



OPEN Association of noninvasive tests of liver fibrosis with chronic kidney disease in MASLD: a systematic review and meta-analysis

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Metabolic dysfunction-associated steatotic liver disease (MASLD) is an emerging risk factor for chronic kidney disease (CKD). While liver biopsy is the gold standard for assessing fibrosis, noninvasive tests (NITs)—including fibrosis-4 (FIB-4), nonalcoholic fatty liver disease fibrosis score (NFS), and vibration-controlled transient elastography—are validated alternatives. However, their association with CKD stage in MASLD remains unclear. This study aimed to evaluate the association between NITs and various CKD outcomes in MASLD. A systematic search identified observational studies published between January 2014 to July 2024 following PRISMA were included. Data extraction and risk-of-bias assessment were performed independently by multiple reviewers. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using a random-effects model. A total of 33 studies comprising 278,355 MASLD were included. High FIB-4 were associated with increased risks of CKD stage ≥ 3 (adjusted OR (AOR): 2.23; 95%CI 1.40–3.53) and advanced CKD including ESRD (OR: 2.75; 95%CI 1.27–5.96). High NFS was associated with albuminuria (AOR: 1.68; 95%CI 1.19–2.38) and CKD stage ≥ 3 (AOR: 2.52; 95%CI 1.78–3.58). Elevated liver stiffness showed a strong association with CKD stage ≥ 3 (AOR: 3.12; 95%CI 2.16–4.49). NITs may serve as indicators of CKD staging in MASLD. Future studies should explore whether targeting liver fibrosis could mitigate CKD progression.

Keywords Chronic kidney disease, Liver fibrosis, Metabolic dysfunction-associated steatotic liver disease, Noninvasive tests, Systematic review and meta-analysis

Fatty liver disease (FLD) or steatotic liver disease (SLD) is a noncommunicable disease associated with many conditions^{1–4} and has an increasing global incidence^{5,6}. The progression of FLD to more severe stages including steatohepatitis and fibrosis has been associated with an increased risk of hepatocellular carcinoma⁷. In addition, FLD has been shown to increase the risk of chronic kidney disease (CKD) and cardiovascular diseases in several cohort studies^{8–12}.

Although a related meta-analysis demonstrated an association between FLD and CKD, the definition of liver fibrosis and disease severity remains unclear. Liver biopsy constitutes the gold standard for diagnosing FLD severity^{13–15}. However, two categories of noninvasive tests (NITs) —blood-based biomarker indices (fibrosis-4 [FIB-4] score, nonalcoholic fatty liver disease (NAFLD) fibrosis Score [NFS], aspartate aminotransferase/platelet ratio [APRI]) and imaging-based vibration controlled transient elastography (VCTE) also known as liver stiffness measurement (LSM) have been validated as noninvasive methods to assess liver fibrosis and are increasingly used in real-world clinical settings¹⁶. Moreover, the sequence of CKD progression has not been explored in a related meta-analysis¹⁷. Only early composite outcome (albuminuria and glomerular filtration rate; eGFR < 60 mL/min/1.73 m²) have previously been demonstrated¹⁸.

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A knowledge gap remains concerning the ability of both categories of NITs to identify early kidney disease and the effects of the progressive stages of renal impairment in the FLD population. To offer comprehensive insights into the correlations, we concentrated on a substantial specific FLD population and the sequential detailed CKD outcomes regarding early albuminuria or proteinuria, the incidence of CKD at a minimum of stage 3, CKD progression to advanced stages, and ultimately end-stage renal disease (ESRD) through a systematic review and meta-analysis methodology.

Methods

Ethical approval for the study was approved by the Institutional Review Board of Vajira Hospital (approval number: COE: 005/2024 X). The systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and were registered in PROSPERO (2024CRD42024564627).

Search strategy

Each article's eligibility was assessed using a stepwise procedure. First, we queried reports recorded in the Medline and Scopus databases from January 2014 to July 2024, using the following MeSH terms, their entry terms, and free-text keywords: "Fatty Liver (MeSH Unique ID: D005234), Non-alcoholic Fatty Liver Disease (MeSH Unique ID: D065626), Liver Cirrhosis (MeSH Unique ID: D008103), Elasticity Imaging Techniques (MeSH Unique ID: D054459), Renal Insufficiency, Chronic (MeSH Unique ID: D051436), Proteinuria (MeSH Unique ID: D011507) and Kidney Failure, Chronic (MeSH Unique ID: D007676)." A comprehensive, systematic search strategy was fully described in the Supplementary File.

Study selection

The study included adults aged over 18 years, diagnosed with metabolic dysfunction-associated steatotic liver disease (MASLD). MASLD is characterized by hepatic steatosis in individuals consuming less than 140 g of alcohol weekly for females and less than 210 g for men, accompanied by at least one cardiometabolic risk factor, including obesity, type 2 diabetes, or metabolic dysregulation. Although transitioning from NAFLD to MASLD, the MASLD-defined population are interchangeable with existing NAFLD literature¹⁹. Levels were categorized according to low, intermediate and high score for each NIT including; NFS: (High ≥ 0.676 , Intermediate -1.455 — 0.675 , Low < -1.455); FIB-4: (High ≥ 2.67 , Intermediate 1.30 – 2.669 , Low < 1.30); and LSM: (High > 8 kPa, Intermediate 6 – 8 kPa, Low < 6 kPa).

Various aspects of CKD outcome were assessed (albuminuria/proteinuria, urine albumin creatinine ratio [UACR]) > 30 mg/g creatinine, the occurrence of CKD $\geq$ stage 3 (estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m²), CKD progression (progression or deterioration to a higher stage) and advanced stage (eGFR) < 30 mL/min/1.73 m² or ESRD (eGFR) < 15 mL/min/1.73 m²). Observational including cross-sectional, cohort studies that reported the association between liver fibrosis and CKD were included.

Eligibility criteria

Inclusion criteria

The titles and abstracts of the articles retrieved were independently screened for appropriateness by the first author (SS, hepatologist) and co-author (NT, clinical data scientist). Endnote, Version 21 was used as the screening tool. All literature identified through the database search was included. The researchers independently reviewed and were blinded to each other's decisions.

Exclusion criteria

After screening all abstracts, we excluded guidelines/reviews, conference abstracts, editorial comments, letters to the editors and case reports/case series. Nonrelevant data such as nonfatty liver populations, animal studies or non-CKD outcomes, no NIT evaluations, non-standard criteria of grouping NITs, duplicated publications or previous meta-analyses were deleted. Studies not published in full text or in English were also excluded. Next, two authors (SS and NT) independently reviewed the full texts of the selected articles to extract detailed pertinent data. A third author (WR, clinical epidemiologist) reviewed all full texts to validate the extracted data. Disagreements regarding study selection were resolved by discussion with a third author (WR), and two other expert nephrologists (PS and TT) clarified the CKD endpoints. All five review team members checked all final input data.

Data extraction

We extracted the author's name, publication year, study design, study site, number of MASLD participants, characteristics of participants such as age, percentage of male participants, body mass index, percentage of participants with diabetes, NITs for liver fibrosis assessment including FIB-4, NFS, LSM, APRI, individual kidney outcome and risk of bias quality of each study. For the NITs, we recorded the categorized groups according to the standard cutoff for each index. Kidney outcomes were defined as the UACR, CKD stage ≥ 3 , CKD progression and end stage renal disease (ESRD). The Newcastle–Ottawa assessment was used to determine the qualified risk of bias of each cross-sectional observational and cohort study using star scoring systems. For cross-sectional studies, scores of 7–9, 5–6, and < 4 were defined as good, satisfactory and unsatisfactory, respectively. For cohort studies, scores of 9, 7–8 and < 6 indicated low, intermediate and high risk of bias, respectively (Table 1).

Statistical analysis

The baseline characteristics of the quantitative data are reported as means with standard deviations or percentages. For kidney outcomes, changes were compared with pooled unadjusted and adjusted odds ratios (OR) with 95% confidence intervals (CI) for each classified outcome. The range of the fibrosis severity group was

Author, published year	Study design (Study year)	Country	N	Age (years)	Male (%)	BMI (kg/m ²)	Diabetes (%)	Liver fibrosis assessment	CKD endpoint measurement	Quality (Newcastle–Ottawa score)
50	Cross-sectional design, nationwide survey (NHANES 2017—2018)	United States	3647	49.1 ± 18.1	48.2	N/A	41.5	LSM	CKD stage ≥ 3	9
24	Cross-sectional design (2018—2019)	Italy	671	46.6 ± 12.9	54.3	28.1 ± 4.1	100	FIB-4	CKD stage ≥ 3	9
34	Retrospective cohort design Median observation period 3.7 years	United States	2523	56.8 ± 12.9	40.5	34.9 ± 7.2	34.2	FIB-4 LSM	CKD stage ≥ 3 Advance CKD stage & ESRD	8
35	Prospective cohort design (UK Biobank 2006—2010)	United Kingdom	10,152	62 (IQR 11)	44.1	32.2 (IQR 6.2)	30.7	FIB-4 NFS	ESRD	7
36	Prospective cohort design (UK Biobank 2006—2010)	United Kingdom	130,725	57.6 ± 7.7	64.2	31.5 ± 4.4	8.7	FIB-4 NFS	ESRD	7
28	Cross-sectional design (2020)	China	3172	69.3 ± 5.8	48.0	26.1 ± 2.8	100	FIB-4 NFS	CKD stage ≥ 3	9
25	Retrospective cross-sectional design (2018—2021)	South Korea	4241	49.7 ± 10.2	88.2	N/A	0	FIB-4 NFS	CKD stage ≥ 3	9
26	Prospective cohort design (2000—2019)	South Korea	1729	55.9 ± 9.8	52.7	25.6 ± 2.9	100	FIB-4 NFS	CKD stage ≥ 3:	7
37	Retrospective cohort design (end at 2017) Median observation period 84.4 months	United States	50,695	51.2 ± 11.6	44.7	N/A	100	NFS APRI	CKD stage ≥ 3	8
45	Retrospective cohort design (2012—2018)	South Korea	5983	51.8 ± 12.9	62.8	25.7 ± 3.6	29.6	LSM	CKD stage ≥ 3	7
43	Retrospective cross-sectional design (2020—2021)	China	4406	49.0 ± 10.4	60.3	25.8 ± 2.5	12.2	FIB-4 NFS	CKD stage ≥ 3	9
12	Cross-sectional design, nationwide survey (NHANES 1988—1994)	United States	3794	48.0 ± 15.0	50.1	31.0 ± 6.1	23.6	NFS	UACR CKD stage ≥ 3	9
46	Cross-sectional design (2015—2020)	Croatia	442	61.0 ± 11.1	47.3	30.6 ± 5.2	100	LSM	CKD stage ≥ 3	8
20	Retrospective cohort design (2002—2019) Median observation period 2191 days (1396—4015)	Japan	584	55.4 ± 10.5	61.6	26.0 ± 5.2	100	FIB-4	UACR CKD stage ≥ 3:	8
32	Cross-sectional design, nationwide survey (2017—2018)	US	1983	51.1 ± 16.0	51.8	N/A	20.3%	FIB-4 NFS	UACR CKD stage ≥ 3:	9
21	Cross-sectional design (2018)	China	1905	60.0 ± 10.0	82.0	27.0 ± 2.8	29.4	FIB-4 NFS	UACR CKD stage ≥ 3:	9
47	Cross-sectional design	Italy	137	69.9 ± 7.0	48.2	28.5 ± 4.7	100	LSM	CKD stage ≥ 3	8
38	Cross-sectional design (2005—2011)	Taiwan	11,376	52.0 ± 6.8	60.2	24.8 ± 3.6	N/A	NFS	CKD stage ≥ 3	9
22	Retrospective cross-sectional design (2013—2018)	Italy	2770	68.0 ± 12.0	59.1	30.2 ± 5.9	100	FIB-4 NFS APRI	UACR CKD stage ≥ 3	9
29	Retrospective cohort design (2013—2019)	Japan	344	54.3 ± 45.9	48.0	30.0 ± 20.5	41.6	FIB-4	CKD stage ≥ 3	7
56	Cross-sectional design (2015 – 2017)	China	1415	52.1 ± 4.9	55.6	25.0 ± 2.9	16.5	FIB-4 LSM	CKD stage ≥ 3	9
30	Retrospective cohort design (1978—2006) Mean observation period 18 ± 9.2 years	Sweden	144	53.2 ± 13.4	57.6	28.0 ± 4.6	22.2	FIB-4 NFS APRI	CKD stage ≥ 3	8
31	Cross-sectional design, nationwide survey (1988—1994)	US	4142	45.3 ± 0.4	50.1	29.0 ± 0.2	7.53	FIB-4 NFS	CKD stage ≥ 3	9
48	Prospective cohort design (2013—2014)	China	1023	60.7 ± 11.3	53.5	28.1 ± 4.3	100	LSM	UACR CKD stage ≥ 3 Advance CKD & ESRD	9
27	Retrospective cohort design (2003—2013)	South Korea	14,223	50.0 ± 8.5	78.2	25.7 ± 2.6	13.6	FIB-4: NFS APRI	CKD stage ≥ 3:	7
39	Cross-sectional design, the CATAnzaro MEtabolic RIsk factors (CATAMERI) study	Italy	570	54.1 ± 13.5	56.0	32.3 ± 6.5	30.7	NFS	CKD stage ≥ 3	9
42	Cross-sectional design, nationwide survey on abdominal obesity (1988—1994)	US	1927	49.9 ± 0.3	39.3	32.9 ± 0.1	21.5	NFS	CKD stage ≥ 3	9
	Cross-sectional design, nationwide survey on non-abdominal obesity (1988—1994)	US	1058	42.1 ± 0.5	69.3	25.0 ± 0.1	8.3	NFS	CKD stage ≥ 3	
Continued										

Author, published year	Study design (Study year)	Country	N	Age (years)	Male (%)	BMI (kg/m ²)	Diabetes (%)	Liver fibrosis assessment	CKD endpoint measurement	Quality (Newcastle–Ottawa score)
40	Prospective cohort design (2010–2015)	China	534	54.8 ± 7.0	27.2	27.2 ± 2.8	14.2	NFS	CKD stage ≥ 3	9
49	Cross-sectional design (2016–2018)	Italy	238	68.0 ± 10.0	52.0	29.0 ± 5.0	100	LSM	CKD stage ≥ 3	9
23	Cross-sectional design (2015–2018)	South Korea	1108	59.6 ± 13.5	57.9	25.7 ± 4.0	100	FIB-4 NFS	UACR	9
41	Cross-sectional design (2002–2009)	Taiwan	13,255	53.9 ± 11.9	65.7	25.7 ± 3.4	12.1	NFS	CKD stage ≥ 3	9
44	Cross-sectional design (2014–2015)	India	100	42.0 ± 11.0	56	27.7 ± 4.2	20.0	LSM	CKD stage ≥ 3	8
33	Cross-sectional design (2010)	Australia	324	64.8 ± 10.9	59.3	31.1 ± 5.1	100	NFS	UACR CKD stage ≥ 3	9

Table 1. Data extraction for meta-analysis. APRI, aspartate aminotransferase platelet ratio index; BMI, body mass index; CKD, chronic kidney disease; NFS, NAFLD fibrosis score; LSM, liver stiffness measurement. BMI, body mass index; CKD, chronic kidney disease; NFS, NAFLD fibrosis score; LSM, liver stiffness measurement; UACR, urine albumin creatinine ratio. APRI, aspartate aminotransferase platelet ratio index; BMI, body mass index; CKD, chronic kidney disease; NFS, NAFLD fibrosis score; LSM, liver stiffness measurement; UACR, urine protein creatinine ratio. BMI, body mass index; CKD, chronic kidney disease; NFS, NAFLD fibrosis score; LSM, liver stiffness measurement; UACR, urine protein creatinine ratio.

recorded according to the cutoff values of each NITs, and individual interest outcomes were compared in terms of the OR of the high reference group with the low, and intermediate groups. Heterogeneity was assessed using the degree of heterogeneity (I^2); $I^2 > 25\%$, $> 50\%$ and $> 75\%$ were defined as low, medium, and high heterogeneity, respectively. All outcomes were assessed using a random-effects model. Publication bias was explored using Egger's test.

Results

Search results totaled 2,982 studies from Medline (1,386 articles) and Scopus (1,596 articles). Of these, the following were excluded: duplicates (11), year before 2014 (416), book/conference proceedings (260), case report/case series (36), systematic review/meta-analyses (210), narrative review/literature reviews (625), perspective and editorial comments (41), consensus/guidelines/guidance (37), and reports (14). After multiple rounds of discussion to calibrate and reach consensus among all reviewers regarding the categorization of nonstandard NITs and outcome definitions, 33 of the remaining 1,332 eligible articles were deemed suitable for inclusion in the systematic review and meta-analysis, representing a total of 278,355 MASLD participants. (Fig. 1).

Study characteristics

Of the 33 studies included in the meta-analysis, among the 17 articles reporting the association of FIB-4 with renal endpoints, 4 studies examined UACR, 13 studies investigated the presence of CKD stage ≥ 3 , and 4 studies assessed the presence of advanced CKD stage and ESRD. Among the 21 articles reporting the association of NFS with renal endpoints, 6 studies examined UACR, 16 studies investigated the presence of CKD stage ≥ 3 and 2 studies assessed the presence of ESRD. Ninth articles presented the association between LSM and renal endpoints, all addressed the presence of CKD stage ≥ 3 . Three articles reported an association between APRI and CKD stage ≥ 3 (Table 1).

Association between fibrosis-4 and chronic kidney disease outcome

FIB-4 and the UACR A meta-analysis of four studies^{20–23} showed that a high FIB-4 level was associated with a higher risk of UACR than a low FIB-4 level (unadjusted OR 1.427 [95% CI 1.165, 1.747] $p=0.001$; $I^2=0$, $p=0.953$; Egger's test = 0.009).

FIB-4 and CKD stage ≥ 3 Our meta-analysis^{20–22,24–27} showed that a high FIB-4 was associated with a higher risk of CKD stage ≥ 3 in the univariable analysis studies (unadjusted OR 2.712 [95% CI 2.012, 3.656] $p<0.001$; $I^2=79.222$, $p<0.001$; Egger's test = 0.518). Consistent with the studies of multivariable analysis^{20,28–31} higher FIB-4 associations were also shown with increased CKD stage ≥ 3 outcomes (adjusted OR 2.225 [95% CI 1.401, 3.533] $p=0.001$; $I^2=67.545$, $p=0.009$; Egger's test = 0.014). Regarding the FIB-4 per 1 score in univariable analysis studies^{27,29,32,56} we found a relationship between FIB-4 and CKD stage ≥ 3 (unadjusted mean difference 0.443 [95% CI 0.311, 0.575] $p<0.001$; $I^2=55.36$, $p=0.106$; Egger's test = 0.712). However, in the multivariate analysis studies the associative trend was less significant^{20,33} (adjusted OR 1.101 [95% CI 0.946, 1.280] $p=0.214$; $I^2=22.808$, $p=0.274$).

FIB-4 and advanced CKD stage including ESRD

In the four univariable analysis studies^{25,34–36}, FIB-4 was associated with advanced CKD stage, and ESRD (unadjusted OR 2.751 [95% CI 1.269, 5.963], $p=0.010$; $I^2=92.430$, $p<0.001$; Egger's test = 0.113).

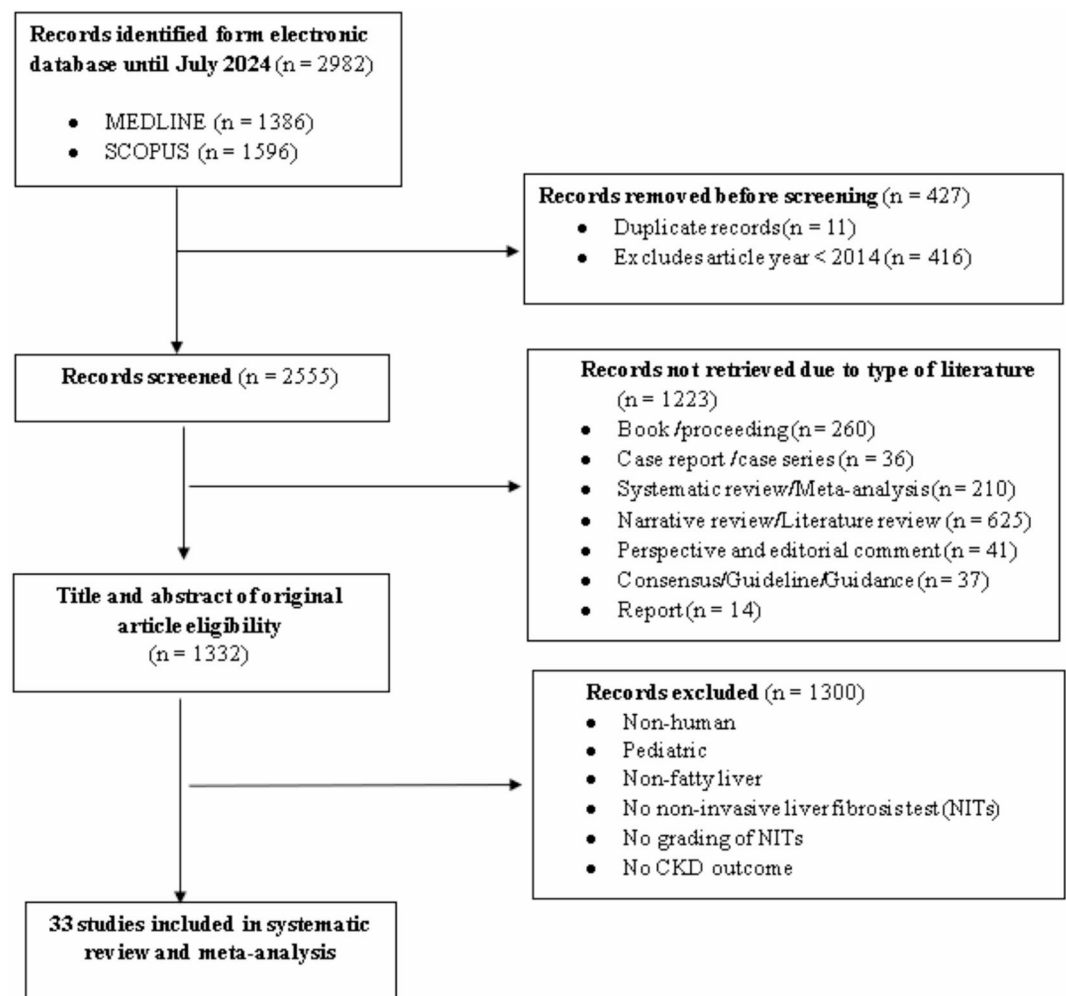


Fig. 1. PRISMA flow diagram for process of article entry for meta-analysis, PRISMA, Preferred Reporting Items for Systematics Reviews and Meta-analyses.

Association between NAFLD fibrosis score and chronic kidney disease outcome

NFS and the UACR Our meta-analysis of univariable analysis studies^{12,21–23,32,33} demonstrated that an elevated NFS correlated with an increased risk of UACR compared to a low NFS (unadjusted OR 3.466 [95% CI 1.901, 6.319] $p < 0.001$; $I^2 = 93.950$, $p < 0.001$; Egger's test = 0.142). Consistent with another two studies^{23,33} the adjusted OR for UACR exhibited a significant association (adjusted OR 1.684 [95% CI 1.191, 2.380] $p = 0.003$; $I^2 = 0$, $p < 0.454$).

NFS and CKD stage ≥ 3 Our meta-analysis^{12,21,22,25–27,37–40} showed that elevated NFS levels correlated with an increased risk of CKD stage ≥ 3 (unadjusted OR 3.022 [95% CI 1.784, 5.119] $p < 0.001$; $I^2 = 96.876$; Egger's test = 0.08). Studies that reported multivariate analyses^{26,28,30,31,39–42} demonstrated that elevated NFS values were also associated with increased CKD stage ≥ 3 outcomes (adjusted OR 2.522 [95% CI 1.779, 3.575], $p < 0.001$; $I^2 = 75.590$, $p < 0.001$; Egger's test 0.04). However, the association of NFS per 1-point increase and CKD showed only a non-significant trend in two studies^{21,43} (unadjusted OR 2.330 [95% CI 0.910, 5.965] $p = 0.078$; $I^2 = 89.983$, $p = 0.002$; Egger's test NA) and (adjusted OR 1.236 [95% CI 0.921, 1.657] $p = 0.158$; $I^2 = 55.766$, $p = 0.133$; Egger's test NA).

NFS and ESRD NFS was associated with ESRD in two studies^{35,36} (unadjusted OR 5.191 [95% CI 1.148, 23.472], $p = 0.032$; $I^2 = 97.586$, $p < 0.001$; Egger's test NA).

Association between liver stiffness measurement and chronic kidney disease outcome

LSM and CKD stage ≥ 3 Six studies^{44–49} showed that elevated LSM correlated to an increased risk of CKD stage ≥ 3 compared with that of lower LSM (unadjusted OR 2.753 [95% CI 1.029, 7.361], $p = 0.044$; $I^2 = 95.326$, $p < 0.001$; Egger's test = 0.527). These results were consistent with the results of the multivariate analysis studies^{44–47,49,50} (adjusted OR 3.116 [95% CI 2.162, 4.489], $p < 0.001$; $I^2 = 0$, $p = 0.529$; Egger's test = 0.012). However, only a nonsignificant trend was observed between LSM per 1-point increase and CKD stage ≥ 3 in both unadjusted and adjusted analyses^{32,46,51,56} (unadjusted OR 1.412 [(95% CI 0.955, 2.089], $p = 0.084$; $I^2 = 86.511$, $p = 0.001$; Egger's test = 0.120) and (adjusted OR 1.237 [95% CI 0.973, 1.573], $p = 0.082$; $I^2 = 81.619$, $p = 0.004$; Egger's test = 0.084).

Association between AST/platelet ratio and chronic kidney disease outcome

APRI and CKD stage ≥ 3 The analysis of three studies^{22,27,37} demonstrated an association between the APRI and CKD at least stage 3 (unadjusted OR 3.621 [95% CI 1.217, 10.772], $p=0.021$; $I^2=96.897$, $p<0.001$; Egger's test = 0.827).

Investigation of heterogeneity

Subgroup analysis was performed in unadjusted OR and adjusted OR that had adequate included paper. High FIB-4 level was associated with a higher risk of UACR than a low FIB-4 level in only Asia country and cross-sectional study (unadjusted OR 1.404 [95% CI 1.129, 1.745] $p=0.002$; unadjusted OR 1.443 [95% CI 1.134, 1.837] $p=0.003$, respectively). High FIB-4 was associated with a higher risk of CKD stage ≥ 3 in both Asia and Europe countries. (unadjusted OR 2.246 [95% CI 1.803, 2.799] $p<0.001$; unadjusted OR 4.780 [95% CI 2.677, 8.536] $p<0.001$, respectively). Cross-sectional and cohort studies provided the significant association between high FIB-4 and high risk of CKD stage ≥ 3 (unadjusted OR 2.499 [95% CI 1.909, 3.270] $p<0.001$; unadjusted OR 2.938 [95% CI 1.587, 5.441] $p<0.001$, respectively).

Higher FIB-4 associations were also shown with increased CKD stage ≥ 3 outcomes in Europe and US countries (adjusted OR 7.250 [95% CI 2.510, 20.940] $p<0.001$; adjusted OR 2.431 [95% CI 1.473, 4.014], $p=0.001$, respectively). Cross-sectional and cohort studies provided the significant association between high FIB-4 and high risk of CKD stage ≥ 3 (adjusted OR 2.431 [95% CI 1.473, 4.014] $p=0.001$, adjusted OR 2.249 [95% CI 1.162, 4.351] $p=0.016$, respectively). FIB-4 was associated with advanced CKD stage, and ESRD in Europe and US (unadjusted OR 2.580 [95% CI 1.845, 3.607], $p<0.001$, unadjusted OR 6.977 [95% CI 4.923, 9.888], $p<0.001$, respectively). Only cohort study demonstrated the significant association between FIB-4 and advance CKD stage, and ESRD. (unadjusted OR 3.621 [95% CI 1.756, 7.469], $p<0.001$).

Elevated NFS correlated with an increased risk of UACR compared to a low NFS in Asia and US (unadjusted OR 2.256 [95% CI 1.788, 2.847] $p<0.001$; unadjusted OR 7.933 [95% CI 5.382, 11.693] $p<0.001$, respectively). Cross-sectional study provided the significant correlated between NFS and UACR (unadjusted OR 3.466 [95% CI 1.901, 6.319] $p<0.001$).

Elevated NFS levels correlated with an increased risk of CKD stage ≥ 3 in all regions including Asia, Europe and US (unadjusted OR 2.313 [95% CI 1.393, 3.840], unadjusted OR 4.365 [95% CI 1.021, 18.664], unadjusted OR 5.396 [95% CI 1.796, 16.210], respectively). Cross-sectional and cohort also provide the significant association between NFS and CKD stage ≥ 3 (unadjusted OR 3.017 [95% CI 1.189, 7.659], and unadjusted OR 3.023 [95% CI 2.620, 3.489], respectively). High NFS scores were also associated with increased CKD stage ≥ 3 outcomes in all regions including Asia, Europe and US (adjusted OR 1.955 [95% CI 1.507, 2.536] $p<0.001$; adjusted OR 10.922 [95% CI 1.430, 83.423] $p=0.021$, adjusted OR 2.248 [95% CI 1.224, 4.129] $p=0.009$, respectively).

Elevated LSM correlated to an increased risk of CKD stage ≥ 3 compared with that of lower LSM in only Asia (unadjusted OR 3.441 [95% CI 1.208, 9.804] $p=0.021$). High LSM were associated with risk of CKD stage ≥ 3 in all regions including Asia, Europe, US countries. (adjusted OR 5.283 [95% CI 2.471, 11.295] $p<0.001$; adjusted OR 3.618 [95% CI 1.915, 6.836] $p<0.001$, and adjusted OR 2.110 [95% CI 1.216, 3.661] $p=0.008$, respectively) and all study designs (cross-sectional: adjusted OR 2.924 [95% CI 1.988, 4.301] $p<0.001$ vs. cohort: adjusted OR 5.400 [95% CI 1.733, 16.822] $p=0.004$).

Discussion

The pathophysiological connection between MASLD and CKD encompasses several interconnected processes mostly influenced by metabolic abnormalities and chronic inflammation. The primary culprit is insulin resistance, which facilitates hepatic fat storage, systemic inflammation, and endothelial dysfunction, hence contributing to liver fibrosis and renal damage. Fructose-induced elevation of uric acid, coupled with gut dysbiosis, results in heightened oxidative stress and the generation of uremic toxins, which further compromise renal function. Dysregulated Wnt/ β -catenin signaling and endoplasmic reticulum stress also contribute to fibrosis and inflammation in both organs. The same molecular pathways underscore MASLD as a systemic disorder rather than merely a liver disease, substantially increasing the risk of CKD^{52,53}.

This meta-analysis builds upon related research by incorporating a more comprehensive evaluation of noninvasive liver fibrosis assessment tools in relation to CKD outcomes within a large, specific MASLD population. These findings highlight a significant relationship between elevated fibrosis scores and an increased risk of CKD, reinforcing the notion that the severity of liver fibrosis plays a crucial role in kidney dysfunction.

Subgroup analyses including race and study designs were performed to explore the heterogeneity that might come from the potential variability across studies. The stronger associations were consistently observed in Asian and European cohorts compared with U.S. The magnitude of risk estimates was generally higher in cohort than in cross-sectional studies. This regional variation may reflect underlying differences in metabolic risk burden and genetic susceptibility that influence the detection of both MASLD and CKD. In term of age, gender, and diabetic status which are the important factors for CKD status, we highlight the effects of them by using the adjusted models (Table 2). Overall, the adjusted models also demonstrated the same way as univariable. That means the association between non-invasive liver biomarker and CKD still consistent. Additionally, we emphasized that FIB-4 corresponds with later stages of CKD and ESRD, suggesting that heightened fibrosis, oxidative stress, and inflammation in MASLD may accelerate the progression of CKD.

In the aspect of non-liver outcome, our meta-analysis regarding dynamic FIB-4 and CKD progression over an average three-year follow-up was unfeasible because of the discrepancies in categorical and continuous FIB-4 measurements between them. Following a 4-year follow-up, an elevated FIB-4 was associated with ESRD prognosis; however, adjustments for comorbidities were not incorporated. Despite the updated guidelines, the serial blood-based FIB-4 cannot accurately predict the dynamic change of liver fibrosis⁵⁴. The utility of baseline or dynamic FIB-4 in monitoring the dynamic CKD progression and ESRD is pertinent for long term evaluations.

Author, published year	N	Finding	Adjusted variables
<i>FIB-4 & CKD stage ≥ 3</i>			
²⁹	344	Adjusted OR: 3.85 (1.09 – 13.54)	Age, gender, BMI, NAS steatosis, NAS inflammation
³⁰	144	Adjusted HR: 7.25 (2.51 – 20.94)	Gender, BMI, DM, HT, CVD, fibrosis stage
³¹	4142	Adjusted OR: 2.27 (1.05 – 4.52)	Gender, BMI, DM, HT, Race, WC, smoking, UA
²⁸	3172	Adjusted OR: 2.59 (1.30 – 5.16)	Age, gender, BMI, SBP, DBP, TC, TG, LDL, HDL, ALT, AST, T-BIL, FPG, HbA1c, PLTs, ALB, UA, BUN, Cr, UACR, eGFR
²⁶	1729	Adjusted HR: 1.75 (1.15 – 2.66)	Age, gender, BMI, duration of DM, SBP, HT, HbA1c, TC, eGFR, sulfonylurea, statin, RASi, Hs-CRP, KTTT
²⁰	584	Adjusted HR: 1.14 (0.79 – 1.64)	Age, gender, BMI, DM, HT, HbA1c, eGFR, smoking, alcohol drinking, anti-diabetic medications, anti-hypertensive medications
<i>NFS & UPCR</i>			
²³	1108	Adjusted OR: 1.55 (1.03 – 2.33)	Age, gender, HbA1c, duration of DM, HT
³³	324	Adjusted OR: 2.08 (1.08 – 3.98)	Age, gender, BMI, duration of DM, HT, HbA1c, TC, ALT, HOMA-IR
<i>NFS & CKD stage ≥ 3</i>			
⁴¹	13,255	Adjusted OR: 2.28 (1.51 – 3.45)	Blood pressure, lipid profile
³⁰	144	Adjusted HR: 31.38 (7.92 – 124.38)	Gender, HT, CVD, fibrosis stage
³¹	4142	Adjusted OR: 4.92 (2.96 – 8.15)	Gender, BMI, DM, HT, Race, WC, smoking, UA
³⁹	570	Adjusted OR: 3.94 (1.11 – 14.05)	Gender, anti-hypertensive medications, statin, glucose tolerance status
⁴⁰	534	Adjusted OR: 2.82 (1.22 – 6.56)	Age, gender, BMI, DM, HT, obesity, NFS, smoking, alcohol drinking, physical activity, TG, SBP, HbA1c, WBC, UACR, eGFR, anti-diabetic medications, anti-hypertensive medications, lipid-lowering medications
⁴² (Abdominal obesity population)	1927	Adjusted OR: 1.39 (1.01 – 1.91)	Age, gender, BMI, DM, LDL, TG, TC, ALB, race, fibrosis stage, marital status, military service, sedentary behavior
⁴² (Non-abdominal obesity population)	1058	Adjusted OR: 1.84 (1.38 – 2.46)	Age, gender, BMI, DM, LDL, TG, TC, ALB, race, fibrosis stage, marital status, military service, sedentary behavior
²⁸	3172	Adjusted OR: 1.71 (0.83 – 3.52)	Age, gender, BMI, SBP, DBP, TC, TG, LDL, HDL, ALT, AST, T-BIL, FPG, HbA1c, PLTs, ALB, UA, BUN, Cr, UACR, eGFR
²⁶	1729	Adjusted HR: 1.58 (1.03 – 2.41)	Age, gender, BMI, duration of DM, SBP, HT, HbA1c, TC, eGFR, sulfonylurea, statin, RASi, Hs-CRP, KTTT
<i>LSM & CKD stage ≥ 3</i>			
⁴⁴	100	Adjusted OR: 5.19 (1.42 – 19.00)	Age, BMI, Severe Obesity, Metabolic Syndrome, DM, FPG, Insulin Resistance, Cr, Presence of raised transaminases, ALT, AST, Severe Steatosis
⁴⁹	238	Adjusted OR: 3.40 (1.20 – 9.50)	Age, gender, smoking, duration of DM, HT, HbA1c, medication, steatosis
⁴⁵	5983	Adjusted HR: 5.40 (2.46 – 11.84)	Age, gender, BMI, eGFR, FPG, LDL, GGT, AST, ALT, SBP, anti-diabetic medications, anti-hypertensive medications, lipid-lowering medications
⁴⁶	442	Adjusted OR: 4.41 (1.19 – 16.00)	Age, gender, BMI, duration of DM, HT, dyslipidemia, ACEi/ARB therapy, statin, anti-diabetic medications, HbA1c, UA, CRP levels
⁴⁷	137	Adjusted OR: 3.28 (1.22 – 8.90)	Age, gender, BMI, duration of DM, HbA1c, smoking, HT, anti-hypertensive medications, dyslipidemia, lipid-lowering medications, HOMA-IR, Hs-CRP
⁵⁰	3647	Adjusted OR: 2.11 (1.48 – 3.01)	Age, gender, BMI
<i>LSM per 1 score & CKD stage ≥ 3</i>			
⁴⁵	5983	Adjusted HR: 1.04 (1.02 – 1.07)	Age, gender, BMI, eGFR, FPG, LDL, GGT, AST, ALT, SBP, anti-diabetic medications, anti-hypertensive medications, lipid-lowering medications
⁵⁰	3647	Adjusted OR: 1.70 (1.22 – 2.39)	Age, gender, BMI
⁵⁶	1415	Adjusted OR: 1.31 (1.21 – 1.43)	Age, DM, UA

Table 2. Studies with multivariable analysis. ALB, serum albumin; ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; BUN, blood urea nitrogen; CKD, chronic kidney disease; Cr, creatinine; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FIB-4, fibrosis-4 score; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin A1c; HDL, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; Hs-CRP, high-sensitivity C-reactive protein; HT, hypertension; KITT, rate constant for plasma glucose disappearance; LDL, low-density lipoprotein cholesterol; NAFLD, nonalcoholic fatty liver disease; LSM, liver stiffness measurement; NAS, NAFLD activity score; NFS, NAFLD fibrosis score; PLTs, platelets; RASi, angiotensin converting enzyme inhibitor or angiotensin II receptor blockers; SBP, systolic blood pressure; T-BIL, total bilirubin; TC, total cholesterol; TG, triglycerides; UA, uric acid; UACR, urinary albumin to creatinine ratio; WBC, white blood cell; WC, waist circumference. ACEi/ARB, Angiotensin converting enzyme inhibitors/angiotensin receptor blockers; ALB, serum albumin; ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; BUN, blood urea nitrogen; CKD, chronic kidney disease; Cr, creatinine; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FIB-4, fibrosis-4 score; FPG, fasting plasma glucose; GGT, Gamma-glutamyl transferase; HbA1c, glycated hemoglobin A1c; HDL, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; Hs-CRP, high-sensitivity C-reactive protein; HT, hypertension; KITT, rate constant for plasma glucose disappearance; LDL, low-density lipoprotein cholesterol; NAFLD, nonalcoholic fatty liver disease; LSM, liver stiffness measurement; NAS, nonalcoholic fatty liver disease activity score; NFS, NAFLD fibrosis score; PLTs, platelets; RASi, angiotensin converting enzyme inhibitor or angiotensin II receptor blockers; SBP, systolic blood pressure; T-BIL, total bilirubin; TC, total cholesterol; T2DM, type 2 diabetes mellitus; TG, triglycerides; UA, uric acid; UACR, urinary albumin to creatinine ratio; WBC, white blood cell; WC, waist circumference.

The NFS is widely used to estimate the progression of liver fibrosis and incorporates both liver function and significant metabolic risk factors. Diabetes, a component of NFS, is associated with MASLD and accelerated liver fibrosis. The strength of the NFS lies in its robust connection with early renal outcomes, demonstrating consistency across more than 1000 instances of MASLD with diabetes. In addition to screening for early albuminuria in diabetes, incorporating NFS assessment for MASLD with concurrent diabetes may enhance early recognition of renal disease. To gain a deeper understanding of MASLD and its correlation with metabolic risk in obesity, investigating this link is vital. Similarly, the significant heterogeneity was largely attributable to regional differences and the metabolic composition of included populations. Subgroup analyses demonstrated consistent positive associations across Asia, Europe, and the U.S., reinforcing the robustness of the relationship between higher NFS and renal dysfunction despite methodological and population variability.

In contrast, heterogeneity in studies assessing LSM appeared primarily due to technical variation in device calibration, operator expertise which are known to affect liver stiffness measurements. VCTE-derived LSM, widely used in assessing liver fibrosis, has been featured in a limited number of meta-analyses. Both liver inflammation and fibrosis affected LSM scores. Fewer studies on VCTE-derived LSM, which may limit the robustness of conclusions drawn about this specific test. Further investigation is needed to clarify the predictive accuracy and consistency of the LSM score. In the context of liver fibrosis, significant confounders affecting the LSM threshold for advanced fibrosis include hepatic inflammation and elevated BMI, which can lead to overestimating LSM values^{54,55}. Despite fewer studies, our findings indicate that elevated LSM is a reliable indicator of CKD risk, particularly in Asian populations.

Although some heterogeneity remained, the direction of effect across all analyses was remarkably consistent, suggesting that the observed variability is quantitative rather than qualitative. This indicates that while effect sizes vary, the underlying relationship between liver fibrosis severity and CKD risk is stable across regions and study types. Understanding the strength of each NIT, provides a deeper understanding of their utility in different CKD outcomes in a large MASLD population, offering a more granular perspective concerning CKD progression. By addressing prior gaps and leveraging contemporary data, our study provides strong evidence for integrating noninvasive fibrosis screening not only for hepatology care but also clinical risk stratification models for CKD events in individuals newly diagnosed with MASLD.

This study encountered limitations. First, the major limitations, such as the observational nature of included studies and potential residual confounding, which hamper the strength of causal associations. Second, the heterogeneity in fibrosis severity thresholds could have potentially led to inconsistencies and would have likely introduced misclassification bias. Without a standardized approach to categorizing fibrosis severity, drawing clear conclusions remains challenging.

Regarding publication bias, Egger's tests demonstrated significant small-study effects in a few analyses, indicating potential publication bias favoring positive findings. Such bias could partly overestimate pooled effect sizes; however, the inclusion of large population-based cohorts mitigates this concern by anchoring the estimates. The consistent directionality of associations across multiple NITs and analytic models further supports the reliability of the overall findings despite these limitations. From our study, the follow up was limited which again makes it difficult to understand the dynamic relationship between liver fibrosis and kidney disease progression. In the future, there is a necessity for larger prospective studies that standardize NIT thresholds and

CKD outcome measures to gain a comprehensive knowledge of this relationship's dynamics. Future research should focus on longitudinal studies to establish causality, as well as interventional trials to assess whether modifying liver fibrosis severity can lead to improved renal outcomes.

Conclusion

Greater liver fibrosis burden, as assessed by noninvasive indices, consistently correlates with higher CKD risk and progression across diverse MASLD populations. Our meta-analysis underscores the strong association between noninvasive liver fibrosis markers and various CKD outcomes. These findings emphasize the need for a multidisciplinary approach for MASLD management incorporating both hepatologists and nephrologists in patient care. Given the growing global burden of MASLD and CKD, the early detection of kidney dysfunction using simple NITs could facilitate timely interventions to mitigate disease progression.

Data availability

The data underlying this article will be shared upon reasonable request to the corresponding author.

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Author contributions

SS, NT, TT, WR, and PS contributed to the conception and design of the study. SS, NT, and WR contributed to data collection. SS, WR and PS contributed to statistical analysis and data interpretation. SS, TT, and WR contributed to drafting of the article. PS critically revised the manuscript. All authors read and approved the final manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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