



# An international Delphi consensus statement on metabolic dysfunction-associated fatty liver disease and risk of chronic kidney disease

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**Background:** With the rising global prevalence of fatty liver disease related to metabolic dysfunction, the association of this common liver condition with chronic kidney disease (CKD) has become increasingly evident. In 2020, the more inclusive term metabolic dysfunction-associated fatty liver disease (MAFLD) was proposed to replace the term non-alcoholic fatty liver disease (NAFLD). The observed association between MAFLD and CKD and our understanding that CKD can be a consequence of underlying metabolic dysfunction support the notion that individuals with MAFLD are at higher risk of having and developing CKD compared with those without MAFLD. However, to date, there is no appropriate guidance on CKD in individuals with MAFLD. Furthermore, there has been little attention paid to the link between MAFLD and CKD in the Nephrology community.

**Methods and Results:** Using a Delphi-based approach, a multidisciplinary panel of 50 international experts from 26 countries reached a consensus on some of the open research questions regarding the link between MAFLD and CKD.

**Conclusions:** This Delphi-based consensus statement provided guidance on the epidemiology, mechanisms, management and treatment of MAFLD and CKD, as well as the relationship between the severity of MAFLD and risk of CKD, which establish a framework for the early prevention and management of these two common and interconnected diseases.

**Keywords:** Metabolic dysfunction-associated fatty liver disease (MAFLD); non-alcoholic fatty liver disease (NAFLD); chronic kidney disease (CKD); consensus

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## Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease worldwide with a global prevalence of about 25–30% (1,2). NAFLD includes a histological spectrum of liver conditions ranging from simple steatosis [non-alcoholic fatty liver (NAFL)] to non-alcoholic steatohepatitis (NASH), advanced fibrosis and cirrhosis (3). NAFLD is always a diagnosis of exclusion in clinical practice; to entertain the diagnosis of NAFLD, clinicians need to exclude “excessive” alcohol consumption and all competing causes of hepatic steatosis. This is despite the fact that the coexistence of NAFLD with other chronic liver diseases (including but not limited to alcohol use disorder) is not rare in clinical practice (4). On the other hand, in the realm of drug development and regulatory approval processes, the definition of a patient population in which the mechanism of the drug can be linked to one underlying dominant pathophysiological process is critical. For these reasons and given the high heterogeneity and stigma around the NAFLD name, in 2020, several experts

proposed the new term metabolic dysfunction-associated fatty liver disease (MAFLD) (5,6). A diagnosis of MAFLD is based on evidence of hepatic steatosis (as assessed by liver biopsy, imaging techniques or blood biomarkers/scores) in persons who are overweight or obese or have type 2 diabetes (T2D), or metabolic dysregulation, regardless of the coexistence of excessive alcohol consumption and other chronic liver diseases. The newly proposed definition of MAFLD better emphasises the pathogenic role of metabolic dysfunction in the development of this common liver disease and uses inclusive criteria for diagnosis (7–10). In this article, we explore the definition of MAFLD characterized by the presence of metabolic dysregulation but excluding severe alcohol use or viral-associated liver disease (i.e., dual aetiology liver disease).

Growing evidence indicates that NAFLD is associated with an increased risk of having or developing chronic kidney disease (CKD) (11–14), which is an established risk factor for end-stage renal disease (ESRD), cardiovascular disease and all-cause mortality (15–18). The magnitude of these risks appears to parallel the severity of NAFLD, especially the amount of liver fibrosis (11,19). In contrast, current data on the strength of the association between MAFLD and subsequent risk of CKD is only now being acquired, given its proposed adoption as a clinically-useful entity (20–23). Several epidemiological studies have documented that MAFLD may be even more closely associated with CKD than NAFLD (Table S1) (24). Sun *et al.* first reported that in 12,571 individuals with liver ultrasonography data from the Third National Health and Nutrition Examination Survey (NHANES) 1988–1994, individuals with MAFLD had lower values of estimated glomerular filtration rate (eGFR) and a greater prevalence of CKD than those with NAFLD (29.6% *vs.* 26.6%,  $P < 0.05$ ) (25). Over a 10-year follow-up among 28,890 Japanese individuals, MAFLD also better identified subjects developing CKD, than NAFLD. Furthermore, the addition of MAFLD to traditional CKD risk factors improved discriminatory capacity to diagnose CKD better than NAFLD (26). Similar findings were observed in other large cohorts of Asian individuals (23,27). In contrast, in two prospective cohort studies from USA and China, the MAFLD and NAFLD definitions were both comparable risk factors for CKD (21,28). That said, despite some inconsistencies between research study findings, the MAFLD definition is a landmark in Hepatology bringing about a new way of thinking about fatty liver disease and the relevance of metabolic dysregulation and increased body fat accumulation that has consequences beyond the

### Highlight box

#### Key findings

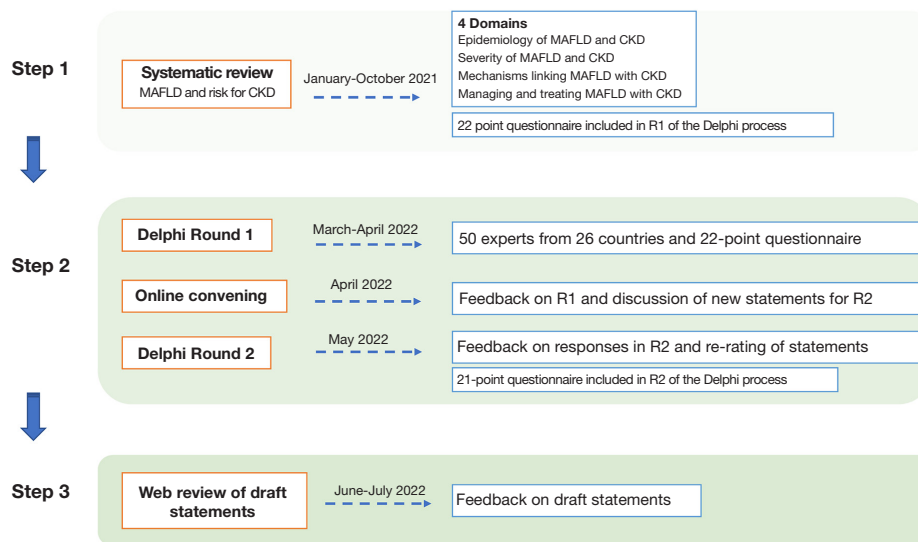
- MAFLD and CKD are highly prevalent and interconnected diseases;
- MAFLD is associated with a higher risk of CKD compared to subjects with NAFLD;
- Individuals with MAFLD and steatohepatitis or advanced fibrosis have a higher prevalence and incidence of CKD than those without;
- Metabolic dysfunction in MAFLD is an important mechanistic link to the association with CKD;
- Apart from disease-specific management, common metabolic factors should be targeted for treatment.

#### What is known and what is new?

- MAFLD is the term proposed to replace NAFLD, comes with positive diagnostic criteria, and highlights the role of metabolic dysfunction to disease pathogenesis;
- NAFLD is associated with chronic kidney disease, but there has been no consensus on the relationship of MAFLD to CKD;
- Through a Delphi process, an international panel arrived at consensus statements on the relationship between MAFLD and CKD.

#### What is the implication, and what should change now?

- Increasing physician awareness of the relationship between MAFLD and CKD and co-management focusing on shared risk factors is important.



**Figure 1** Flow diagram of the Delphi process adopted for the development of consensus statements on MAFLD and the risk of CKD. MAFLD, metabolic dysfunction-associated fatty liver disease; CKD, chronic kidney disease; R1, round 1; R2, round 2.

liver. Importantly, MAFLD brings liver disease into closer alignment with our current understanding of obesity and metabolic syndrome, both of which contribute to development of kidney injury (29). Unfortunately, few outside the field of Hepatology are familiar with the newly-proposed MAFLD terminology and its definition; and there is limited awareness of the link between MAFLD and CKD, amongst the Nephrology community.

The objective of this study was therefore to build consensus among international experts in the field on the link between MAFLD and CKD using a Delphi-based approach. The consensus statements set out current ideas on the link between MAFLD and CKD in specific areas ranging from epidemiology to mechanisms, management and treatment.

## Methods

### Study design

The Delphi method was originally developed at the RAND Corporation (Santa Monica, CA, USA) in the 1950s to forecast the effect of technology on warfare. Today, groups of experts use online tools to anonymously answer questionnaires and receive feedback that represents the “group response” and revise their answers to see whether they can approach expert consensus. Thus, the Delphi method is a structured multistage process which aims

to transform expert opinion into group consensus on a given subject (30). The Delphi method can be successfully applied to areas of controversy or when data are inadequate, and involves a series of questionnaires interspersed with controlled feedback (31). In the present study, we used a modified Delphi process via an online survey with the goal of reaching a consensus on the link between MAFLD and the risk of CKD (3). A two-round Delphi survey (i.e., the R1-survey on 15 April 2022, and R2-survey on 16 June 2022) employed a structured interaction in which a multidisciplinary panel of 50 international experts from 26 countries evaluated and re-evaluated consensus statements in multiple rounds until agreements were reached (*Figure 1*). The web-based Delphi survey was delivered to each member of the expert panel via email with a secure link using Google forms (link for R1 survey: <https://forms.gle/oPNEQqfv53UpsTC59>; for R2 survey: <https://forms.gle/tntWm2Nk2s4EeEmg9>). The data collection periods for each survey ranged between one and four weeks. The R1-survey contained four domains and 22 draft statements with four-point Likert-type categories for respondents to indicate their level of agreement with the statements (that is, ‘Agree’/‘Somewhat agree’/‘Somewhat disagree’/‘Disagree’) (as specified in *Table S2*). In the first round, respondents who agreed or somewhat agreed with a statement could provide comments or suggest edits while those who disagreed or somewhat disagreed needed to explain why. Further discussion was undertaken by email

**Table 1** Demographic composition of the expert panel

Characteristics	Round 1	Round 2
Surveys sent, n	60	50
Total respondents, n (%)	50/60 (83.3)	50/50 (100.0)
Participant type, %		
Researcher	6	6
Nephrologist	20	20
Gastroenterologist/hepatologist	62	62
Endocrinologist/diabetologist	10	10
Methodologist	2	2
Age (years), %		
<40	12	12
40–65	84	84
>65	4	4
Gender, %		
Women	12	12
Men	88	88
Region of practice, %		
Asia	48	48
North America	8	8
South America	2	2
Europe	32	32
Africa	6	6
Oceania	4	4

to report the results of R1-survey and the comments in R1-survey. The R2-survey reflected suggestions developed from the R1-survey, including revised, merged or deleted statements and, finally, contained 21 statements. Only respondents who completed the R1-survey were eligible to take the R2-survey (Table S3), and all respondents in the R1-survey participated in the R2-survey. Participants had the option of keeping their first-round ratings or having them re-scored. After the R2-survey, we included summaries of the edits made to each statement from respondents and emailed all respondents to consider their level of agreement or disagreement with the statements. For the Delphi process, the consensus statements were developed by the expert panel and we assigned a grade to each statement and recommendation to indicate the level of agreement utilising a grading system

used in other published Delphi studies, in which ‘U’ denotes unanimous (100%) agreement, ‘A’ 90–99% agreement, ‘B’ 78–89% agreement, and ‘C’ 67–77% agreement (3,32). A preliminary consensus draft on these recommendations from the expert panel was sought over a 1-week period via a shared Google document. Any disagreements were resolved through discussion until consensus was reached.

### Recruitment of expert panel members

Members of the international expert panel (n=50) were selected from the representative Continents. To be included, they were active researchers with expertise in the management of fatty liver and/or kidney diseases.

The following criteria were used to select members of the expert panel participating in the Delphi survey:

- (I) To be corresponding authors of published articles on the association between MAFLD or NAFLD and the risk of CKD.
- (II) To be representative members from scientific Societies of Nephrology, Hepatology, Endocrinology/Diabetology, and Obesity.
- (III) To be core members of the NAFLD Consensus Consortium and/or the Kidney Disease: Improving Global Outcomes (KDIGO) organization.

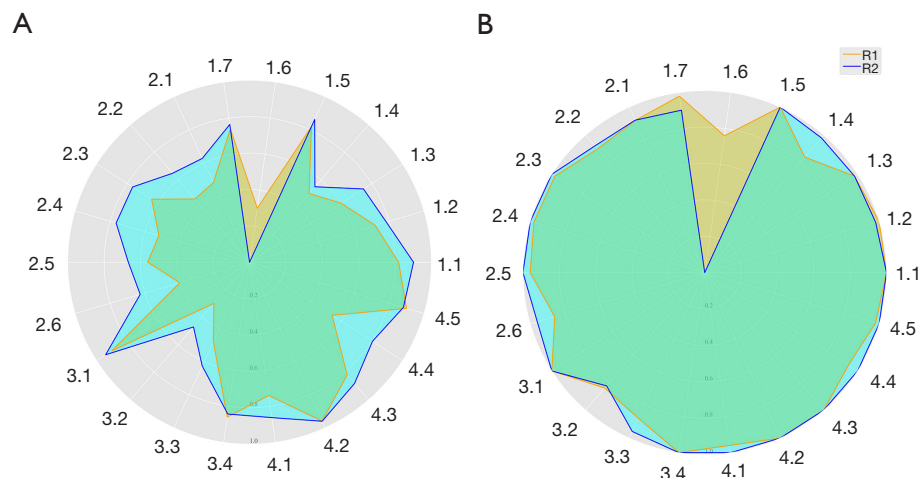
Members of the expert panel were expected to meet at least one of the three aforementioned criteria. To achieve global representation, we selected members from six continents, i.e., Asia, Europe, North America, South America, Africa and Oceania (Table 1).

### Findings

Here, we report the final consensus statements along with a summary of the broader relevant literature. Across the two-based Delphi surveys, there was an increase in consensus for all proposed statements. The mean percentage of “agreement” responses increased from 63.9% to 76.1% and “agreement or somewhat agreement” responses increased from 94.3% in the R1-survey to 97.3% in the R2-survey (Figure 2). In the end, there was unanimous “agreement or some agreement” on 12 consensus statements and >85% agreement on 7/12 statements (Table 2).

### Epidemiology of MAFLD and CKD—statements 1.1–1.6 (Grade U in 1.1 and 1.5; Grade A in 1.2 to 1.4, 1.6)

Studies using the NAFLD definition have estimated a



**Figure 2** Scores for agreement in Delphi process. (A) Scores for agreement by experts in R1 and R2; (B) the total scores for agreement and somewhat agreement of experts in R1 and R2. R1, round 1; R2, round 2.

global prevalence of this condition of about 30% in the general adult population. NAFLD is considered part of a multisystem disease associated with an increased risk of developing not only liver-related complications but also cardiovascular disease (33) and CKD (34). Given this current understanding of the pathogenesis of NAFLD, the term MAFLD focuses attention on the pathogenic role of metabolic dysfunction in the development and progression of this liver disease and its accompanying systemic extra-hepatic complications (35–37).

Recently, it has been reported that during a median follow-up of 23 years, individuals with MAFLD had a 24% higher risk of cardiovascular mortality [hazard ratio (HR) 1.24; 95% confidence interval (CI): 1.01–1.51;  $P=0.041$ ] and a 17% higher risk of all-cause mortality (HR 1.17; 95% CI: 1.04–1.32;  $P<0.01$ ) compared to those without MAFLD (38). It is, therefore, not surprising that MAFLD is associated with a higher prevalence of CKD compared to that observed in the non-MAFLD population. For example, from the cross-sectional NHANES 1999–2002, 2003–2006, 2007–2010 and 2011–2016 cohort databases, individuals with MAFLD had a greater odds of any CKD stage and albuminuria compared with those without MAFLD (28). Using the NHANES 1988–1994 database, the authors reported that compared to the NAFLD or non-metabolic risk NAFLD groups, subjects with MAFLD had lower eGFR values and a higher prevalence of both CKD and abnormal albuminuria (25). Collectively, these findings suggest that MAFLD is associated with a higher risk of CKD compared to subjects with fatty liver but without

coexisting metabolic disorders.

In most published studies, using the term NAFLD, liver disease was associated with a nearly 2-fold increased prevalence of CKD and this association persisted both in patients with T2D and in those without diabetes, even after adjustment for common risk factors for CKD (12,39,40). In a large retrospective cohort study of German individuals with NAFLD, Kaps *et al.* reported that NAFLD was associated with higher risk of developing CKD over 10 years of follow-up (41). This association remained significant across different age and patient subgroups, such as those with T2D, obesity, hypertension or ischaemic heart disease. In contrast, NAFLD was not independently associated with the future risk for ESRD requiring haemodialysis. In a study where the MAFLD population was stratified by presence or absence of T2D, individuals with MAFLD and T2D had a higher prevalence of CKD stage  $\geq 1$  than their counterparts without T2D [odds ratio (OR) 1.18; 95% CI: 1.05–1.32;  $P<0.05$ ] or those with T2D alone [OR 2.09; 95% CI: 1.78–2.46;  $P<0.05$ ] (25). Using the NHANES 2017–2018 database, the authors found that the metabolic comorbidities of MAFLD such as T2D, hypertension and hyperuricemia were all independently associated with CKD (22). Therefore, these findings suggest that MAFLD is associated with CKD in both patients with or without T2D, even after adjustment for common risk factors for CKD.

Although the association between MAFLD and CKD from cross-sectional studies appears to be strong and consistent, whether MAFLD is also an independent risk

**Table 2** Consensus statements on MAFLD and risk of CKD

Domain and statements	Grade
1. Epidemiology of MAFLD and CKD	
1.1 The prevalence of CKD in individuals with MAFLD is higher compared to that in the non-MAFLD population	U
1.2 MAFLD is an independent risk factor for CKD in patients with T2D, even after adjustment for common risk factors for CKD	A
1.3 MAFLD is an independent risk factor for CKD in patients without T2D, even after adjustment for common risk factors for CKD	A
1.4 MAFLD is associated with a greater risk of CKD than patients with liver fat but without evidence of systemic metabolic dysregulation	A
1.5 MAFLD is associated with an increased incidence of CKD	U
1.6 CKD increases the risk of overall mortality among patients with MAFLD	A
2. Severity of MAFLD and CKD	
2.1 The prevalence of CKD more strongly associates with steatohepatitis compared to simple steatosis	A
2.2 The incidence of CKD more strongly associates with steatohepatitis compared to simple steatosis	A
2.3 MAFLD with advanced fibrosis (stage F3/4) has a higher prevalence of CKD than MAFLD without advanced fibrosis (stage F0–2)	U
2.4 MAFLD with advanced fibrosis (stage F3/4) has a higher incidence of CKD than MAFLD without advanced fibrosis (stage F0–2)	U
2.5 Advanced liver fibrosis in patients with MAFLD is independently associated with an increased risk of incident CKD in patients with T2D	U
2.6 Liver stiffness measured by transient elastography is independently associated with an increased presence of albuminuria	A
3. Mechanisms linking MAFLD with CKD	
3.1 MAFLD and CKD share multiple risk factors such as abdominal obesity, insulin resistance, dyslipidemia, hypertension and dysglycemia	U
3.2 The MAFLD-associated genetic polymorphism <i>PNPLA3</i> rs738409 variant is associated with CKD	B
3.3 Alterations in gut microbiota may be linked to both MAFLD and CKD	A
3.4 Metabolic dysfunction is an important mechanistic link between MAFLD and CKD	U
4. Managing and treating MAFLD and CKD	
4.1 Lifestyle intervention including a hypocaloric diet and regular physical exercise is associated with improvements in both MAFLD and CKD, though the extent of benefit might be different for both diseases	U
4.2 Cardiometabolic risk factors should be treated in patients with MAFLD and CKD	U
4.3 The use of antihypertensive treatment (if required) is important in MAFLD for decreasing risk of CKD	U
4.4 Increased clinical vigilance for presence of severe MAFLD might be considered in patients with CKD	U
4.5 Patients with MAFLD and CKD should ideally be treated in a multidisciplinary team setting, though the ideal care model has not been identified	U

'U' denotes unanimous (100%) agreement, 'A' 90–99% agreement, 'B' 78–89% agreement, and 'C' 67–77% agreement. MAFLD, metabolic dysfunction-associated fatty liver disease; CKD, chronic kidney disease; T2D, type 2 diabetes.

factor for CKD remains uncertain. In a cohort study of middle-aged and elderly Chinese subjects without CKD at baseline, the authors found that the incidence rates of CKD in those without fatty liver and those with MAFLD were 8.2% (95% CI: 7.3–9.2%) and 12.9% (95% CI: 11.7–14.1%), over a mean follow-up of 4.6 years (21). These authors also found that MAFLD was associated with a higher risk of incident CKD (HR 1.64, 95% CI: 1.39–1.94). This finding is consistent with results from an updated meta-analysis of 13 observational studies showing that fatty liver disease was significantly associated with a nearly 1.5-fold increased long-term risk of incident CKD stage  $\geq 3$  (11). In 268,946 individuals from the NHANES 2009–2015 database, the investigators found that MAFLD identified a higher proportion of individuals at risk of developing CKD than NAFLD over a median follow-up of 5.1 years (27). Similar results were reported in another cohort study with a 10-year follow-up, where the risk for incident CKD was 1.12 (95% CI: 1.02–1.26) in MAFLD individuals, even after adjustment of traditional renal risk factors (26). Moreover, a Mendelian randomization study supported the existence of a causal effect of fatty liver disease on lower eGFR levels and CKD (42). Thus, the aforementioned studies suggest that individuals with MAFLD are at higher risk of new-onset CKD even after adjustment for common cardiometabolic risk factors compared to subjects with fatty liver who do not have metabolic dysregulation.

Moderate to advanced stages of CKD may also increase the risk of overall mortality among patients with NAFLD (CKD stages 2–3a: HR 2.31, 95% CI: 1.70–3.15; CKD stages 3b–5: HR 4.83, 95% CI: 2.40–9.71) (43). Interestingly, in that study, mortality risk was significantly increased in NAFLD patients with CKD due to metabolic comorbidities, and not influenced by CKD *per se*. According to the newly proposed MAFLD definition, most of these NAFLD individuals had MAFLD. In contrast, a small prospective study showed that NAFLD patients with CKD had a higher risk of overall mortality than NAFLD patients without coexisting CKD. However, after adjustment for metabolic comorbidities, this risk was no longer significant (44). Although further studies are needed, the evidence from the current studies indicate that recognition of CKD may increase the risk of overall mortality in patients with MAFLD, and the new term MAFLD improves our ability to identify individuals at higher risk of developing CKD.

Studies also support a role for NAFLD as a risk factor for CKD in childhood (45,46). For example, in a cohort of 596 children who were overweight or obese, an association

between NAFLD and early kidney dysfunction (defined as microalbuminuria or eGFR  $< 90$  mL/min/1.73 m<sup>2</sup>) was suggested (45). Other studies indicate that the link between NAFLD and CKD could be modulated by some genetic factors. For example, the risk patatin-like phospholipase domain-containing protein 3 (*PNPLA3*) allele may increase the risk of developing both NAFLD and CKD. However, in other studies, carriers of the hydroxysteroid 17-beta dehydrogenase 13 (*HSD17B13*) at-risk A gene or the trans-membrane 6 superfamily 2 (*TM6SF2*) 167K allele had higher eGFR levels in patients with NAFLD (47–49). Overall, given that current evidence on the relationship between MAFLD and CKD in childhood is not robust, a specific consensus statement cannot be generated. New data to inform this are eagerly awaited. In our two-round Delphi survey process, about 25% of experts disagreed with the statement in the R1-survey, so this statement was deleted in the R2-survey.

#### **Severity of MAFLD and CKD—statements 2.1–2.6 (Grade U in 2.3 to 2.5; Grade A in 2.1 to 2.2, 2.6)**

As per its definition, the MAFLD criteria are more likely to capture those who have coexisting metabolic comorbidities compared to NAFLD criteria, and to identify individuals with advanced liver fibrosis (50,51). Given the close association between fibrotic fatty liver disease and CKD, it is reasonable to infer that the severity of MAFLD may be closely associated with CKD. Though there are only a few studies exploring the relationship between the severity of MAFLD and risk of CKD, the available evidence suggests that MAFLD individuals with steatohepatitis or advanced fibrosis had a higher prevalence and incidence of CKD than those without advanced fibrosis or those with simple steatosis. An observational study demonstrated that advanced liver fibrosis but not steatosis was associated with abnormal albuminuria in Chinese patients with NAFLD and T2D (all of whom fit the MAFLD definition) (52). In a meta-analysis of 13 observational cohort studies with a median follow-up of 9.7 years, Mantovani *et al.* also showed that imaging-defined NAFLD was associated with a moderately increased risk of incident CKD stage  $\geq 3$  (random-effects HR 1.43; 95% CI: 1.33–1.54) (11). Similarly, from 5 small studies with liver histology, the presence of advanced fibrosis (F3/4 stage) was associated with a higher prevalence (random-effects OR 5.20; 95% CI: 3.14–8.16) and incidence (random-effects HR 3.29; 95% CI: 2.3–4.71) of CKD than either non-advanced fibrosis



(F0–2) or simple steatosis, respectively (53).

While evidence for the existence of a significant association between severity of NAFLD and risk of prevalent and incident CKD is robust, the association between severity of MAFLD and the risk of having or developing CKD remains uncertain (54,55). In a study from the NHANES-III database, it was reported that MAFLD with increased liver fibrosis scores was strongly associated with a greater risk of having CKD stage  $\geq 1$  or  $\geq 3$  and abnormal albuminuria (25). Another small prospective study of T2D patients with and without NAFLD followed for 75 months showed that the presence of NAFLD with high-risk fibrosis (defined as NAFLD fibrosis score  $>0.181$ ) conferred a greater eGFR reduction (58.7% vs. 37%;  $P=0.04$ ) and higher risk of CKD progression (defined as decrease in  $>50\%$  eGFR) ( $P<0.001$ ) (56). In a meta-analysis, participants with T2D and steatohepatitis (where by definition all subjects had MAFLD) there was a 3.8-fold risk of prevalent CKD (95% CI: 1.47–9.81,  $I^2=0\%$ ,  $n=3,119$  participants) and a 2.5-fold increased risk of incident CKD (95% CI: 1.05–6.17,  $I^2=0\%$ ,  $n=396$  participants) compared with their counterparts who had simple steatosis (53). Furthermore, in subjects who had T2D and NAFLD with advanced fibrosis (F3/F4) (subjects all fulfilling the MAFLD criteria), there was a 5.1-fold increased risk of prevalent CKD (95% CI: 1.46–17.21,  $I^2=0\%$ ,  $n=3,120$  participants) and a 4.2-fold increased risk of incident CKD (95% CI: 2.10–8.38,  $I^2=0\%$ ,  $n=397$  participants), compared to those subjects with non-advanced fibrosis (stage F0–2) (53). The above-mentioned studies indicate that MAFLD patients with steatohepatitis have a higher prevalence and incidence of CKD compared to those with simple steatosis alone. Further, MAFLD with advanced fibrosis has a higher prevalence and incidence of CKD than MAFLD without advanced fibrosis.

Transient elastography (TE) is extensively used in clinical practice as a non-invasive technique for measuring liver stiffness, a correlate of liver fibrosis. Consistently, TE identifies a subgroup of NAFLD patients who are at higher risk of developing liver-related clinical events (57–59). Our prior study also showed that the association between liver stiffness (assessed by TE) and risk of abnormal albuminuria was consistent with histological data obtained by liver biopsy (34). A meta-analysis of 7 cross-sectional studies also showed that increased liver stiffness was associated with an increased odds for both CKD (OR 2.49; 95% CI: 1.89–3.29;  $P<0.001$ ) and abnormal albuminuria (OR 1.98; 95% CI: 1.29–3.05;  $P=0.002$ ) in patients with NAFLD (60). Another

small study from 42 outpatients with established T2D showed that significant liver fibrosis [i.e., defined as liver stiffness  $\geq 7.0/6.2$  kPa (medium/extra-large probe)] was associated with an increased likelihood of CKD (OR 4.54; 95% CI: 1.24–16.60), independently of common cardiometabolic risk factors (61). Thus, liver stiffness, which is a surrogate of liver fibrosis and inflammation, is independently associated with an increased risk of CKD or albuminuria. While there are no specific studies on patients with MAFLD, data are awaited to better clarify the association between the severity of MAFLD and CKD progression.

It is important to emphasise that none of the aforementioned studies used renal biopsy to examine the pathology of CKD, so whether MAFLD is associated with a specific type of kidney injury is currently unknown. Moreover, it is also important to highlight that while we identify CKD by using a functional classification of CKD stages based on eGFR and proteinuria, we do not have a corresponding scale for evaluating the degree of hepatic function impairment. Recently, Aubert *et al.* reported that patients with diabetic kidney disease (confirmed by renal biopsy) and advanced liver fibrosis (F3–F4 stages) tended to have a greater annual eGFR decline ( $-3.27\pm 3.07$  vs.  $-6.29\pm 4.72$  mL/min/1.73 m<sup>2</sup>) compared to those with diabetic kidney disease without advanced liver fibrosis during a 75-month follow-up period (56).

### *Mechanisms linking MAFLD with CKD—statements*

#### **3.1–3.4 (Grade U in 3.1 and 3.4, Grade A in 3.3, Grade B in 3.2)**

Current evidence suggests that MAFLD may be an independent risk factor for CKD (29). A large cross-sectional study also showed that the metabolic syndrome and its individual components are independently associated with CKD (62). Therefore, as highlighted in the consensus statements, metabolic dysfunction in MAFLD might be an important mechanistic link between MAFLD and CKD as discussed below.

Firstly, convincing evidence showed that obesity plays an important role in the development and progression of both MAFLD and CKD (63–66). For example, in a retrospective study evaluating native kidney biopsies, obesity-related kidney disease increased in parallel with the worldwide epidemic of obesity. In that study, 56% of patients had overt proteinuria alone and 44% had overt proteinuria and CKD (67). At a mechanistic level, the renal physiologic responses to obesity include increases in glomerular filtration rate, renal

plasma flow, filtration fraction and tubular reabsorption of sodium, which exerts a high fluid shear stress on renal podocytes, thereby promoting maladaptive renal hypertrophy, podocyte detachment and global glomerulosclerosis.

Secondly, T2D has a substantial adverse impact on health and increases risk of both kidney and liver diseases. Strong evidence shows that chronic hyperglycaemia is a driving force for the development and progression of MAFLD and CKD, possibly through intraglomerular hypertension induced by glomerular hyperfiltration, increased formation of advanced glycation end-products, microinflammation and subsequent extracellular matrix expansion (68,69). Meanwhile, adipokines may also play important roles in kidney disease progression by promoting maladaptive responses of renal cells to the mechanical forces of hyperfiltration, thereby leading to podocyte depletion, proteinuria, focal segmental glomerulosclerosis and interstitial fibrosis (70).

Thirdly, abnormal lipid metabolism promotes increased triglyceride and cholesterol ester accumulation in the liver and kidneys (71). Increased lipids accumulate in mesangial cells, which may, in turn, transform to a type of foam cell, which activates insulin growth factor-1 and contributes to the loss of glomerular integrity. More importantly, renal fat accumulation as a result of increased fatty acid synthesis [which is mainly mediated by sterol regulatory element-binding protein 1c (SREBP-1c) and its target enzymes] may induce low-grade inflammation, oxidative stress and increased expression of multiple profibrotic growth factors (72-74). Finally, increased fat accumulation is associated with SREBP expression and activity, thus resulting in the development of renal disease (75). These results provide mechanistic data suggesting that metabolic dysfunction links MAFLD and CKD.

Findings from genome-wide association studies in large cohorts of well-phenotyped individuals show that the rs738409 C>G SNP encoding the I148M genetic variant of *PNPLA3* accounts for the largest fraction of genetic predisposition to fatty liver disease (76,77). Carriage of this genetic variant has also been associated with an increased risk of liver-related mortality and extrahepatic complications, especially kidney injury (46,78,79). *PNPLA3* is highly expressed both in the liver (by hepatic stellate cells and hepatocytes) and in the kidneys. Studies have shown that individuals with the *PNPLA3* rs738409 GG genotype are more likely to have lower levels of eGFR, and higher prevalence of both abnormal albuminuria and CKD, compared to those carrying the *PNPLA3* rs738409 GC and CC genotypes (46,80-83). Another study showed that this

*PNPLA3* genetic variant or other NAFLD-related genetic polymorphisms did not directly contribute to eGFR decline, but that metabolic risk factors were more important (84). However, such study did not retrieve data on albuminuria, so that the CKD diagnosis was based only on eGFR values. Evidence about the association between MAFLD, *PNPLA3* rs738409 variant and CKD is still limited since the data have only accrued for less than 2 years. Further studies are therefore needed to better understand the role of the *PNPLA3* rs738409 variant (or other MAFLD-related genetic polymorphisms) in the development and progression of CKD, and to elucidate the function of the mutant *PNPLA3* protein in the kidney.

Recent studies have unveiled a role for the liver-gut-kidney axis in both health and disease states (85-88). Gut microbiota is thought to be one of the major contributing factors to the pathophysiology of CKD associated with fatty liver. Gut microbiome homeostasis is important for health and its imbalance can lead to bacterial translocation, as well as the release of microbial products like lipopolysaccharide, indoxyl sulphate, p-cresyl sulphate and trimethylamine N-oxide (TMAO) into the circulation, where they may contribute to low-grade inflammation. These factors may also increase the risk of both MAFLD and CKD (85,89,90). On the other hand, MAFLD may alter gut microbiota composition and contribute to the development and progression of CKD associated with MAFLD. For instance, gut microbiota metabolizes dietary components such as choline and carnitine to produce TMAO, which may induce kidney and liver injuries. A cohort study of 521 subjects with 5-year follow-up showed that compared to non-CKD individuals, patients with CKD had higher plasma levels of TMAO and that plasma TMAO levels were associated with a near 1.9-fold increase in mortality risk after adjustment for traditional renal risk factors (91). Meanwhile, compared to non-steatotic controls, patients with fatty liver disease had higher plasma TMAO levels, which were positively correlated with serum bile acid concentrations and the mRNA expression of hepatic CYP7A1 (92). Experimentally, administration of TMAO to mice induced progressive renal tubulo-interstitial injury and fibrosis, while in mice fed a high-fat diet TMAO administration exacerbated hepatic steatosis by inhibiting hepatic farnesoid X receptor signalling and up-regulating hepatic *de novo* lipogenesis (92). Although current evidence is inconclusive and further studies are needed, the aforementioned studies suggest that alterations in gut microbiota may be linked to both MAFLD and CKD.

A study has identified various immune mechanisms which play a key role in NAFLD pathogenesis, especially triggering low-grade inflammation, and which are rooted in intrahepatic and extrahepatic systems (93). Extrahepatic factors include multiple organ crosstalk between inflammatory signals derived from the gut, adipose tissue, skeletal muscles and bone marrow, and some intrahepatic factors such as the cholangiocytes that are recognised as a potential driver of low-grade inflammation in NAFLD. However, to date, we are uncertain on how specific immune cell subsets interact and how they interact with stromal liver cells during NAFLD development and progression. Even less is known about how immune-mediated molecular mechanisms are implicated in the pathologic interaction between the liver and kidney in MAFLD. It is known that low-grade inflammation plays a key role in the development and progression of CKD. A prospective study of 2,838 Chinese patients with T2D (with or without chronic hepatitis B virus infection who were followed for a median of 3.5 years) showed that the presence of liver inflammation was associated with increased risk of ESRD, and this was independent of other potential confounding factors (94). Finally, emerging evidence supports a potential pathogenic role of the hepato-renal reflex in CKD development which may be triggered by subclinical portal hypertension (95), although further research in this area is needed.

#### ***Managing and treating MAFLD and CKD—statements 4.1–4.5 (Grade U for 4.1–4.5)***

Currently, there are no specific treatment guidelines for patients with CKD and MAFLD. However, MAFLD and CKD share multiple cardiometabolic risk factors and therapeutic strategies for MAFLD and CKD should be similar and primarily focussed on improving all coexisting renal and metabolic risk factors.

Lifestyle intervention (including a hypocaloric diet and regular physical activity) is associated with improvements in both MAFLD and CKD, though the extent of benefit might be different for each disease (96–100). For example, a large prospective study in real-world clinical practice showed that modest (7–10%) and good ( $\geq 10\%$ ) weight reduction induce significant improvements in liver histology in patients with steatohepatitis (101). A recent study that included 261 patients with biopsy-proven NASH also showed that a one-stage reduction in liver fibrosis and resolution of steatohepatitis was associated with an improvement in kidney function parameters (102). Recently,

an aerobic exercise intervention study of patients with biopsy-proven MAFLD showed that a 12-week intervention reduced liver fibrosis and hepatocyte ballooning by one stage in 58% ( $P=0.034$ ) and 67% ( $P=0.02$ ) of these patients, respectively (103). Another study including obese patients with T2D and CKD reported that a combined diet and exercise intervention reduced proteinuria compared to a diet only (104). A further study of overweight and obese patients with T2D showed that weight loss improved renal function parameters (105). Therefore, a body of evidence supports the notion that lifestyle interventions play an important role in the prevention and management of both MAFLD and CKD.

Current evidence indicates that MAFLD and CKD are two risk factors for adverse cardiovascular outcomes and all-cause mortality (106–109). Increasing evidence recommends that patients with MAFLD should be treated early and aggressively for obesity and other coexisting cardiometabolic risk factors (110,111). Most available drugs that target cardiometabolic risk factors exert their actions either directly or indirectly on glucose and lipid metabolism. Newer classes of glucose-lowering agents, such as glucagon like peptide-1 (GLP-1) receptor agonists (mostly subcutaneous liraglutide and semaglutide) and SGLT2 inhibitors, not only exert some beneficial effects on the liver (especially hepatic steatosis and necro-inflammation), but also have clinically meaningful effects on cardiovascular and kidney outcomes (112–117). Statin use also markedly reduces the risk of fatal and nonfatal cardiovascular disease events associated with MAFLD (118,119) and may contribute to reduce the risk of MAFLD development (120). Similarly, in patients with CKD not requiring dialysis, statin use decreases the risk of all-cause mortality and major adverse cardiovascular events (121). Therefore, an early and aggressive treatment of coexisting cardiometabolic risk factors will help prevent or slow the development and progression of both MAFLD and CKD.

Hypertension is an established cardiovascular risk factor and a major component of the metabolic syndrome. The coexistence of hypertension and MAFLD has been reported to be common and to increase metabolic and cardiovascular risks (122). The strong association and similar pathogenic profile of MAFLD and hypertension suggests that treatment with antihypertensive agents might be beneficial in hypertensive subjects with MAFLD (123). Although no large randomized controlled trials have specifically investigated the long-term effect of antihypertensive agents on MAFLD, inhibitors of the renin-angiotensin-aldosterone system (RAAS) may be of benefit (124). For example, in a

small intervention study of 54 subjects with hypertension and fatty liver disease assigned to receive either valsartan or telmisartan, both treatments led to amelioration of insulin resistance and hepatic fibrosis improvement (123). A meta-analysis of seven interventional studies (1,066 participants) reported that treatment with RAAS inhibitors may exert beneficial effects on hepatic fibrosis or cirrhosis patients based on effects on liver histological endpoints (125). Another intervention study reported that telmisartan decreased liver fat content and serum free fatty acid levels in hypertensive patients with MAFLD (126). Several studies showed that RAAS inhibitors were associated with beneficial effects on proteinuria and the rate of eGFR decline in patients with CKD (127,128). Similarly, in a cross-sectional study of CKD individuals with or without NAFLD, treatment with RAAS inhibitors was associated with lower liver stiffness in those with NAFLD, compared to those without (129,130). Finally, and more interestingly, treatment with angiotensin-converting enzyme (ACE)-inhibitors may have beneficial effects on liver fibrosis (131). In a cohort study of 12,327 Asian individuals with NAFLD followed for at least 5 years, the authors found that treatment with ACE-inhibitors (but not with angiotensin II receptor antagonists) in those with hypertension, was associated with a lower risk of developing liver-related events, liver cancers, and cirrhotic complications, especially amongst those with CKD (131). Therefore, treatment with antihypertensive agents, especially RAAS inhibitors (if required), is clinically important in hypertensive patients with MAFLD for decreasing the risk of CKD.

Taken together, the current evidence from published studies suggest that increased clinical vigilance for the presence of MAFLD should be considered in patients with CKD. Patients with MAFLD and CKD should ideally be managed in teams, though the ideal model of care has not been identified.

### Study strengths and limitations

Although the Delphi method is a consensus-building initiative, it also comes with strengths and limitations. As an important strength, we employed 50 experts from six continents and more than 26 countries, comprising hepatologists, nephrologists, endocrinologists, diabetologists and other specialists with extensive research and clinical expertise. Delphi studies often involve a combination of in-person, in-depth deliberation and survey rounds for voting. However, in light of the geographical spread of the panel members and the COVID-19 travel

restrictions, we employed alternative modes for group discourse in which members were able to provide written comments on the draft by email and two survey rounds. We incorporated risk factors from the preliminary findings of our review and translated them into Delphi survey statements. We received and incorporated a large volume of open-ended comments across all four data collection components. Such feedback provided a mechanism for reconciling the different views. We however acknowledge that a combination of in-person and written feedbacks might have resulted in more comprehensive contributions overall. The increasing levels of agreement with the consensus statements across the two survey rounds, together with the high level of participation [83.3% (50/60) in the R1-survey and 100% (50/50) in the R2-survey], further strengthens our confidence in the results. The experts' ability to include detailed comments on each of the draft statements enabled us to improve them, as reflected in the increasing level of agreement with the statements in the second round, from 93.05% in the R1-survey to 97.8% in the R2-survey. Unlike NAFLD and CKD where after 40 years there has been an organic consensus, for MAFLD and CKD we are just beginning to acquire the relevant data to set a baseline for ongoing improvements in knowledge.

### Conclusions

MAFLD and CKD are two highly prevalent and interconnected conditions, posing a challenge to global public health. In this Delphi-based consensus statement, several international experts from different countries developed and endorsed a set of consensus statements that provide guidance on the epidemiology, mechanisms, management and treatment of MAFLD and CKD, as well as the relationship between the severity of MAFLD and risk of CKD. These consensus statements establish a framework for the early prevention and management of these two common and interconnected diseases.

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### Footnote

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