtained by non-invasive diagnostic modalities, affect the development of CKD in individuals with NAFLD.

Hence, we investigated whether the degree of liver steatosis and fibrosis, which was measured using transient elastography (TE), predicts the risk of incident CKD in individuals with NAFLD without baseline CKD.

Methods

Study population Patients who underwent TE and were diagnosed with NAFLD [25], between March 2012 and August 2018, were considered eligible for this retrospective, longitudinal cohort study at Severance Hospital of the Yonsei University Health System (YUHS), a tertiary medical centre in Seoul, South Korea (electronic supplementary material [ESM] Fig. 1).

Participants who met the following criteria were excluded: (1) TE assessment failure or unreliable liver stiffness (LS) values; (2) age younger than 18 years; (3) history of CKD, ESKD or kidney transplantation; (4) baseline eGFR below 60 ml min^{-1} [1.73 $m]^{-2}$; (5) unknown baseline eGFR; (6) baseline proteinuria; (7) baseline serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) above 3.3 μkat/l [26]; (8) missing baseline data on hepatitis B surface antigen or anti-hepatitis C virus antibody; (9) history of malignancy; and (10) follow-up period of less than 3 months (ESM Fig. 1).

The study protocol was designed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Review Board of YUHS.

Informed consent was waived by the Institutional Review Board due to the retrospective study design.

Data collection and follow-up Demographic, anthropometric, medication and laboratory data were retrieved from electronic medical records at the time of the initial TE examination, which was considered baseline. Hypertension was defined as a systolic BP above 140 mmHg, a diastolic BP above 90 mmHg, or current use of antihypertensive agents. Diabetes mellitus was defined as a fasting serum glucose level ≥7 mmol/l or current use of glucose-lowering agents. Serum creatinine levels were determined using an isotope dilution MS-traceable method at a central laboratory, with calibration against the reference. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation [27].

Participants visited the outpatient clinic of our institution at intervals of 3–6 months, where follow-up anthropometric and laboratory data that included blood chemistry tests and urinalysis were collected. Participants were followed up from study entry to the point of incident CKD or proteinuria onset, loss to follow-up or end of study, whichever came first. Loss to follow-up and the end of the study period (31 August 2020) were censoring events.

TE examination and calculation of the FibroScan-AST score TE was performed as part of clinical care in patients who were suspected of having, were likely to develop or had already been diagnosed with chronic liver diseases that included NAFLD. Among currently available non-invasive tests in the risk stratification of individuals with chronic liver diseases, TE is commonly performed by hepatologists due to its ability to rapidly and easily assess both steatotic and fibrotic burden [28, 29]. Although conventional ultrasound is still recommended as the first-line diagnostic tool in the assessment of liver steatosis [29], it cannot accurately assess the degree of liver fibrosis, which is the single most important prognostic factor in individuals with NAFLD [30]. Due to the ability of TE to overcome this limitation, most clinical management guidelines on the diagnosis and management of NAFLD recommend TE as well as other non-invasive blood-based tests, if available, to confer additional diagnostic and prognostic accuracy, particularly in individuals at high risk of developing advanced liver fibrosis [2, 3, 25, 29]. In line with these recommendations, TE was used to measure steatotic and fibrotic burdens in participants in this study.

In TE, a probe that generates a mechanical and ultrasound waves was used to measure tissue elasticity. This was performed to determine an LS value (kPa) and a controlled attenuated parameter (CAP) value (dB/m), which give an indication of liver fibrosis and steatosis, respectively [31]. At the time of enrolment, all TE measurements were obtained using the Fibroscan 502 or 502 touch machine (EchoSens, Paris, France) by experienced nurses. TE was performed on the right lobe of the liver, with the participant lying in the dorsal decubitus position with the right arm in maximal abduction. The IQR obtained during TE served as an index of intrinsic variability of values. In the present study, only values with at least ten validated measurements, a success rate of at least 60% and an IQR/median ratio of less than 30% were considered reliable.

LS cut-off values for the different fibrosis stages (F0–F4) were defined as follows: F0 < 5.5 kPa; F1 from 5.5 to less than 7.5 kPa; F2 from 7.5 to less than 9.5 kPa; F3 from 9.5 to less than 11.0 kPa; and F4 ≥ 11.0 kPa [32]. For the presence of NAFLD based on CAP values, NAFLD was defined as CAP value >222 dB/m [33].

In addition, recognising that fibrosis is the downstream effect of precursor effects, and that the extent of steatosis could also be an important factor in evaluating the risk of CKD, we also calculated the FibroScan-AST (FAST) score to assess whether progressive NASH, determined by a recently proposed, well-validated score, could also predict the development of decline in kidney function [34].

Kidney outcomes The primary outcome was the development of incident CKD, defined as the occurrence of eGFR below 60 ml min^{-1} [1.73 $m]^{-2}$ or proteinuria (≥1+ on dipstick test) on two consecutive measurements during follow-up. The secondary outcome was a 25% decline in eGFR measured on two consecutive visits.

Statistical analysis The missing data analysis methods used missing at random assumptions. ESM Table 1 lists the types of missing data. For missing data imputation, the multivariate imputation by chained equations (MICE) method of multiple multivariate imputation in STATA was used. Five complete datasets were created to achieve maximum accuracy, each with missing values suitably imputed in the multivariable Cox regression analyses to account for missing values. To check the plausibility of the imputed data generated by the imputation model, summary statistics of the observed and imputed data were checked to ensure that the means and SDs of the observed and imputed data were similar (ESM Table 2). The variable estimates were averaged to give a single mean estimate, and SEs were adjusted according to Rubin's rules. Continuous variables are expressed as means ± SDs or as medians (IQRs). Categorical variables are expressed as *n* (%). The normality of data distribution was assessed using the Shapiro–Wilk test. The *p* value for trend (p_{trend}) was calculated by TE-defined fibrosis stages. For categorical variables, the χ^2 test for trend was used. Cumulative incidences of incident

Table 1 Baseline characteristics

Variable	Total (n=5983)	TE-defined fibrosis stage			p_{trend}
		F0 (n=4122, 68.9%)	F1/F2 (n=1526, 25.5%)	F3/F4 (n=335, 5.6%)	
Demographic and anthropometric data					
Age, years	51.8±12.9	52.5±11.7	49.6±14.9	53.0±15.9	0.042
Male, n (%)	3756 (62.8)	2624 (63.7)	970 (63.6)	162 (48.4)	<0.001
BMI, kg/m^2	25.7±3.6	25.1±3.2	26.8±3.9	28.0±5.1	<0.001
Systolic BP, mmHg	125.4±15.4	124.9±15.4	126.6±15.3	127.6±16.1	<0.001
Hypertension, n (%)	2063 (34.5)	1199 (29.1)	671 (44.0)	193 (57.6)	<0.001
Diabetes mellitus, n (%)	1772 (29.6)	960 (23.3)	631 (41.3)	181 (54.0)	<0.001
Medication, n (%)					
Antihypertensive agents	1240 (20.7)	708 (17.2)	406 (26.6)	126 (37.6)	<0.001
Glucose-lowering agents	1002 (16.7)	516 (12.5)	371 (24.3)	115 (34.3)	<0.001
Lipid-lowering agents	1658 (27.7)	1017 (24.7)	518 (33.9)	123 (36.7)	<0.001
Laboratory data					
Fasting glucose, mmol/l	6.2±1.9	6.1±1.7	6.4±2.0	6.7±1.3	<0.001
Total cholesterol, mmol/l	4.8±1.1	4.9±1.0	4.9±1.1	4.7±1.1	<0.001
HDL-cholesterol, mmol/l	1.2±0.3	1.3±0.3	1.2±0.3	1.2±0.3	<0.001
LDL-cholesterol, mmol/l	2.9±0.9	2.9±0.9	2.9±0.9	2.9±1.0	<0.001
Triacylglycerols, mmol/l	1.5 (1.1–2.1)	1.5 (1.1–2.1)	1.6 (1.2–2.3)	1.6 (1.2–2.1)	<0.001
GGT, μkat/l	0.6 (0.4–1.1)	0.6 (0.4–1.0)	0.7 (0.4–1.2)	0.8 (0.5–1.3)	<0.001
AST, μkat/l	0.5±0.4	0.5±0.3	0.7±0.4	1.0±0.5	<0.001
ALT, μkat/l	0.7±0.5	0.5±0.4	0.9±0.6	1.1±0.7	<0.001
Serum creatinine, μmol/l	69.5±14.9	69.9±14.8	69.3±15.0	64.7±15.0	<0.001
eGFR, ml min^{-1} [1.73 m]$^{-2}$	99.3±14.1	98.5±13.1	101.1±15.8	100.8±16.4	<0.001
TE data					
LS, kPa	4.7 (3.8–6.0)	4.2 (3.6–4.7)	6.5 (6.0–7.6)	11.9 (10.5–15.0)	
CAP, dB/m	276 (247–311)	264 (241–294)	305 (274–335)	308 (269–339)	<0.001

Continuous variables are expressed as means ± SD; categorical variables are expressed as n (%); triacylglycerols, GGT, LS and CAP values are shown as median (IQR)

CKD and 25% decline in eGFR were estimated using Kaplan–Meier analyses and logrank tests. Cox proportional hazards models were developed to determine the association between TE-defined fibrosis stages and the risk of incident CKD and kidney function decline. Proportional hazards assumptions were confirmed using Schoenfeld residuals. Data are expressed as HRs with 95% CIs. Three models with increasing degrees of adjustment to account for potential baseline confounding factors were used: model 1 was not adjusted for any covariates; model 2 included age, sex and BMI; model 3 was as for model 2 and also included baseline eGFR, fasting glucose, LDL (LDL), γ-glutamyltransferase (GGT), AST, ALT, systolic BP and use of antihypertensive, glucose-lowering and lipid-lowering agents. If the participants had undergone multiple TE examinations during the study period, data from the first examination was adopted for statistical analysis. Statistical significance was defined as $p < 0.05$. All analyses were conducted using STATA version 15 (Stata Corp., College Station, TX, USA).

Results

Baseline characteristics After excluding 10,924 individuals according to the exclusion criteria, a total of 5983 participants were selected for statistical analysis (ESM Fig. 1). The proportion of participants with TE assessment failure or unreliable LS values was 3.6%, which was similar to that reported in other Asian studies [35]. Baseline characteristics of participants are presented in Table 1. The mean age was 51.8 years and 3756 (62.8%) participants were male. A total of 2063 (34.5%) participants had hypertension and 1772 (29.6%) had diabetes mellitus. Moreover, 1240 (20.7%), 1002 (16.7%) and 1658 (27.7%) participants were using antihypertensive, glucose-lowering and lipid-lowering agents, respectively. At baseline, the mean eGFR was 99.3 ml min^{-1} [1.73 m]$^{-2}$. The median LS and CAP values were 4.7 kPa and 276 dB/m, respectively.

When the participants were divided into three groups according to TE-defined fibrosis stages (F0 vs F1/F2 vs F3/

F4), the proportion of participants with hypertension and diabetes mellitus was higher (all $p < 0.001$) in those with higher fibrosis stages. BMI, systolic BP, fasting glucose, triacylglycerols, GGT, AST, ALT, and eGFR were significantly higher (all $p < 0.001$), whereas total cholesterol, HDL-cholesterol and LDL-cholesterol were significantly lower (all $p < 0.001$) in participants with higher fibrosis stages.

Development of incident CKD When participants were stratified according to development of incident CKD during the follow-up period, those who developed CKD were significantly older, more likely to be women, more likely to have hypertension and diabetes as comorbidities and more likely to be receiving antihypertensive, glucose-lowering and lipid-lowering agents (all $p < 0.01$). Systolic BP, fasting glucose, triacylglycerols, AST and LS were significantly higher, whereas baseline total cholesterol, HDL-cholesterol, LDL-cholesterol and eGFR were significantly lower in participants who eventually developed incident CKD (all $p < 0.01$). In contrast, BMI, GGT, ALT and CAP were statistically similar between the groups (all $p > 0.05$) (ESM Table 3).

Unadjusted association between kidney outcomes and degree of liver fibrosis During 17,801 person-years of follow-up (mean follow-up of 3.0 years), 62 participants developed incident CKD (3.5 per 1000 person-years [95% CI 2.7, 4.5]) (Table 2). A total of 55 vs 7 participants developed incident CKD based on the eGFR vs proteinuria criteria, respectively. When the participants were grouped according to TE-defined fibrosis stages, incident CKD occurred in 26 (2.2 per 1000 person-years), 24 (4.8 per 1000 person-years) and 12 (11.1 per 1000 person-years) participants in stages F0, F1/F2 and F3/F4, respectively (Table 2).

For the secondary outcome, during 17,577 person-years of follow-up (mean follow-up of 3.0 years), 201 participants developed a 25% decline in eGFR (11.4 per 1000 person-years [95% CI 10.0, 13.1]) (Table 2). When the participants were grouped according to TE-defined fibrosis stages, 25% decline in eGFR occurred in 105 (9.0 per 1000 person-years), 66 (13.5 per 1000 person-years) and 30 (29.1 per 1000 person-years) participants in stages F0, F1/F2 and F3/F4, respectively. The cumulative incidences of both incident CKD and 25% decline in eGFR were consistently higher in participants with higher TE-defined fibrosis stage (all $p < 0.001$ by the logrank test) (Figs. 1, 2).

Adjusted association between kidney outcomes and degree of liver fibrosis The associations between kidney outcomes and degree of liver fibrosis were further adjusted in multivariate Cox proportional hazards models (Tables 3, 4). When the LS parameter was treated as a continuous variable, the adjusted HR for incident CKD and 25% decline in eGFR was 1.04 (95% CI 1.02, 1.07) and 1.04 (95% CI 1.03, 1.06), respectively. When the LS parameter was treated as a categorical variable grouped according to TE-defined fibrosis stages, the F3/F4 group was at a significantly higher risk of both incident CKD (unadjusted HR 4.59 [95% CI 2.31, 9.11]) and 25% decline in eGFR (unadjusted HR 3.08 [95% CI 2.05, 4.63]), compared with the F0 group. These findings were similarly maintained even after adjusting for potential confounding factors, where the F3/F4 group was at a significantly higher risk of both incident CKD (adjusted HR 5.40 [95% CI 2.46, 11.84]) and 25% decline in eGFR (adjusted HR 3.22 [95% CI 1.96, 5.28]), when compared with the F0 group.

Association between kidney outcomes and the FAST score The association between kidney outcomes and the FAST score was determined in univariate and multivariate Cox proportional hazards models (ESM Tables 4, 5). For every 0.1 increase in the FAST score, the unadjusted HR for incident

Table 2 Kidney outcomes

Outcome	Total	TE-defined fibrosis stage			*p* value[a]
		F0	F1/F2	F3/F4s	
Incident CKD					
Person-years	17,801.0	11,756.1	4963.3	1081.6	
Events, *n* (%)	62 (1.0)	26 (0.6)	24 (1.6)	12 (3.6)	
Incidence rate, per 1000 person-years	3.5 (2.7, 4.5)	2.2 (1.5, 3.2)	4.8 (3.2, 7.2)	11.1 (6.3, 19.5)	<0.001
25% decline in eGFR					
Person-years	17,576.9	11,647.3	4899.9	1029.8	
Events, *n* (%)	201 (3.4)	105 (2.5)	66 (4.3)	30 (9.0)	
Incidence rate, per 1000 person-years	11.4 (10.0, 13.1)	9.0 (7.4, 10.9)	13.5 (10.6, 17.1)	29.1 (20.4, 41.7)	<0.001

Incidence rates are shown with 95% CI within parentheses

[a] *p* value estimated by logrank test

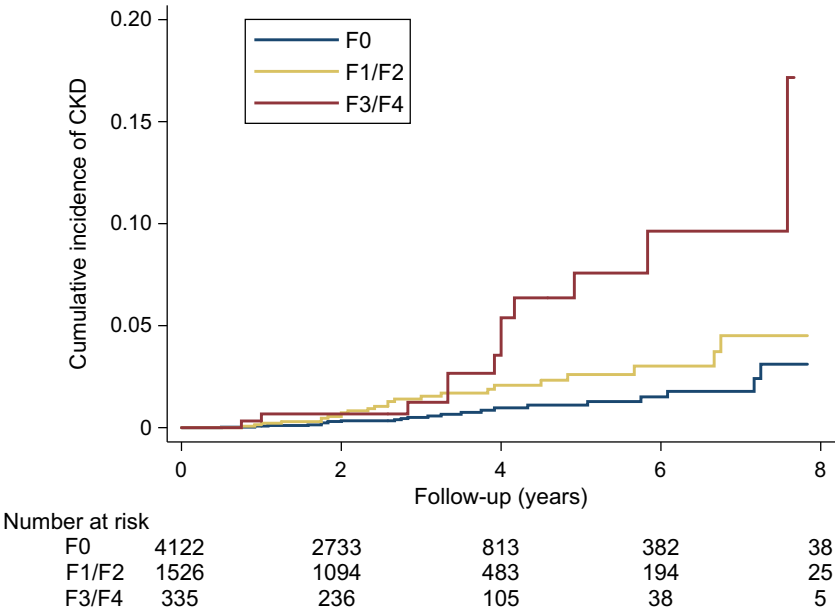

Fig. 1 Cumulative incidence of CKD by TE-defined fibrosis stage. Logrank test $p < 0.001$

CKD was 1.12 (95% CI 1.00, 1.25) but did not show statistical significance after adjustment for confounding factors (HR 1.11 [95% CI 0.97, 1.27]). When the FAST score was treated as a categorical variable, higher tertiles of the FAST score did not show statistically significant difference.

Regarding 25% decrease in eGFR, for every 0.1 increase in FAST score, the unadjusted and adjusted HR was 1.09 (95% CI 1.02, 1.16) and 1.10 (95% CI 1.02, 1.19), respectively. When treated as a categorical variable, compared with the lowest tertile, the highest tertile revealed an unadjusted and adjusted HR of 1.53 (95% CI 1.09, 2.15) and 1.57 (95% CI 1.02, 2.42), respectively.

The cumulative incidences of both incident CKD and 25% decline in eGFR were higher in participants with higher FAST score but the difference only achieved statistical significance for the secondary outcome ($p = 0.006$) (ESM Figs. 2, 3).

Discussion

Although NAFLD is a disease characterised by a wide spectrum of liver injury, little is known about how varying degrees of fibrotic burden affect the development of CKD in individuals with NAFLD. In this large cohort study,

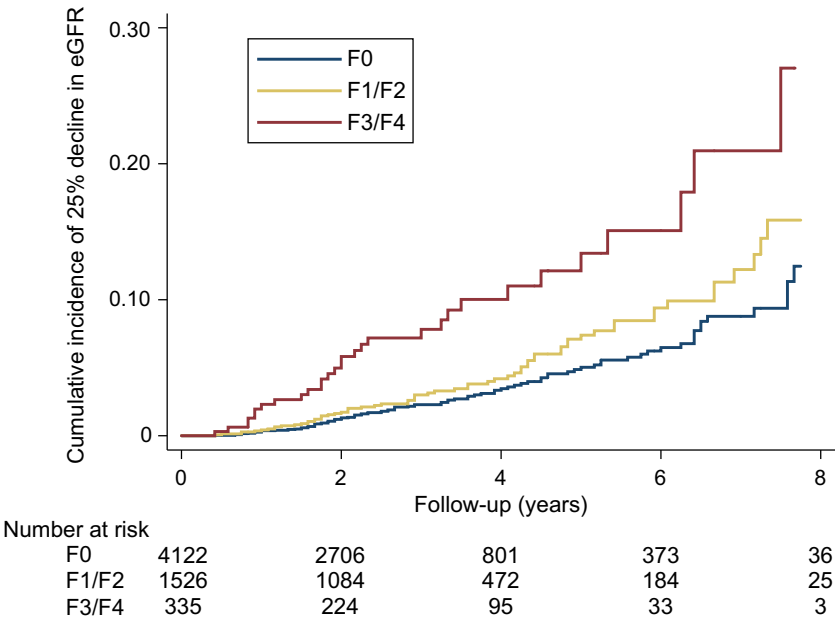

Fig. 2 Cumulative incidence of 25% decline in eGFR by TE-defined fibrosis stage. Logrank test $p < 0.001$

Table 3 HRs for incident CKD by TE-defined fibrosis

TE-defined fibrosis	Model 1[a]		Model 2[b]		Model 3[c]	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Values as continuous variables						
LS, per 1 kPa	1.05 (1.03, 1.07)	<0.001	1.04 (1.02, 1.07)	<0.001	1.04 (1.02, 1.07)	0.001
Values as categorical variables						
F0 (<5.5 kPa)	Reference		Reference		Reference	
F1/F2 (5.5–9.4 kPa)	2.01 (1.15, 3.50)	0.014	2.39 (1.36, 4.22)	<0.001	1.78 (0.89, 3.56)	0.103
F3/F4 (≥9.5 kPa)	4.59 (2.31, 9.11)	<0.001	4.64 (2.27, 9.50)	<0.001	5.40 (2.46, 11.84)	<0.001

[a] Model 1: unadjusted model

[b] Model 2: adjusted for age, sex and BMI

[c] Model 3: Model 2, with additional adjustments for baseline eGFR, fasting glucose, LDL-cholesterol, GGT, AST, ALT, systolic BP and use of antihypertensive, glucose-lowering and lipid-lowering agents

higher fibrotic burden measured using TE was independently associated with unfavourable long-term kidney outcomes. With participants grouped into TE-defined fibrosis stages, the F3/F4 group exhibited approximately four times higher risk of eventually developing incident CKD or kidney function decline, when compared with the F0 group. Notably, this association seems to be independent of numerous confounding baseline demographic, anthropometric and laboratory variables, comorbidities related to the metabolic syndrome, including hypertension and diabetes, and use of relevant medications. Our findings could add further evidence to a growing body of literature indicating a strong causal association between NAFLD and CKD, independent of known confounding factors.

Since Targher et al., for the first time, showed that NAFLD in people with type 2 diabetes was associated with an increased risk of CKD [16], many large cross-sectional population and hospital-based studies have revealed similar findings in different population groups [17–20, 36–39]. In addition, a recent meta-analysis of 33 studies by Musso et al. showed that NAFLD, NASH and advanced fibrosis were associated with a higher prevalence and incidence of CKD [13]. However, most of the studies were cross-sectional, and there is only a paucity of longitudinal cohort studies with sufficient follow-up duration, all of which used ultrasonography to diagnose NAFLD [16, 21–24]. Furthermore, in studies that have investigated the association between histologically defined NAFLD severity and kidney outcomes, some have reported that NASH was associated with poorer kidney outcomes [18, 40, 41], whereas another study reported that liver fibrosis, but not NASH, was associated with microalbuminuria [42], indicating that results have been inconsistent. More recently, Mantovani et al. also showed similar findings in a meta-analysis of 13 observational studies involving over one million individuals but none of the studies used TE to assess fibrotic burden [14].

Most diagnoses of NAFLD are established with radiological imaging, such as ultrasonography, by the presence of more

Table 4 HRs for 25% decrease in eGFR by TE-defined fibrosis

TE-defined fibrosis	Model 1[a]		Model 2[b]		Model 3[c]	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Values as continuous variables						
LS, per 1 kPa	1.05 (1.03, 1.06)	<0.001	1.04 (1.03, 1.06)	<0.001	1.04 (1.03, 1.06)	<0.001
Values as categorical variables						
F0 (<5.5 kPa)	Reference		Reference		Reference	
F1/F2 (5.5–9.4 kPa)	1.39 (1.02, 1.89)	0.036	1.52 (1.11, 2.08)	0.010	1.43 (0.97, 2.10)	0.067
F3/F4 (≥9.5 kPa)	3.08 (2.05, 4.63)	<0.001	3.14 (2.05, 4.79)	<0.001	3.22 (1.96, 5.28)	<0.001

[a] Model 1: unadjusted model

[b] Model 2: adjusted for age, sex and BMI

[c] Model 3: Model 2, with additional adjustments for baseline eGFR, fasting glucose, LDL-cholesterol, GGT, AST, ALT, systolic BP and use of antihypertensive, glucose-lowering and lipid-lowering agents

than 5% hepatic fat accumulation, after exclusion of potential causes of fatty liver diseases such as alcohol, virus, drugs or autoimmunity [43]. However, one of the many limitations of ultrasonography is that early stages of steatosis cannot be differentiated, and it is not until morphological changes of the liver have occurred that progression of fibrosis to advanced stages or cirrhosis can be identified [44]. In contrast to conventional ultrasound, TE has the ability to detect both liver steatosis and fibrosis simultaneously with high reproducibility and safety, with validations done in different populations [28, 29, 45]. Due to these advantages, TE is increasingly being used in large-scale epidemiological studies [29, 46]. Our study utilised this relatively safe, accurate and novel diagnostic tool to not only identify individuals with NAFLD but also examine how differing fibrosis grades affect long-term kidney outcomes.

To date, there is a paucity of studies that have looked into the association between TE measurements and kidney outcomes. Both Mikolasevic et al. (n = 62) and Qin et al. (n = 1415) showed that the steatotic and fibrotic burdens assessed by TE were associated with a higher prevalence of CKD [19, 20]. In another Hong Kong cohort study of individuals with type 2 diabetes (n = 1763), Yeung et al. demonstrated that advanced liver fibrosis measured by TE was independently associated with a higher risk of albuminuria [17]. It is important to note that all of these studies were cross-sectional in nature. To our knowledge, no studies to date have assessed the longitudinal association between steatotic and fibrotic burdens measured by TE and long-term kidney outcomes with the aim of investigating the potential causal relationship between NAFLD and CKD. Our cohort is the first study with sufficient sample size and follow-up data to indicate that advanced liver fibrosis measured by TE independently predicts CKD development in individuals with NAFLD.

The notion that advanced fibrosis of the liver may be associated with decreased kidney function was first posited by Targher et al., where the presence of histologically defined NASH and higher severity of NASH histology was associated with decreased kidney function independently of several potential confounding factors [18]. Although proinflammatory and profibrogenic cytokines, such as IL-6, fibroblast growth factor-21 and TGF-β, have been speculated to drive the progression of both NAFLD and CKD disease processes, the exact pathophysiological mechanisms behind the link between the two diseases have yet to be elucidated [47]. Although histological confirmation by liver biopsy, considered the gold standard in defining NAFLD severity, would further elucidate this relationship, liver biopsy is an invasive diagnostic modality not without risks, and is not feasible to perform in a large cohort of individuals. To further support our findings, we found that the FAST score, a recently proposed, well-validated score that allows for identification of individuals with progressive NASH [34], was also associated with adverse kidney outcomes. Given the findings of our study, TE could be considered as an alternative, non-invasive method by which to assess fibrosis severity and the risk of future kidney function decline in individuals with NAFLD without known CKD.

We are aware of several limitations of our study, which remain unresolved. First, due to the retrospective nature of the study, the introduction of potential selection bias by recruiting only individuals with available TE results, without consecutive sampling, should be kept in mind in appropriate interpretation. In addition, risk assessment was only performed once, due to the fact that most participants received a TE examination only once during the entire study period (n = 5008, 83.7%). Future studies could look into the effects of changes in steatotic and fibrotic burdens defined by TE on long-term kidney outcomes. Second, baseline and follow-up proteinuria measurements were only done by the semi-quantitative dipstick method. Given that 24 h urine samples or spot measurements of urine protein or albumin/creatinine ratio are considered more accurate than the dipstick test [48], precise quantification of proteinuria could have further supported the findings of this study. Third, considering that there are numerous important known risk factors in the development of CKD such as proteinuria or HbA_{1c} levels [48], there is a strong possibility of residual confounding due to the lack of adjustments for these unmeasured confounders. Although we made adjustments for potential confounders that included important demographic, anthropometric and laboratory variables related to the metabolic syndrome, complex interactions among these factors may make the findings of this study difficult to interpret. Fourth, although we demonstrated a significant relationship between the degree of fibrosis and risk of 25% decline in eGFR, a larger number of outcome events for incident CKD would have further strengthened the validity of this study. Fifth, our findings may not be generalisable to populations outside of South Korea, given that social factors, environmental exposures and the metabolic syndrome-related chronic disease burdens may be distinct from other countries. Finally, considering that estimates of body fat distribution are important determinants of impaired metabolic health, NAFLD, fibrosis and incident CKD [49], measurements of waist and hip circumferences could have further validated the findings of our study.

In conclusion, in this large cohort of individuals with NAFLD without baseline CKD, advanced fibrosis of the liver measured by TE was significantly associated with a higher risk of incident CKD and kidney function decline. The

findings of our study suggest that the fibrotic burden of NAFLD may play a potential role in CKD development. TE may be a useful tool in identifying individuals with NAFLD at a high risk of developing adverse long-term kidney outcomes.

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Data availability The data that support the findings of this study are available from the corresponding authors upon reasonable request.

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Authors' relationships and activities SUK has served as an advisory committee member for Gilead Sciences, Bayer, Eisai and Novo Nordisk and is a speaker for Gilead Sciences, GSK, Bayer, Eisai, AbbVie, EchoSens, MSD, Eisai, Otsuka and Bristol-Myers Squibb. SUK has also received a research grant from AbbVie and Bristol-Myers Squibb. The other authors declare that there are no relationships or activities that might bias, or be perceived to bias, their work.

Contribution statement CYJ conceived the idea, designed the study, developed this further with SUK and BSK, and performed the majority of data analysis. GWR, HWK and SHA supervised the study. All authors contributed to the interpretation of results and writing of the manuscript and approved the final version. SUK and BSK are the guarantors of this work and accept full responsibility for the work; had access to the data, integrity and accuracy of the data analysis; and controlled the decision to publish.

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