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Risk Stratification of Chronic Kidney Disease in Adults Using Noninvasive Fibrosis Tests Based on the American Diabetes Association Algorithm

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ABSTRACT

Aims: Although the American Diabetes Association (ADA) recently established a diagnostic algorithm for the early detection of liver fibrosis among high-risk individuals, its implications for chronic kidney disease (CKD) risk stratification remain unclear. We investigated whether the ADA diagnostic algorithm can effectively stratify CKD risk in individuals at risk of cirrhosis.

Materials and Methods: This retrospective cohort study included 9264 adults without pre-existing CKD who underwent vibration-controlled transient elastography from April 2006 to October 2018. Participants were categorized into three groups: (1) no metabolic criteria; (2) low-risk (FIB-4 < 1.3 or 1.3–2.67 with liver stiffness [LS] < 8 kPa) and (3) high risk (FIB-4 > 2.67, or 1.3–2.67 with LS ≥ 8 kPa). The primary outcome was incident CKD, defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m² or proteinuria (≥ 1+) on two consecutive tests. Secondary outcomes included ≥ 25% eGFR decline on two visits and 3- and 5-year risk of CKD.

Results: During a mean follow-up of 3.7 years, 440 (4.7%) participants developed incident CKD. When stratified by the ADA algorithm, multivariable Cox models revealed a 1.52-fold (95% confidence interval [CI], 1.09–2.13) higher risk of incident CKD in the high-risk group than those with no metabolic abnormalities. The high-risk group also had a 2.30-fold higher risk (95% CI, 1.83–2.90) of a 25% eGFR decline (mean follow-up 3.5 years) than those with no metabolic abnormalities.

Conclusions: The two-step ADA algorithm can effectively stratify CKD risk in individuals at high risk of future cirrhosis.

1 | Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), previously termed nonalcoholic fatty liver disease (NAFLD), encompasses a broad spectrum of liver injury, beginning with simple steatosis and potentially progressing to metabolic dysfunction-associated steatohepatitis, severe liver fibrosis and cirrhosis [1–4]. Among these conditions, liver

fibrosis is not only a key driver of liver-related morbidity and mortality [5, 6], but is also significantly associated with the development of chronic kidney disease (CKD) [7, 8]. However, although MASLD and CKD frequently coexist as manifestations of systemic metabolic dysfunction, they represent distinct pathophysiological processes rather than strictly parallel disease trajectories. Despite this well-established association, awareness of MASLD and its related health risks remains

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low among both at-risk individuals and healthcare providers. Consequently, MASLD is frequently underrecognised and inadequately managed, leading to missed opportunities for timely intervention [9].

Consequently, to guide healthcare professionals in preventing liver disease among individuals with prediabetes, type 2 diabetes (T2D), or obesity with cardiovascular risk factors, the American Diabetes Association (ADA) recently developed a screening algorithm for individuals at a high risk of future cirrhosis [9]. This pathway recommends the Fibrosis-4 index (FIB-4) as an initial, widely accessible, low-cost screening tool to estimate the likelihood of advanced hepatic fibrosis. Although a FIB-4 score <1.3 reliably excludes advanced fibrosis, those with intermediate or high FIB-4 values are referred for vibration-controlled transient elastography (VCTE) for improved risk stratification. However, despite their proven utility in predicting hepatic fibrosis progression and liver-related outcomes, these clinical care pathways have not been evaluated for their ability to stratify kidney-related risks.

Although individuals with prediabetes and T2D are already at increased risk of developing CKD, the development of MASLD, which is also a significant risk factor for CKD [7, 8, 10–15], may further increase the risk of kidney disease. Prior research, including our own work, has indicated that elevated liver stiffness (LS) on VCTE ($LS \geq 9.5$ kPa) and advanced composite indices such as the Agile 3+ and Agile 4 scores can help predict CKD risk [14, 15]. However, these approaches use different LS thresholds which limit their generalizability, and multicomponent scores such as Agile 3+ and Agile 4 may be too complex for routine implementation in primary care settings [16]. Furthermore, although the ADA algorithm recommends referral of individuals with $FIB-4 > 2.67$ and/or $LS \geq 8$ kPa to hepatologists for the assessment of at-risk metabolic dysfunction-associated steatohepatitis (MASH) or cirrhosis, whether this high-risk category should also prompt referral to nephrologists for intensified CKD evaluation and surveillance remains unknown.

Given that the association between liver fibrosis and CKD risk is already well-recognized, the objective of this study was to assess whether the recently developed ADA screening algorithm, which incorporates both FIB-4 and VCTE, could more effectively stratify CKD risk in individuals at high risk of future cirrhosis. By evaluating this streamlined approach, we aimed to determine the potential utility of the ADA algorithm in directing clinical attention and intensified surveillance toward those at the highest risk of kidney outcomes.

2 | Materials and Methods

2.1 | Study Population

This study cohort, defined as V-LINK 2025_v1.0_YUHS_SC_MASLD and YUHS_GN_MASLD, is from the VCTE-based Liver Fibrosis Investigation Network (V-LINK), which was established in 2025 as a multicentre, longitudinal, retrospective cohort designed to evaluate liver fibrosis using VCTE across a broad spectrum of chronic liver diseases. These

include MASLD, chronic hepatitis B and C, autoimmune hepatitis and alcohol-related liver disease. The primary aim of the V-LINK cohort is to investigate the diagnostic and prognostic utility of noninvasive tests, particularly VCTE, in liver fibrosis assessment. The cohort is regularly updated, either through scheduled follow-up for outcome ascertainment or on a proposal-driven basis, in accordance with investigator-initiated research needs.

This study included adults without pre-existing CKD who underwent VCTE between April 2006 and October 2018. Participants were excluded if they met any of the following criteria: (1) VCTE assessment failure or unreliable LS values; (2) age <18 years; (3) history of CKD, end-stage kidney disease (ESKD), or kidney transplantation; (4) baseline estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m²; (5) unknown baseline eGFR; (6) baseline proteinuria; (7) baseline serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >200 U/L [17]; (8) missing baseline platelet count; (9) missing baseline hepatitis B surface antigen (HBsAg) or anti-hepatitis C virus antibody (anti-HCV Ab) data; (10) HBsAg or anti-HCV Ab (+); (11) history of malignancy; and (12) follow-up period <3 months (Figure S1). Therefore, inclusion for study enrolment required a baseline eGFR ≥ 60 mL/min/1.73m² and the absence of pre-existing CKD, ESKD, kidney transplantation, or proteinuria. Participants were also required to have available FIB-4 data, negative serology for viral hepatitis, no history of malignancy and serum AST and ALT levels ≤ 200 U/L.

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 (IRB number: 4-2023-0082). The requirement for informed consent was waived by the Institutional Review Board because of the retrospective study design.

2.2 | Data Collection and Follow-Up

Demographic, anthropometric, medication and laboratory data were obtained from the electronic medical records at the time of the initial VCTE assessment, which served as the baseline visit. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg, a diastolic blood pressure ≥ 90 mmHg, or the use of antihypertensive medications. T2D was defined as fasting plasma glucose level ≥ 126 mg/dL or the use of glucose-lowering medications. Prediabetes was defined as fasting plasma glucose level of 100–125 mg/dL, or a haemoglobin A1c 5.7%–6.4%. Obesity with at least one cardiovascular risk factor was defined as BMI ≥ 25 kg/m² and the presence of at least one of the following: (1) blood pressure $\geq 130/85$ mmHg or treatment with antihypertensive agents; (2) serum triglycerides ≥ 150 mg/dL or use of lipid-lowering therapy; or (3) high-density lipoprotein cholesterol <40 mg/dL in men or <50 mg/dL in women, or use of lipid-lowering agents. Serum creatinine was quantified using a colorimetric Jaffe method on the Beckman Coulter system (Brea, CA, USA). To ensure analytical accuracy, the assay was calibrated to an isotope-dilution mass spectrometry-traceable

reference standard. Estimated glomerular filtration rate was calculated using the CKD Epidemiology Collaboration creatinine equation [18]. During the study period, serum AST and ALT levels used for FIB-4 calculation were measured using an International Federation of Clinical Chemistry and Laboratory Medicine–traceable enzymatic method on a Hitachi 747 (Hitachi, Tokyo, Japan) analyser with SICDIA reagents (Shinyang Chemical Co. Seoul, South Korea) without P5P supplementation, maintaining high analytical reliability with 2018-based between-run coefficients of variation of 1.69% and 1.83%, respectively.

Participants attended outpatient clinic visits at intervals of 6–24 months, during which repeat anthropometric measurements and laboratory testing, including blood chemistry profiles and urinalysis—were performed. Participants were followed from enrolment until the occurrence of incident CKD or new-onset proteinuria, loss to follow-up, or the end of the study period, whichever occurred first. Loss to follow-up was treated as a censoring event.

2.3 | Clinical Assessment

As part of routine practice, VCTE was performed in individuals with chronic liver disease, those considered at increased risk, those undergoing evaluation for possible liver disease, including MASLD. The examination was performed using either a FibroScan 502 or 502 Touch device (Echosens, Paris, France), which assesses hepatic tissue elasticity through combined mechanical and ultrasound wave propagation. All measurements were obtained at enrolment by trained and experienced nursing staff. VCTE provides two quantitative parameters: LS (expressed in kilopascals), which reflects the degree of hepatic fibrosis, and the controlled attenuation parameter (reported in decibels per meter), reflecting hepatic steatosis. FIB-4 was calculated as follows: $(\text{age [years]} \times \text{AST [U/L]}) / (\text{platelet count [10}^9/\text{L]} \times \sqrt{\text{ALT [U/L]}})$ [19].

2.4 | Two-Step Approaches Using the ADA Guidelines

The ADA endorses a two-tiered fibrosis risk stratification strategy that incorporates initial FIB-4 assessment followed by VCTE in those at increased risk for advanced fibrosis (Figure S1) [9]. Under this framework, individuals at highest risk of future cirrhosis, defined as those with prediabetes, T2D, or obesity accompanied by at least one cardiovascular risk factor, undergo FIB-4 calculation as the first screening step. Individuals with $\text{FIB-4} < 1.3$ are categorized as low-risk. Those with $\text{FIB-4} \geq 1.3$ are considered at increased risk and proceed to second-tier testing with VCTE. High-risk individuals with $\text{FIB-4} > 2.67$ bypass further noninvasive testing and should be referred directly to a liver specialist for comprehensive evaluation and management. Among participants with intermediate FIB-4 values (1.3–2.67), a $\text{LS} \geq 8 \text{ kPa}$ on VCTE similarly warrants referral to a liver specialist. In this study, participants were classified into three risk groups: (1) no metabolic criteria (individuals without prediabetes, T2D, or obesity

accompanied by at least one cardiovascular risk factor); (2) low-risk ($\text{FIB-4} < 1.3$ or $1.3\text{--}2.67$ with $\text{LS} < 8 \text{ kPa}$) and (3) high risk ($\text{FIB-4} > 2.67$ or $\text{FIB-4} 1.3\text{--}2.67$ with $\text{LS} \geq 8 \text{ kPa}$).

2.5 | Diagnosis of MASLD

MASLD was defined by the presence of steatotic liver disease (SLD) detected either on abdominal ultrasound or by a CAP value $\geq 275 \text{ dB/m}$ on VCTE [20], together with at least one cardiometabolic risk factor. These risk factors included: (1) $\text{BMI} \geq 23 \text{ kg/m}^2$ or waist circumference $\geq 90 \text{ cm}$ in men or $\geq 80 \text{ cm}$ in women; (2) fasting plasma glucose $\geq 100 \text{ mg/dL}$, a diagnosis of T2D, or use of antidiabetic medications; (3) blood pressure $\geq 130/85 \text{ mmHg}$ or treatment with antihypertensive agents; (4) serum triglycerides $\geq 150 \text{ mg/dL}$ or use of lipid-lowering therapy; or (5) high-density lipoprotein cholesterol $< 40 \text{ mg/dL}$ in men or $< 50 \text{ mg/dL}$ in women, or use of lipid-lowering agents [21]. Individuals with excessive alcohol consumption ($\geq 210 \text{ g/week}$ for men or $\geq 140 \text{ g/week}$ for women) or other concurrent chronic liver diseases were excluded from meeting the MASLD criteria.

2.6 | Kidney Outcomes

The primary outcome was the development of incident CKD, defined as an $\text{eGFR} < 60 \text{ mL/min/1.73m}^2$ or proteinuria ($\geq 1+$ on dipstick testing) on two consecutive measurements during follow-up. As part of this analysis, the 3- and 5-year cumulative risks of incident CKD were also calculated. The secondary outcome was a 25% decline in eGFR documented on two consecutive visits.

2.7 | Statistical Analysis

Continuous variables are expressed as means and standard deviations or as medians and interquartile ranges (IQRs). Categorical variables are expressed as numbers and percentages. Normality of data distribution was assessed using the Shapiro–Wilk test. Trends across risk categories were examined using p values for trend. For categorical variables, the chi-square test for trend was applied. Intergroup comparisons (no metabolic criteria vs. low-risk + high-risk groups, and low-risk vs. high-risk groups) were performed using the Wilcoxon rank-sum test for continuous variables and Pearson's chi-square test for categorical variables. Cumulative incidences of incident CKD, 25% decline in eGFR, 3- and 5-year risk of CKD were estimated by Kaplan–Meier analyses and log-rank tests. Cox proportional hazards models were developed to determine the association between risk group and kidney outcomes. Proportional hazards assumptions were confirmed using Schoenfeld residuals. Data are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). Three models with increasing degrees of adjustment were used to account for potential baseline confounding factors. Model 1 was unadjusted; model 2 included age, sex and BMI; model 3 was further adjusted for hypertension, use of dyslipidaemia agents, baseline eGFR, fasting glucose, gamma-glutamyl transferase, total cholesterol and triglycerides. If participants underwent multiple transient

elastography examinations during the study period, data from the first examination were used for statistical analysis.

Several sensitivity analyses were additionally performed to test the robustness of the findings. First, obesity was defined using alternative BMI thresholds (≥ 23 and ≥ 27 kg/m²) to assess the effect of different obesity definitions on the observed associations. Second, age-adjusted FIB-4 cutoffs were applied to account for the known influence of age on FIB-4 interpretation. Finally, FIB-4 was modelled both as a continuous variable and as a categorical variable based on established clinical thresholds (< 1.3 , 1.3 – 2.67 and ≥ 2.67) to assess the consistency of results across different analytical specifications.

To assess whether the association between the high-risk group and the primary outcome could be affected by medication use and diabetes status, effect modification was additionally tested in prespecified subgroups according to the use of angiotensin-converting enzyme inhibitor or angiotensin II receptor blockers (ACEi/ARBs; no vs. yes), diabetes status (no vs. yes), use of anti-diabetic agents (no vs. yes) and use of anti-dyslipidaemic agents (no vs. yes).

To account for missing data, we used multiple imputation under the assumption that the data were missing at random (Table S1). The MICE (multivariate imputation by chained equations) method in STATA was employed to generate five complete datasets. The imputation model included the variables listed in Table S1 to improve the estimate precision. Each imputed dataset was then used in the multivariable Cox regression analyses. Final variable estimates were averaged across the five models, and standard errors were combined using Rubin's rules. Statistical significance was defined as $p < 0.05$. All analyses were conducted using STATA version 19 (STATA Corp., College Station, TX, USA).

3 | Results

3.1 | Baseline Characteristics

After excluding 49 897 participants according to the exclusion criteria, a total of 9264 participants were enrolled in this study (Figure S2), and their baseline characteristics are presented in Table 1. The mean age was 52.5 years, and 5064 (54.7%) participants were male. A total of 2904 (31.3%) and 1901 (20.5%) participants had hypertension and T2D, respectively. In addition, 1863 (20.1%) and 4442 (47.9%) had prediabetes and obesity with at least 1 cardiovascular factor. Moreover, 1794 (19.4%), 1034 (12.4%) and 1582 (19.7%) participants were using anti-hypertensive, anti-diabetic and anti-dyslipidaemic agents, respectively. The mean baseline eGFR was 97.2 mL/min/1.73 m². The mean LS and median CAP values were 5.8 kPa and 240 dB/m, respectively.

When participants were divided into three groups according to ADA risk stratification (no metabolic criteria vs. low-risk vs. high-risk), the proportion of participants with hypertension and T2D was higher (all $p < 0.001$) in the low-risk and high-risk groups. The proportion of participants taking anti-hypertensive, anti-diabetic and anti-dyslipidaemic agents also increased across the higher risk groups. A significant downward trend was

observed for platelet count, total cholesterol, low-density lipoprotein cholesterol and eGFR, whereas an upward trend was observed for fasting glucose, AST, ALT and CAP across higher risk groups (all $p_{\text{trend}} < 0.005$; Table 1).

When participants were divided into two groups according to the presence of MASLD, 3240 (35.0%) participants had MASLD. The proportions of participants with hypertension, T2D and obesity with at least one cardiovascular risk factor were significantly higher among those with MASLD. The proportion of participants taking anti-hypertensive, anti-diabetic and anti-dyslipidaemic agents was also significantly higher in the MASLD group. Baseline eGFR was lower and LS was higher in those with MASLD (Table S2).

3.2 | Unadjusted Association Between Risk Groups and Kidney Outcomes

During 34 009 person-years of follow-up (mean follow-up 3.7 years), 440 participants developed incident CKD (1.3 per 100 person-years [95% CI, 1.2–1.4]). Among these cases, 196 were identified by eGFR criteria alone, 165 by proteinuria criteria alone and 79 by both criteria. When participants were grouped according to ADA risk groups (no metabolic criteria vs. low-risk vs. high-risk), incident CKD occurred in 69 (0.7 per 100 person-years), 241 (1.2 per 100 person-years) and 130 (3.6 per 100 person-years) participants in the no metabolic criteria, low-risk and high-risk group, respectively (Table 2, Figure 1A).

For 25% decline in eGFR, during 32 396 person-years of follow-up (mean follow-up of 3.5 years), 968 participants developed a 25% decline in eGFR (3.0 per 100 person-years [95% CI, 2.8–3.2]). When participants were grouped into ADA risk groups, 25% decline in eGFR occurred in 159 (1.7 per 100 person-years), 539 (2.7 per 100 person-years) and 270 (8.4 per 100 person-years) participants in the no metabolic criteria, low-risk and high-risk group, respectively. The cumulative incidences of both incident CKD and a 25% decline in eGFR were consistently higher in the higher risk groups (all $p < 0.001$ by log-rank test; Table 2, Figure 1B).

3.3 | Adjusted Association Between Risk Groups and Kidney Outcomes

The association between risk groups and kidney outcomes was further evaluated using multivariable Cox proportional hazards models (Table 3). When participants were grouped into ADA risk groups, the high risk group was associated with a significantly higher risk of both incident CKD (unadjusted HR 4.67 [95% CI, 3.49–6.26]) and 25% decline in eGFR (unadjusted HR 4.86 [95% CI, 4.00–5.92]) than the no metabolic criteria group. These associations remained significant after adjustment for potential confounding factors. In the fully adjusted model, the high-risk group was associated with a significantly higher risk of both incident CKD (adjusted HR 1.52 [95% CI, 1.09–2.13]) and 25% decline in eGFR (adjusted HR 2.30 [95% CI, 1.83–2.90]) than that of the no metabolic criteria group. Using the low risk group as the reference, the high risk group was associated with a significantly higher risk of both incident CKD (adjusted HR 1.72

TABLE 1 | Baseline characteristics of participants according to ADA-defined risk groups.

Variables	Total (<i>n</i> = 9264)	ADA-defined risk groups			<i>p</i> _{trend}
		No metabolic criteria (<i>n</i> = 2690, 29.0%)	Low-risk (<i>n</i> = 5730, 61.9%)	High-risk (<i>n</i> = 844, 9.1%)	
Demographic and anthropometric data					
Age, years	52.5 (12.8)	48.6 (13.2)*	52.7 (11.9)**	62.8 (10.6)	< 0.001
Male, <i>n</i> (%)	5064 (54.7)	1260 (46.8)*	3425 (59.8)**	379 (44.9)	< 0.001
Systolic blood pressure, mmHg	122.9 (15.6)	119.0 (14.8)*	124.7 (15.3)**	122.3 (16.9)	< 0.001
Body mass index, kg/m ²	24.1 (3.3)	22.2 (2.2)*	25.3 (3.4)**	25.0 (3.5)	< 0.001
Hypertension, <i>n</i> (%)	2904 (31.3)	414 (15.4)*	1979 (34.5)**	511 (60.5)	< 0.001
Diabetes mellitus, <i>n</i> (%)	1901 (20.5)	0*	1487 (26.0)**	414 (49.1)	< 0.001
Pre-diabetes mellitus, <i>n</i> (%)	2114 (22.8)	0*	1859 (32.4)	255 (30.2)	< 0.001
Obesity with at least 1 CV risk factor, <i>n</i> (%)	4442 (47.9)	0*	3936 (68.7)**	506 (60.0)	< 0.001
MASLD, <i>n</i> (%)	3240 (35.0)	622 (23.1)*	2229 (38.9)**	389 (46.1)	< 0.001
Medication					
Anti-hypertensive agents, <i>n</i> (%)	1794 (19.4)	255 (9.5)*	1211 (21.1)**	328 (38.9)	< 0.001
ACEi/ARBs	663 (7.2)	80 (3.0)*	496 (8.7)	87 (10.3)	< 0.001
β-blockers	660 (7.1)	59 (2.2)*	511 (8.9)	90 (10.7)	< 0.001
Calcium channel blockers	645 (7.0)	55 (2.0)*	499 (8.7)**	91 (10.8)	< 0.001
Mineralocorticoid receptor antagonists	81 (0.9)	16 (0.6)*	41 (0.7)**	24 (2.8)	< 0.001
Anti-diabetic agents, <i>n</i> (%)	1034 (12.4)	0*	809 (15.5)**	225 (29.3)	< 0.001
Biguanides	554 (6.0)	0*	483 (8.4)	71 (8.4)	< 0.001
Dipeptidyl peptidase-4 inhibitors	318 (3.4)	0*	274 (4.8)	44 (5.2)	< 0.001
Sulfonylureas	208 (2.2)	0*	176 (3.1)	32 (3.8)	< 0.001
Thiazolidinediones	108 (1.2)	0*	89 (1.6)	19 (2.3)	< 0.001
Sodium-glucose cotransporter 2 inhibitors	109 (1.2)	0*	96 (1.7)	13 (1.5)	< 0.001
Glucagon-like peptide-1 agonists	5 (0.0)	0*	4 (0.1)	1 (0.1)	0.700
Insulin	207 (2.2)	0*	181 (3.2)	26 (3.1)	< 0.001
Anti-dyslipidaemic agents, <i>n</i> (%)	1582 (19.7)	214 (9.2)*	1113 (22.2)**	255 (36.4)	< 0.001
Laboratory data					
Platelet count, × 10 ⁹ /L	233.9 (64.7)	237.6 (62.3)*	243.6 (58.0)**	156.7 (64.5)	< 0.001

(Continues)

TABLE 1 | (Continued)

Variables	Total (n = 9264)	ADA-defined risk groups			<i>p</i> _{trend}
		No metabolic criteria (n = 2690, 29.0%)	Low-risk (n = 5730, 61.9%)	High-risk (n = 844, 9.1%)	
Fasting glucose, mg/dL	106.6 (30.0)	92.7 (15.0)*	111.4 (31.9)**	118.8 (36.2)	<0.001
HbA1c, %	6.2 (1.1)	5.4 (0.4)	6.2 (1.2)	6.6 (1.3)	<0.001
Total cholesterol, mg/dL	181.8 (40.9)	184.1 (38.1)*	183.8 (41.0)**	166.2 (43.8)	<0.001
HDL cholesterol, mg/dL	50.6 (13.6)	55.1 (14.3)*	49.1 (12.4)**	47.0 (14.9)	<0.001
LDL cholesterol, mg/dL	107.8 (34.6)	109.4 (31.1)*	109.7 (35.6)**	93.3 (34.4)	<0.001
Triglycerides, mg/dL	132.2 (94.0)	107.9 (71.4)*	146.9 (103.1)**	119.5 (80.4)	<0.001
GGT, U/L	30 (18–58)	23 (15–48)*	30 (19–55)**	54 (30–116)	<0.001
AST, U/L	29.5 (18.2)	26.5 (16.4)*	27.6 (12.6)**	52.3 (33.8)	<0.001
ALT, U/L	30.0 (23.2)	24.7 (19.4)*	31.3 (22.9)**	38.0 (31.0)	<0.001
Creatinine, mg/dL	0.79 (0.18)	0.77 (0.17)*	0.81 (0.18)**	0.76 (0.17)	<0.001
eGFR, mL/min/1.73m ²	97.2 (14.3)	100.7 (14.8)*	96.4 (13.7)**	91.0 (13.7)	<0.001
FIB-4	1.5 (1.5)	1.3 (1.3)	1.2 (0.5)	4.2 (3.0)	<0.001
VCTE data					
LS, kPa	5.8 (6.3)	5.0 (4.2)*	4.7 (2.1)**	16.1 (15.5)	<0.001
CAP, dB/m	240 (212–277)	223 (201–248)*	249 (219–287)	252 (216–287)	<0.001
Follow-up duration, months	42.2 (30.4)	41.9 (30.5)	41.8 (29.8)	46.0 (34.0)	<0.001

Note: Continuous variables are expressed as median (interquartile range) or mean (standard deviation), and categorical variables are expressed as number (percentage). As the summary statistics are for the complete dataset, numbers for categorical variables may not add up. * denotes $p < 0.05$ for comparison between no metabolic criteria and the combined low-risk and high-risk group, and ** denotes $p < 0.05$ for comparison between low-risk and high-risk groups. Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ADA, American Diabetes Association; ALT, alanine aminotransferase; ARB, angiotensin II receptor blocker; AST, aspartate aminotransferase; CAP, controlled attenuated parameter; CV, cardiovascular; eGFR, estimated glomerular filtration rate; FIB-4, fibrosis-4; GGT, gamma-glutamyltransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LS, liver stiffness; MASLD, metabolic dysfunction-associated steatotic liver disease; VCTE, vibration-controlled transient elastography.

[95% CI, 1.37–2.16]) and 25% decline in eGFR (adjusted HR 2.03 [95% CI, 1.74–2.38]) (Table S3).

3.4 | Association Between Risk Group and Risk of 3- and 5-Year CKD

For 3- and 5-year risk of CKD, 213 (1.0 per 100 person-years [95% CI, 0.8–1.1]) and 318 (1.1 per 100 person-years [95% CI, 1.0–1.3]) participants developed CKD by 3- and 5-years, respectively. When stratified by ADA risk, the high risk group had the highest risk of developing CKD at both 3- (3.3 per 100 person-years [95% CI, 2.6–4.2]) and 5-year (3.3 per 100 person-years [95% CI, 2.7–4.1]) (all $p < 0.001$ by log-rank test; Table 2, Figure 1C,D).

This association was further assessed using multivariable Cox proportional hazards models (Table 3). When participants were grouped into ADA risk groups, the high risk group did not have a statistically significant higher risk of developing CKD at 3 or 5 years than the no metabolic criteria group.

When the low-risk group was used as the reference, the high risk group was associated with a significantly higher risk of

both incident CKD (adjusted HR 1.98 [95% CI, 1.44–2.72]) and a 25% decline in eGFR (adjusted HR 1.80 [95% CI, 1.38–2.34]) (Table S3).

3.5 | Association Between Risk Groups and Risk of Kidney Outcomes According to Different Obesity Definitions

When obesity was defined as BMI ≥ 23 kg/m², the high risk group was associated with a significantly higher risk of 25% decline in eGFR (adjusted HR 2.16 [95% CI, 1.68–2.76]), compared with the no metabolic criteria group. Although the high risk group also appeared to have higher risks of incident CKD, 3- and 5-year CKD, these associations were not statistically significant (Table S4).

When obesity was defined as BMI ≥ 27 kg/m², the high risk group was associated with a significantly higher risk of both incident CKD (adjusted HR 1.56 [95% CI, 1.13–2.15]) and a 25% decline in eGFR (adjusted HR 2.19 [95% CI, 1.76–2.72]), compared with the no metabolic criteria group (Table S5).

TABLE 2 | Kidney outcomes according to ADA-defined risk groups.

Outcome	Total (n = 9264)	No metabolic criteria (n = 2690, 29.0%)	Low-risk (n = 5730, 61.9%)	High-risk (n = 844, 9.1%)	p ^a
Incident CKD					
Person-years	34009.0	9638.0	20713.0	3658.1	
Events, n (%)	440 (4.7)	69 (2.6)	241 (4.2)	130 (15.4)	
Incidence rate, per 100 person-years	1.3 (1.2–1.4)	0.7 (0.6–0.9)	1.2 (1.0–1.3)	3.6 (3.0–4.2)	< 0.001
25% decline in eGFR					
Person-years	32396.1	9324.4	19859.5	3212.2	
Events, n (%)	968 (10.4)	159 (5.9)	539 (9.4)	270 (32.0)	
Incidence rate, per 100 person-years	3.0 (2.8–3.2)	1.7 (1.5–2.0)	2.7 (2.5–3.0)	8.4 (7.5–9.5)	< 0.001
3-year CKD					
Person-years	22218.1	6304.0	13821.8	2092.4	
Events, n (%)	213 (2.3)	32 (1.2)	112 (2.0)	69 (8.2)	
Incidence rate, per 100 person-years	1.0 (0.8–1.1)	0.5 (0.4–0.7)	0.8 (0.7–1.0)	3.3 (2.6–4.2)	< 0.001
5-year CKD					
Person-years	28387.3	8034.4	17475.0	2877.9	
Events, n (%)	318 (3.4)	52 (1.9)	170 (3.0)	96 (11.4)	
Incidence rate, per 100 person-years	1.1 (1.0–1.3)	0.6 (0.5–0.8)	1.0 (0.8–1.1)	3.3 (2.7–4.1)	< 0.001

Abbreviations: ADA, American Diabetes Association; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

^ap values were calculated using a global log-rank test comparing all three risk groups.

3.6 | Association Between Risk Groups and Risk of Kidney Outcomes Using Age-Adjusted FIB-4 Thresholds

When participants aged ≥ 65 years were reclassified using the age-adjusted FIB-4 threshold, the association between risk groups and risk of kidney outcomes remained significant (Table S6). The high risk group was associated with a significantly higher risk of incident CKD (adjusted HR 1.57 [95% CI, 1.12–2.20]), 25% decline in eGFR (adjusted HR 2.31 [95% CI, 1.84–2.91]) and 3-year risk of CKD (adjusted HR 1.64 [95% CI, 1.01–2.64]).

3.7 | Association Between FIB-4 and Kidney Outcomes

When the association between FIB-4 and kidney outcomes was assessed, multivariable Cox models revealed that FIB-4 in its continuous form (per 1-unit increase) was significantly associated with incident CKD (adjusted HR 1.12 [95% CI, 1.09–1.15]), a 25% decline in eGFR (adjusted HR 1.10 [95%

CI, 1.08–1.12]), 3-year (adjusted HR 1.12 [95% CI, 1.08–1.15]) and 5-year risk of CKD (adjusted HR 1.13 [95% CI, 1.09–1.16]) (Table S7). When FIB-4 was treated as a categorical variable (< 1.3 , $1.3\text{--}2.67$, and ≥ 2.67), the group with the highest fibrotic burden (FIB-4 ≥ 2.67) was associated with a significantly higher risk of incident CKD (adjusted HR 1.75 [95% CI, 1.34–2.29]), 25% decline in eGFR (adjusted HR 2.12 [95% CI, 1.76–2.55]), 3-year (adjusted HR 1.89 [95% CI, 1.28–2.79]) and 5-year risk of CKD (adjusted HR 1.78 [95% CI, 1.29–2.44]) than the group with the lowest fibrotic burden (FIB-4 < 1.3). Restricting the analysis to participants with the highest risk of future cirrhosis, defined as those with prediabetes, T2D or obesity accompanied by at least one cardiovascular risk factor yielded similar associations (Table S8).

3.8 | Subgroup Analysis

When interactions across subgroups defined by ACEi/ARB use, T2D status, use of anti-diabetic agents and use of anti-dyslipidaemic agents were tested to assess effect modification for the primary outcome, no significant interactions were found.

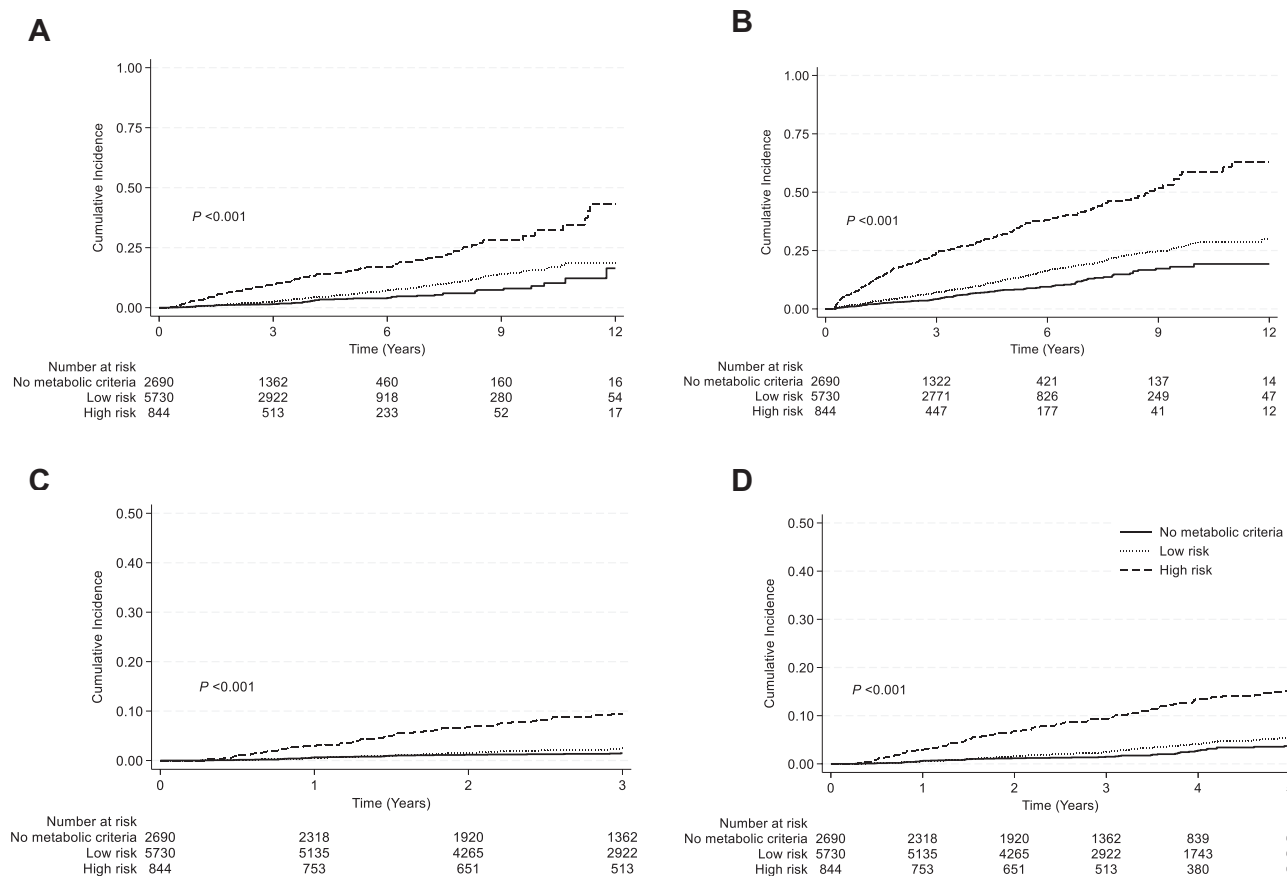


FIGURE 1 | Cumulative incidence of (A) incident CKD, (B) 25% eGFR decline, (C) 3-year risk of CKD and (D) 5-year risk of CKD according to ADA-defined risk groups. ADA, American Diabetes Association; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

This suggests that the association between the high-risk group and incident CKD risk was significant across the aforementioned subgroups (Table S9).

4 | Discussion

In this large, multicentre, longitudinal retrospective cohort study, the ADA algorithm effectively stratified CKD risk in individuals at a high risk of future cirrhosis that included individuals with prediabetes, T2D and obesity with at least 1 cardiovascular risk factor. Stratification according to ADA-defined risk groups showed that individuals with FIB-4 > 2.67 and/or LS ≥ 8 kPa had an approximately twofold higher risk of incident CKD or kidney function decline than individuals with no metabolic abnormalities. When this risk was directly compared to the low risk group, the high risk group was associated with an approximately twofold risk of both incident CKD and 25% decline in eGFR. Notably, this association was independent of potential confounding baseline demographic, anthropometric, laboratory and comorbidities related to the metabolic syndrome, such as hypertension and diabetes. The robustness of this association was further supported by sensitivity analyses, as the association between ADA risk groups and kidney outcomes remained consistent even when age-adjusted FIB-4 thresholds or alternative BMI definitions for obesity were applied. Based on these findings, the proposed

ADA risk stratification algorithm may also be useful in CKD risk stratification. Although individuals in the highest risk category could benefit from a nephrologist referral for intensified CKD evaluation and surveillance, the results of this study also suggest that it is equally important for treating physicians to emphasize intensive lifestyle modifications and pharmacological management to slow the progress of hepato-metabolic-kidney deterioration and potentially reverse early-stage organ dysfunction, particularly in those with FIB-4 > 2.67 and/or LS ≥ 8 kPa.

The results of this study align with earlier investigations examining the effect of hepatic fibrotic burden on CKD risk [13–15]. In a longitudinal cohort of 1763 individuals with T2D, advanced liver fibrosis assessed using VCTE was independently associated with a higher prevalence of parenchymal kidney injury, particularly albuminuria [13]. More recently, we also reported that fibrotic burden measured by VCTE predicts incident CKD and subsequent kidney function decline [14], and that the Agile 3+ and Agile 4 scores, which integrate fibrosis indicators with readily available clinical variables such as age, sex, diabetes status and laboratory findings, may similarly predict future CKD [15]. The present study reinforces these findings by demonstrating a significant independent association between baseline FIB-4 score and kidney outcomes across the entire cohort. Notably, this independent association persisted within high-risk subgroups, including those with prediabetes, T2D, or obesity with at least one

TABLE 3 | HRs for kidney outcomes according to ADA-defined risk groups.

Outcome	Model 1		Model 2		Model 3	
	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>
Incident CKD						
No metabolic criteria	Reference		Reference		Reference	
Low-risk	1.63 (1.25–2.13)	<0.001	1.39 (1.05–1.84)	0.021	0.88 (0.66–1.19)	0.416
High-risk	4.67 (3.49–6.26)	<0.001	2.93 (2.14–4.02)	<0.001	1.52 (1.09–2.13)	0.014
25% decline in eGFR						
No metabolic criteria	Reference		Reference		Reference	
Low-risk	1.60 (1.34–1.90)	<0.001	1.45 (1.20–1.74)	<0.001	1.13 (0.93–1.38)	0.205
High-risk	4.86 (4.00–5.92)	<0.001	3.53 (2.85–4.37)	<0.001	2.30 (1.83–2.90)	<0.001
3-year CKD						
No metabolic criteria	Reference		Reference		Reference	
Low-risk	1.59 (1.07–2.35)	0.021	1.32 (0.88–1.98)	0.182	0.78 (0.50–1.19)	0.249
High-risk	6.45 (4.24–9.81)	<0.001	3.35 (2.13–5.27)	<0.001	1.54 (0.95–2.50)	0.079
5-year CKD						
No metabolic criteria	Reference		Reference		Reference	
Low-risk	1.50 (1.10–2.05)	0.011	1.28 (0.93–1.77)	0.135	0.78 (0.56–1.10)	0.165
High-risk	4.99 (3.56–7.00)	<0.001	2.86 (1.98–4.12)	<0.001	1.41 (0.96–2.08)	0.083

Note: Model 1: unadjusted model. Model 2: adjusted for age, sex, and BMI. Model 3: model, with additional adjustments for hypertension, baseline eGFR, fasting glucose, anti-diabetic medications, anti-dyslipidaemic agents, GGT, total cholesterol, and triglycerides.
Abbreviations: ADA, American Diabetes Association; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyltransferase; HR, hazard ratio.

cardiovascular risk factor, in whom the risk of kidney outcomes was marginally higher. Furthermore, we show that applying the ADA risk stratification algorithm, which uses a stepwise FIB-4 plus VCTE-based approach, can also effectively stratify CKD risk. The findings of this study demonstrate that, compared with those without metabolic abnormalities, those with prediabetes, T2D, or obesity, and with a significant fibrotic burden measured by FIB-4 or VCTE have an approximately twofold higher risk of developing incident CKD or a 25% decline in eGFR. Although the ADA suggests that this highest risk group should be referred for management by a liver specialist, those with the highest fibrotic burdens and underlying diabetes or obesity could also benefit from early nephrology referrals and implementation of intensive lifestyle modification and pharmacological management before the development of kidney disease.

Although the recently established ADA consensus was primarily developed for targeted referral of individuals with prediabetes or T2D who are at highest risk of developing MASLD and eventual cirrhosis, whether these highest risk individuals may also benefit from a nephrologist referral for CKD evaluation and surveillance has not previously been examined. This is underscored by the finding that those categorized as being at highest risk of future cirrhosis (i.e., FIB-4 > 2.67 and/or LS ≥ 8 kPa) exhibited an approximately 1.5-fold greater likelihood of developing CKD at 3 and 5 years than those without metabolic abnormalities such as prediabetes, T2D, or obesity. Given that CKD is regarded as a coronary artery disease equivalent in

terms of all-cause mortality risk [22], and often remains clinically silent until advanced stages requiring dialysis or kidney transplantation [23], those who would otherwise be referred to a hepatologist for further assessment of at-risk MASH or cirrhosis, according to the ADA framework, could also benefit from a nephrologist referral for further CKD assessment.

Moreover, the results of this study provide a more straightforward strategy for CKD risk stratification among individuals already at elevated risk of future cirrhosis. Although the link between MASLD and CKD is well established [7, 8, 24, 25], there has been limited guidance on which specific individuals should be considered high risk and referred to nephrology, and no formal consensus currently exists. For example, we previously showed that individuals with LS ≥ 9.5 kPa on VCTE, as well as those classified as high risk by the Agile 3+ or Agile 4 scores, experienced the highest rates of CKD onset and kidney function decline [14, 15]. However, LS thresholds vary across studies [26], and the Agile 3+ and Agile 4 scores may be too complex for consistent use in primary care settings [16]. The present study streamlines this process by demonstrating that only the ADA-defined high-risk group—those with FIB-4 > 2.67 and/or LS ≥ 8 kPa—was significantly associated with CKD development and kidney function decline. Furthermore, the fact that these results remained robust regardless of the BMI criteria used or the adjustment of FIB-4 for age ≥ 65 years suggests that the algorithm could be useful and robust as a screening tool. This simplified criterion may enable more precise and efficient

nephrology referrals, ensuring that attention is directed toward those at greatest risk.

Although the precise pathophysiological mechanisms linking MASLD to kidney disease remain poorly understood, potential mechanisms underlying the association between hepatic fibrosis diagnosed using FIB-4 and VCTE and kidney disease include metabolic factors, chronic low-grade inflammation and shared genetic or environmental risk factors [24]. The proatherogenic dyslipidaemia and altered composition of small molecules, proteins and fatty acids in lipoproteins observed in individuals with metabolic syndrome may contribute to parenchymal kidney damage, oxidative stress, chronic low-grade inflammation, fibrosis and subsequent decline in kidney function [27]. Moreover, the insulin resistance frequently observed in this high-risk population may cause cellular dysfunction, particularly within hepatic microsomes. This impairment may reduce the liver's ability to synthesize vitamin D, and lower vitamin D levels have been correlated with increased histological severity in MASLD, specifically with respect to hepatic steatosis, ballooning, lobular inflammation and fibrosis [28, 29].

Furthermore, the fact that metabolic kidney disease often progresses from early functional changes to irreversible structural damage underscores the clinical relevance of our findings. Although urinary albuminuria and serum eGFR are sensitive tools for detecting early kidney function deterioration [30], they may not fully reflect the extent of underlying parenchymal damage. The present study demonstrates that the degree of liver fibrosis—as measured by FIB-4 and VCTE—could serve as a potential marker of advanced systemic metabolic disease. Consequently, identifying a high fibrotic burden in the liver may help clinicians recognize a more advanced, potentially irreversible stage of nephropathy in which structural kidney changes are already progressing, as a result of the shared pathophysiological milieu of inflammation and oxidative stress common to both MASLD and CKD [24].

This study has several limitations. First, its retrospective design raises the possibility of selection bias. Because we included only individuals with available VCTE measurements—rather than applying consecutive sampling—this may influence the interpretation of our results. Second, the study population was derived from a tertiary care setting and limited to individuals who had undergone VCTE. Because VCTE is typically indicated for patients already suspected of or at risk for liver disease, this introduces a degree of selection bias toward a higher-risk population. Although this focus aligns with the ADA algorithm's intended target population, it may limit the generalizability of the findings to a broader, unselected primary care screening population that has not undergone both FIB-4 and VCTE testing. Therefore, external validation in true primary care settings is warranted. Third, the study lacks histopathological confirmation of CKD aetiology through kidney biopsies. Consequently, differentiation among specific CKD aetiologies, such as diabetic nephropathy, hypertensive nephrosclerosis, or glomerular disease, was not possible. Although kidney biopsy-proven data are often difficult to obtain in large-scale cohorts, further studies including biopsy data could help elucidate the specific histopathological mechanisms underlying the association between liver fibrosis and kidney outcomes. Nevertheless, subgroup analyses according to diabetes status revealed that ADA-defined risk stratification predicted incident

CKD independent of baseline diabetes status, suggesting that the ADA algorithm could effectively stratify risk regardless of CKD subtypes. Fourth, the study would have been strengthened by more precise assessment of proteinuria. Both baseline and follow-up evaluations relied on semi-quantitative dipstick testing, which is less accurate than 24-h urine collections or spot urine protein/albumin-to-creatinine ratios [31]. Nevertheless, subgroup analyses according to the use of antiproteinuric medications such as ACEi and ARBs showed that the use of these medications did not significantly affect the association between ADA risk groups and kidney outcomes. Finally, because the study cohort consisted exclusively of a Korean population, the generalizability of these findings to other ethnic groups remains to be established. Given known ethnic variations in the epidemiology and clinical manifestations of both MASLD and CKD, the proposed risk-stratification approach requires external validation in diverse, multiethnic cohorts to account for differences in genetic, social and environmental metabolic risk factors.

In conclusion, this large, multicentre, longitudinal retrospective cohort study demonstrates that the two-step algorithm proposed by the ADA can effectively stratify CKD risk in individuals at high risk of future cirrhosis. These findings further support an integrated management strategy in which hepatic and renal risk assessments are aligned, and individuals identified by the ADA algorithm as having the highest likelihood of advanced fibrosis may be considered for both hepatology and nephrology referrals. However, further prospective studies are warranted to validate these associations and determine whether integrated risk stratification approaches, as well as monitoring of dynamic risk changes over time lead to improved clinical outcomes.

Author Contributions

C.-Y.J. conceived the idea, designed the study, further developed the study with S.U.K. and performed the majority of data analysis. H.W.L., J.I.L., and H.A.L. supervised the study. All authors contributed to the interpretation of results and writing of the manuscript and approved the final version. C.Y.J. and S.U.K. are the guarantors of this work and accept full responsibility for the work; they have access to the data, integrity and accuracy of the data analysis; and controlled the decision to publish.

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The authors have nothing to report.

Disclosure

This manuscript was reviewed by native speakers for English proof readings (Editage; certificate, YUCMR_10139).

Ethics Statement

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 (IRB number: 4-2023-0082). Informed consent was waived by the Institutional Review Board due to the retrospective study design.

Conflicts of Interest

Seung Up Kim has served as an advisory committee member for Gilead Sciences, Bayer, Eisai and Novo Nordisk. He is a speaker for Gilead

Sciences, GSK, Bayer, Eisai, AbbVie, EchoSens, MSD, Eisai, Otsuka and Bristol-Myers Squibb. He has also received a research grant from AbbVie and Bristol-Myers Squibb. The other authors declare no conflicts of interest.

Data Availability Statement

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

Peer Review

The peer review history for this article is available at <https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.70730>.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Types of missing data. **Table S2:** Baseline characteristics of participants according to the presence of MASLD. **Table S3:** HRs for kidney outcomes according to ADA-defined risk groups, with the low-risk group as the reference. **Table S4:** HRs for kidney outcomes according to ADA-defined risk groups, where obesity was defined as BMI ≥ 23 kg/m². **Table S5:** HRs for kidney outcomes according to ADA-defined risk groups, where obesity was defined as BMI ≥ 27 kg/m². **Table S6:** HRs for kidney outcomes according to ADA-defined risk groups using age-adjusted FIB-4 thresholds (Age ≥ 65). **Table S7:** HRs for kidney outcomes by FIB-4 in the whole cohort. **Table S8:** HRs for kidney outcomes by FIB-4 among participants with the highest risk of future cirrhosis. **Table S9:** Subgroup analysis showing the effect of the high-risk group on the risk of incident CKD. **Figure S1:** Application of the ADA two-step approach in this cohort. **Figure S2:** Flow diagram of the study.