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Mohamed A Nasreldin *

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Review Article

The Entanglement between Metabolic Associated Non- Alcoholic Fatty liver Disease and Chronic Kidney Disease Progression is more than just a Strong Correlation. A Narrative Review

Mohamed A Nasreldin [1*], Sayed Essam [1], Muaz Ahmed [1], Mahmoud Alnokeety [1], Tamer Elsalamony [1], Abdulsalam Noor [1], Ibraheem Saeed [1]

[1] University of south wales (UK), University of IAU (KSA), USW (UK), University of Cairo, KFHU (KSA).

***Corresponding Author:** Mohamed A Nasreldin, University of Dammam, KFHU, KSA.

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Abstract

The aim of this narrative review is to shed light on the correlation between metabolic-associated fatty liver disease (MAFLD) and chronic kidney disease progression (CKD). There is robust evidence from the current and recent literature that MAFLD is strongly associated with CKD incidence and progression regardless of the other confounding factors such as DM, hypertension, dyslipidemia, age, and gender. we believe that MAFLD and CKD are two important health issues, both have a global and economic burden that will continue to rise over the coming years. Primary and secondary care physicians, particularly nephrologists should be fully aware of the impact of MAFLD on CKD patients so they can participate actively in the management plan of these patients to reduce the comorbidities and economic costs associated with it.

Methodology:

The review identified and included the most recent few studies that described the problem of interest. Recommendations are given based on our perception, interpretation, and synthesis of data from the reviewed literature.

Results:

The existence of a strong correlation between MAFLD and CKD was persistent across all the reviewed studies and articles. This correlation was independent of other traditional risk factors such as hypertension, diabetes mellitus, hyperlipidemia, gender, and age.

Conclusion:

The global prevalence of MAFLD among the general population is high reaching 30% and almost 50% of CKD patients have MAFLD. There is a strong and independent association between MAFLD and CKD incidence and progression, thus patients diagnosed with CKD should be screened for MAFLD and managed accordingly to prevent and delay CKD progression.

Keywords: NAFLD; NASH; MAFLD; CKD; fatty liver disease; microalbuminuria; hypertension; DM

Introduction

Nonalcoholic fatty liver disease (NAFLD) is characterized by the presence of hepatic steatosis when no other causes for secondary hepatic fat accumulation are present. NAFLD can progress to cirrhosis. It is important to know that NAFLD is subclassified into nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). In NAFL, hepatic steatosis is present without evidence of significant inflammation, whereas in NASH, hepatic steatosis is associated with hepatic inflammation.

The worldwide prevalence of NAFLD is 35%, In a prospective study of 400 US military personnel and their families (mean age 55 years), the prevalence of NAFLD diagnosed by ultrasound was 46%. The diagnosis of MAFLD is based on the presence of hepatic steatosis (detected by serum biomarker scores, imaging techniques or liver biopsy) and at least one of the following metabolic criteria: (a) obesity, (b) T2DM, and (c)

metabolic disorders, i.e., at least two additional factors amongst increased waist circumference, hypertension, hypertriglyceridemia, low serum HDL-cholesterol levels, impaired fasting glucose, insulin resistance or subclinical inflammation. It is essential to mention that several observational studies have recently revealed and reported that the definition of MAFLD, compared with NAFLD may significantly improve the stratification of patients at higher risk of developing hepatic and extra-hepatic complications, such as CKD progression, the topic of this narrative review. Chronic kidney disease (CKD) is associated with an increased risk of morbidity and mortality, as well as with a high economic cost [18]. The prevalence of CKD worldwide is approximately 10% and it is expected that CKD might become the fifth cause of death globally in 2040. Several retrospective and prospective observational studies and systematic reviews during the last fifteen years proved the existence of a strong correlation between NAFLD and CKD progression, however the new term of MAFLD is more helpful and meaningful in stratification of CKD patients at substantial risk of progression. Several epidemiological studies and meta-analyses have demonstrated that NAFLD (detected by blood biomarkers/scores, imaging techniques, International Classification of Diseases codes or liver biopsy) is associated with an increased risk of incident CKD, independent of established CKD risk factors, diabetes, hypertension, proteinuria, and other potential confounders (20-25). The correlation between the two diseases is complex and important at the same time because both diseases are current global health issues and will continue to be a global and economic burden in the future if no serious preventive measures are put in place.

NAFLD and Risk of CKD progression:

The meta-analysis of 13 observational longitudinal studies involving nearly 1 200 000 middle-aged individuals (28.1% with NAFLD; n=3 43 248) from different countries revealed that the long-term risk of developing CKD stage ≥3 is increased ~1.45-fold in individuals with NAFLD (Mantovani, et al. 2020). This risk increases with the severity of liver fibrosis. The table [1] demonstrates the findings of a systematic analysis of 9 studies by (Mantovani, et al. 2017)

Table 1 – Principal observational cohort studies examining the association between NAFLD and the risk of incident stage ≥3 CKD.

Authors, year (Ref.)	Study characteristics	Diagnosis of NAFLD	Diagnosis of CKD & number of incident cases	Covariate adjustments	Main findings
Ryu S et al., 2007 [19]	Community-based cohort study: 10,337 nondiabetic and non-hypertensive South Korean male workers with normal kidney function and no overt proteinuria at baseline. Follow-up: 3 years	Liver enzymes (i.e., serum GGT levels)	eGFR <60 ml/min/ 1.73 m^2 and/or overt proteinuria (urinary dipstick ≥1); 366 patients developed incident CKD during follow-up	Age, BMI, alcohol intake, smoking, baseline eGFR, triglycerides, HDL-cholesterol, C-reactive protein, HOMA-insulin resistance, and incident cases of hypertension and diabetes	Elevated serum GGT levels (i.e., top quartile) were independently associated with increased risk of incident CKD (aHR 1.87; 95% CI 1.31–2.67)
Chang Y et al., 2008 [20]	Community-based cohort study: 8329 nondiabetic and non-hypertensive South Korean men with normal kidney function and no overt proteinuria at baseline. Follow-up: 3.2 years	Ultrasonography; the prevalence of NAFLD was 30.2%	eGFR <60 ml/min/ 1.73 m^2 and/or overt proteinuria (urinary dipstick ≥1); 324 patients developed incident CKD during follow-up	Age, BMI, alcohol intake, hypertension, smoking, fasting glucose, baseline eGFR, triglycerides, HDL-cholesterol, LDL-cholesterol, HOMA-insulin resistance, C-reactive protein, incident cases of hypertension and diabetes	NAFLD was independently associated with increased risk of incident CKD (aHR 1.60; 95% CI 1.3–2.0)
Targher G et al., 2008 [21]	Prospective cohort study (Valpolicella Heart Diabetes Study): 1760 Italian type 2 diabetic outpatients with preserved kidney function and no overt proteinuria, free of cardiovascular disease and known chronic liver diseases at baseline. Follow-up: 6.5 years	Ultrasonography; prevalence of NAFLD was 73.2%	eGFR <60 ml/min/ 1.73 m^2 and/or overt proteinuria; 547 patients developed incident CKD during follow-up (428 developed decreased eGFR alone, 112 developed proteinuria, irrespective of eGFR, and 7 developed kidney failure; no patients developed nephrotic syndrome)	Age, sex, BMI, waist circumference, blood pressure, smoking, diabetes duration, hemoglobin A1c, triglycerides, HDL-cholesterol, LDL-cholesterol, baseline eGFR, use of antihypertensive, lipid-lowering, antiplatelet and hypoglycemic agents	NAFLD was independently associated with increased risk of incident CKD (aHR 1.49; 95% CI 1.1–2.2)
Arase Y et al., 2011 [22]	Retrospective cohort study: 5561 Japanese middle-aged individuals with NAFLD and normal kidney function without overt proteinuria at baseline. Follow-up: 5.5 years	Ultrasonography and liver enzymes (i.e., serum GGT levels). Prevalence of NAFLD was 100%	eGFR <60 ml/min/ 1.73 m^2 and/or overt proteinuria (urinary dipstick ≥1+); 263 patients developed incident CKD during follow-up	Age, sex, hypertension, diabetes, total cholesterol, triglycerides, HDL-cholesterol, serum liver enzymes, hemoglobin, white blood cells, platelets, baseline eGFR	Among patients with NAFLD, elevated serum GGT levels were independently associated with an increased risk of incident CKD (aHR 1.35; 95% CI 1.02–1.8)
Targher G et al., 2014 [23]	Prospective cohort study: 261 Italian type 1 diabetic adult outpatients with normal kidney function, free of cardiovascular disease and known chronic liver diseases at baseline. Follow-up: 5.2 years	Ultrasonography; prevalence of NAFLD was 50.2%	eGFR <60 ml/min/ 1.73 m^2 and/or overt proteinuria; 61 patients developed incident CKD during follow-up (28 developed decreased eGFR with abnormal albuminuria, 21 developed reduced eGFR alone, and 12 developed macroalbuminuria alone; no patients developed kidney failure; no patients developed nephrotic syndrome)	Age, sex, diabetes duration, hemoglobin A1c, hypertension, baseline eGFR, presence of microalbuminuria	NAFLD was independently associated with an increased risk of incident CKD (aHR 1.85; 95% CI 1.03–3.3). Measurement of NAFLD provided incremental risk reclassification beyond that of conventional CKD risk factors
Huh JH et al., 2017 [24]	Prospective cohort study: 4761 South Korean adults with normal kidney function and no overt proteinuria and free of cardiovascular disease and known chronic liver	Fatty liver index (FLI); prevalence of NAFLD (defined as FLI ≥60) was 12.6%	eGFR <60 ml/min/ 1.73 m^2; 724 individuals developed incident CKD during follow-up	Age, sex, smoking, diabetes status, physical exercise, alcohol intake, protein intake, systolic blood pressure, total cholesterol, C-reactive protein, baseline eGFR	FLI ≥60 was independently associated with increased risk of incident CKD (aHR 1.46; 95% CI 1.19–1.79). FLI provided incremental

(continued on next page)

Table 1 (continued)

Authors, year (Ref.)	Study characteristics	Diagnosis of NAFLD	Diagnosis of CKD & number of incident cases	Covariate adjustments	Main findings
	diseases at baseline. Mean follow-up: 10 years				risk reclassification beyond that of conventional CKD risk factors
Shen ZW et al., 2017 [25]	Prospective cohort study: 21,818 Chinese adults with normal kidney function and no overt proteinuria at baseline, who received routine health examination. Follow-up: 5 years	Liver enzymes (i.e., serum GGT levels)	eGFR <60 ml/min/ 1.73 m^2 and/or overt proteinuria (urinary dipstick ≥1+); 1456 individuals developed incident CKD during follow-up	Age, sex, BMI, alcohol intake, serum creatinine, albumin, alanine aminotransferase, hemoglobin, white blood count, triglycerides, total cholesterol, hypertension, smoking, history of cardiovascular disease, history of diabetes	Elevated serum GGT levels (i.e., top quartile) were independently associated with an increased risk of incident CKD (aHR 1.33, 95% CI 1.07–1.64)
Kunutsor SK and Laukkanen JA, 2017 [26]	Prospective cohort study (Kuopio Ischemic Heart Disease Study): 2338 Finnish middle-aged men with normal kidney function at baseline. Median follow-up: 25.6 years	Liver enzymes (serum GGT levels)	eGFR <60 ml/min/ 1.73 m^2; 221 individuals developed incident CKD during follow-up	Age, BMI, systolic blood pressure, history of hypertension, smoking, history of coronary heart disease, history of diabetes, total cholesterol, HDL-cholesterol, alcohol intake, baseline eGFR	Elevated serum GGT levels (i.e., top quartile) were not independently associated with increased risk of incident CKD (aHR 0.97, 95% CI 0.64–1.47)
Sinn DH et al., 2017 [27]	Retrospective cohort study: 41,430 South Korean adults with normal kidney function and no overt proteinuria at baseline, free from known chronic liver diseases. Follow-up: 4.2 years	Ultrasonography; advanced NAFLD fibrosis assessed by the NFS (≥−1.455), FIB4 score (≥1.45) or APRI index (≥0.5); prevalence of NAFLD was 34.3%	eGFR <60 ml/min/ 1.73 m^2; 691 participants developed incident CKD during follow-up	Age, sex, BMI, smoking, alcohol intake, systolic blood pressure, hemoglobin A1c, LDL-cholesterol, use of hypoglycemic and lipid-lowering medications, baseline eGFR, time-varying development of diabetes and hypertension over the follow-up	NAFLD was independently associated with increased risk of incident CKD (aHR 1.21, 95% CI 1.03–1.44). The association between NAFLD and CKD was consistent in all subgroups analyzed. In addition, advanced NAFLD fibrosis (as detected by a NFS ≥−1.455) was associated with even a higher risk of incident CKD (aHR 1.59, 95% CI 1.31–1.93). When NAFLD participants were classified according to APRI index and FIB4 score, those with higher APRI index or FIB4 score also had an increasing risk of incident CKD

Abbreviations: aHR, adjusted hazard ratio; AST, aspartate aminotransferase; APRI, AST to platelet ratio index; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FIB4, fibrosis-4 score; GGT, gamma-glutamyltransferase; HOMA, homeostasis model assessment; NFS, NAFLD fibrosis score.
Note: eGFR was estimated by using either the four-variable Modification of Diet in Renal Disease (MDRD) study equation or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) study equation (that was used by the last five studies reported in this table).

One can conclude from this systematic analysis that Patients with NAFLD are higher risk of incident CKD than those without NAFLD (random-effects hazard ratio [HR] 1.37, 95% CI 1.20–1.53; I 2 = 33.5%). These findings are consistent with the other studies that looked at the correlation between NAFLD and CKD in the current literature.

Correlation between MALD and CKD:

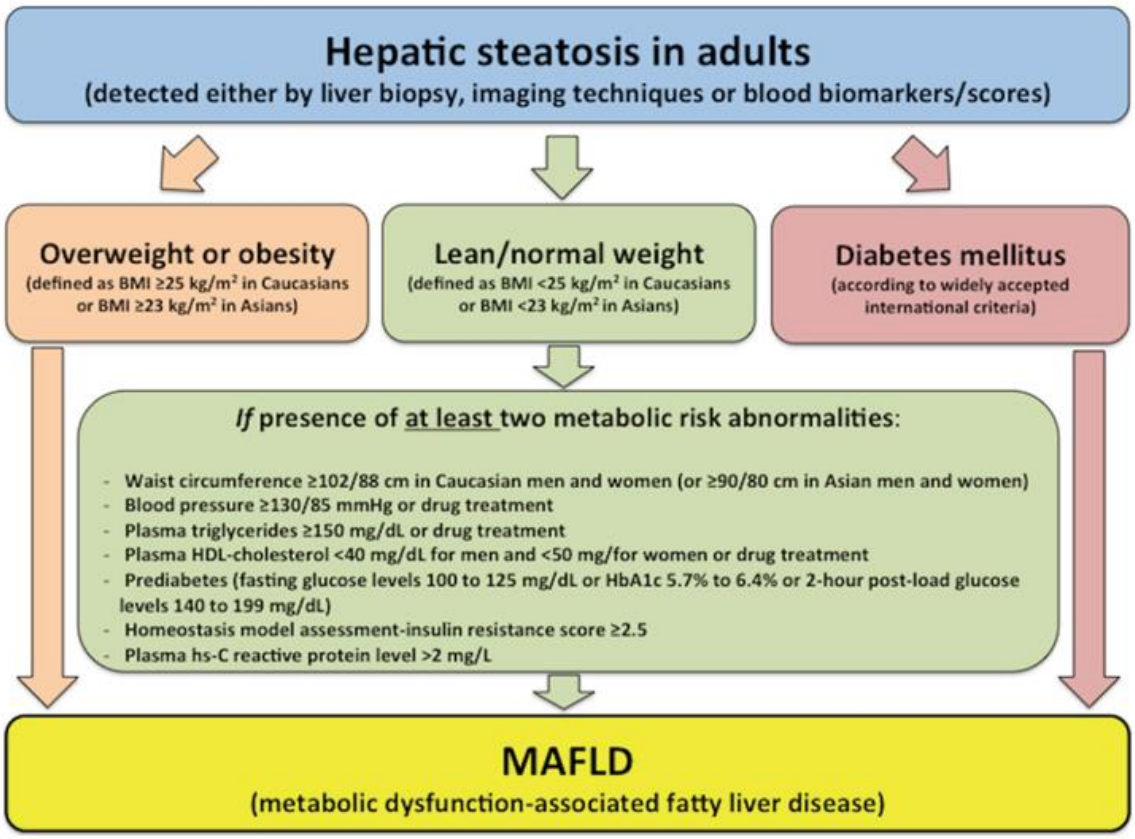
The table (2) below demonstrates the association between metabolic associated nonalcoholic liver disease (MALD) and chronic kidney disease (CKD), (Mantovani, et al.2022).

Reference	Study Characteristics	Definition of NAFLD/MAFLD	Prevalence of NAFLD and MAFLD	Definition of CKD	Main Results
[37]	Cross-sectional and prospective (mean follow-up 5.1 years) study: 268,946 US participants attending the National Health Insurance Service health (2009–2015) in the USA	Fatty liver index	• NAFLD: 27% • MAFLD: 33%	eGFR < 60 mL/min/1.73 m^2 and/or proteinuria (i.e., ≥trace on dipstick test)	• Patients with MAFLD had a significantly higher risk of developing CKD (adjusted HR 1.64, 95% CI 1.44–1.88) than patients with NAFLD. • This relationship was maintained after adjustments for confounding factors (adjusted HR 1.18, 95% CI 1.01–1.39). • The risk of incident CKD was even higher in those with overlapping fatty liver disease
[38]	Cross-sectional study: 12,571 US individuals included in the Third National Health and Nutrition Examination Survey (1988–1994) in the USA	Ultrasonography	• NAFLD: 36% • MAFLD: 30%	eGFR < 90 mL/min/1.73 m^2 and or urinary albumin-to-creatinine ratio (ACR) ≥3 mg/mmol	• MAFLD individuals had lower eGFR values (74.96 ± 18.21 vs. 76.46 ± 18.24 mL/min/1.73 m^2, $p < 0.001$) and a greater prevalence of CKD (29.6% vs. 26.6%, $p < 0.05$) when compared to NAFLD individuals • MAFLD was independently associated with an increased risk of CKD (OR 1.12, 95% CI 1.01–1.24), especially in the presence of advanced fibrosis as assessed by non-invasive markers (OR 1.34, 95% CI 1.06–1.69). • NAFLD was not independently associated with an increased risk of CKD (OR 1.06, 95% CI 0.96–1.17).

Reference	Study Characteristics	Definition of NAFLD/MAFLD	Prevalence of NAFLD and MAFLD	Definition of CKD	Main Results
[39]	Cross-sectional, prospective (median follow-up 4.6 years) study: 27,371 Japanese participants in medical health checkup program in Kyoto (2004–2014)	Ultrasonography	• NAFLD: 2.3% • MAFLD: 20.8%	eGFR < 60 mL/min/1.73 m^2 and/or proteinuria	• Compared to those without steatosis, patients with MAFLD had a higher risk of CKD (adjusted OR 1.83, 95% CI 1.66–2.01), whereas patients with NAFLD did not (adjusted OR 1.02, 95% CI 0.79–1.33) • MAFLD was independently associated with an increased risk of incident CKD (adjusted HR 1.30, 95% CI 1.14–1.36), while NAFLD was not (adjusted HR 1.11, 95% CI 0.85–1.41)
[40]	Cross-sectional and prospective (median follow-up 4.6 years) study: 4869 US subjects from the National Health and Nutrition Examination Surveys (NHANES 2017–2018) in the USA	CAP >240 dB/min	• MAFLD: 57%	eGFR < 60 mL/min/1.73 m^2 and/or proteinuria	• There was a higher prevalence of CKD in MAFLD subjects than in non-MALFD subjects (22.2% vs. 19.1%, respectively, $p = 0.048$). • After 1:1 propensity score matching by gender, age, and race, MAFLD was not independently associated with CKD
[41]	Cross-sectional study: 19,617 US subjects from the National Health and Nutrition Examination Surveys in the USA over four periods: 1999–2002; 2003–2006; 2007–2010; 2011–2016	Fatty liver index >30	• NAFLD 1999–2002: 26% 2003–2006: 29% 2007–2010: 32% 2011–2016: 33% • MAFLD 1999–2002: 28% 2003–2006: 31% 2007–2010: 34% 2011–2016: 36%	eGFR < 60 mL/min/1.73 m^2 and/or albumin-to-creatinine ratio (ACR) ≥30 mg/g	• The risk of having CKD in the MAFLD group was only moderately higher than in the NAFLD group
[42]	Cohort study (median follow-up 4.6 years): 6873 Chinese subjects from The Shanghai Nicheng Cohort Study	Ultrasonography	• NAFLD: 40% • MAFLD: 46.7%	eGFR < 60 mL/min/1.73 m^2 and/or albumin-to-creatinine ratio (ACR) ≥30 mg/g	• Similar risks of incident CKD in the MAFLD group (relative risk 1.71, 95% CI 1.44–2.04) and NAFLD group (relative risk 1.70, 95% CI 1.43–2.01)

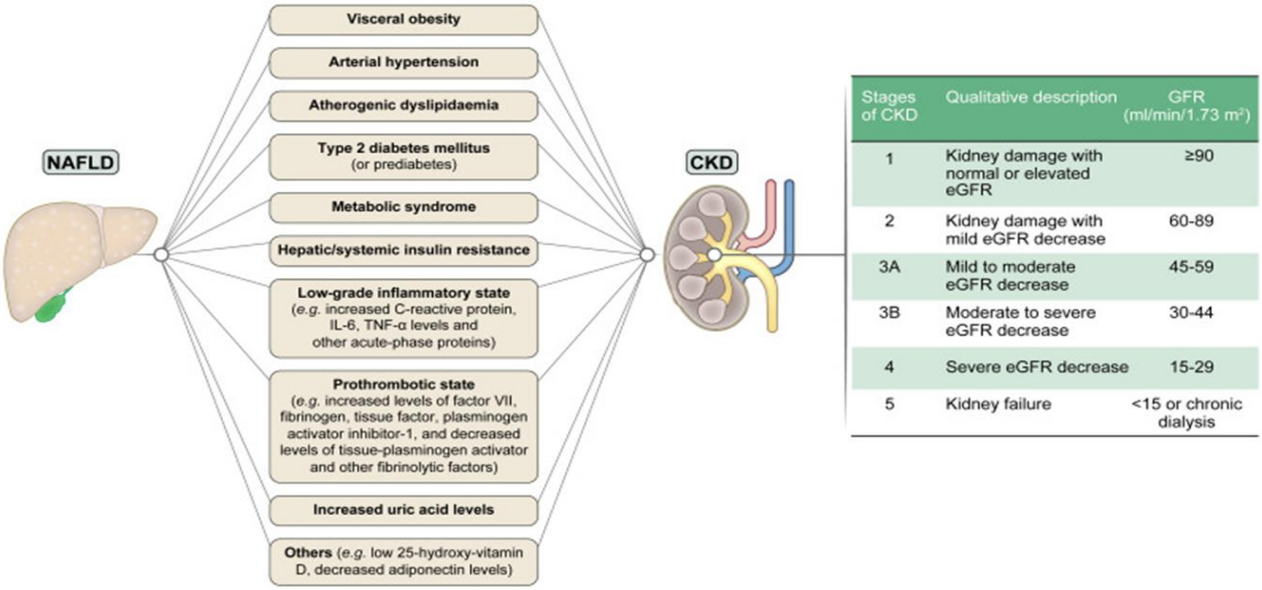
Abbreviations: ACR, albumin-to-creatinine ratio; CAP, controlled attenuation parameter; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MAFLD, metabolic associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease; OR, odds ratio.

We believe that the notion of metabolic associated nonalcoholic fatty liver disease (MAFLA) is clearer and more comprehensive for nephrologist, general internists, family medicine physicians, endocrinologists, and primary care physicians, when they stratify patients at high risk of developing CKD or CKD progression, albeit there is no great statistical difference between MAFLD and NAFLD in terms of CKD risk. However, several studies in the previous systematic review had shown that the risk of CKD and CKD progression is higher in the MALD group compared to NAFLD group. Thus, a holistic approach to manage this category of patients is extremely important at the level of primary and secondary care. The figure below can help and guide the concerned physicians to detect MALD as early as possible.



Pathogenesis:

The pathogenesis of MAFLD and CKD is very complex, and it is still difficult to say that MAFLD can cause CKD, though there is robust evidence about the existence of a strong correlation between the two conditions regardless of the existence of other confounding factors such as diabetes mellitus, hypertension, and proteinuria. The illustration below demonstrates how the traditional risk factors are entangled between the two diseases.



Stages of CKD	Qualitative description	GFR (ml/min/1.73 m²)
1	Kidney damage with normal or elevated eGFR	≥90
2	Kidney damage with mild eGFR decrease	60-89
3A	Mild to moderate eGFR decrease	45-59
3B	Moderate to severe eGFR decrease	30-44
4	Severe eGFR decrease	15-29
5	Kidney failure	<15 or chronic dialysis

Genetic role:

The *PNPLA3* rs738409 polymorphism which is associated with a predisposition to NASH has recently been shown to associate with worse kidney function, (Guangrong Dai, et al. 2019). One can extrapolate from this genetic evidence, that any patient with MAFLD is at high risk of CKD and CKD progression.

Nephrologists and MAFLD, what can be done?

Nephrologists are amongst the first line physicians who can detect MAFLD because of high rate of patient's referral and consultations as well as high rate of requesting abdominal ultrasound. However, the lack of current strong evidenced guidelines and management policy make the

concise management of such patients weak. To entice the attention of nephrologists and renal medicine clinicians to this health problem, one must speak of CKD progression risk based on the CKD stages and albuminuria (KDIGO guidelines) as illustrated in the table below. The risk of CKD progression and cardiovascular disease increase as the patients GFR decreases but it is not just the GFR that determines the risk of CKD progression but also the level of albuminuria, i.e., a patient with CKD stage 1 and proteinuria A3 will have the same risk of CKD progression as a patient with CKD stage 3b without microalbuminuria. One can imagine if MAFLD status is added to the table of CKD stages and albumin to creatinine ratio how the colors of CKD progression risk would change. This suggestion can help nephrologists to stratify patients at risk of CKD progression better than before and to manage patients with MAFLD and CKD properly rather than just advising them to reduce weight because weight loss at this stage is a treatment goal and should be achieved by all available means and monitored. Patients with advanced MAFLD with liver fibrosis should be referred to hepatologist as early as possible.

Classification of chronic kidney disease using GFR and ACR categories

GFR and ACR categories and risk of adverse outcomes			ACR categories (mg/mmol), description and range		
			<3 Normal to mildly increased	3–30 Moderately increased	>30 Severely increased
			A1	A2	A3
GFR categories (ml/min/1.73m²), description and range	≥90 Normal and high	G1	No CKD in the absence of markers of kidney damage		
	60–89 Mild reduction related to normal range for a young adult	G2			
	45–59 Mild–moderate reduction	G3a[1]			
	30–44 Moderate–severe reduction	G3b			
	15–29 Severe reduction	G4			
	<15 Kidney failure	G5			

Increasing risk

Increasing risk

[1] Consider using eGFRcystatinC for people with CKD G3aA1 (see recommendations 1.1.14 and 1.1.15)

Abbreviations: ACR, albumin:creatinine ratio; CKD, chronic kidney disease; GFR, glomerular filtration rate

Adapted with permission from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group (2013) KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney International (Suppl. 3): 1–150

Diagnosis of MAFLD:

The diagnosis of MAFLD can be performed based on the presence of:

- Hepatic steatosis (detected by serum biomarker scores, imaging techniques or liver biopsy) and at least one of the following metabolic criteria:
- (a) overweight/obesity,
- (b) T2DM,
- (c) metabolic dysregulation.

Non-Medical Management:

- Dietician consultation.
- Regular exercise
- Participation in weight reduction programs.

Medical Management:

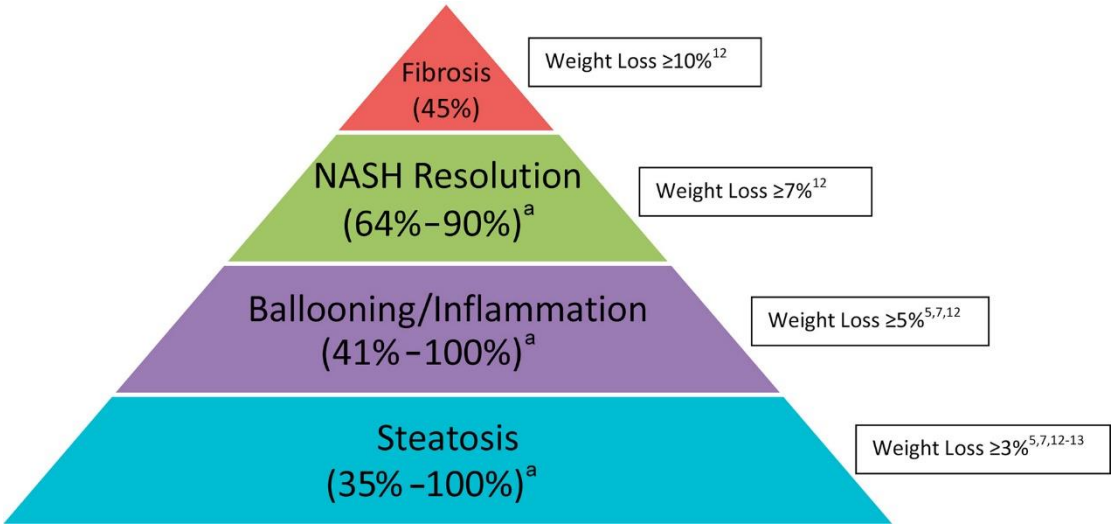
Unfortunately, there is no specific cure for MAFLD but luckily these days there are many drugs and treatment options that can help reduce weight

and proteinuria at the same time and reduce the risk of renal function decline as well as reducing the risk of cardiovascular disease. Medications such as metformin, SGLT2 inhibitors, G LIKE 1 receptor agonists etc. Some authors suggest Vitamin E (800 international units per day) (level of evidence is Grade 2C).

Surgical Management:

Bariatric surgery, patients with NASH or advanced fibrosis (but without decompensated cirrhosis) for bariatric surgery if they do not meet their weight loss goals after six months of lifestyle interventions.

The main goal of either medical or surgical management is to reduce weight because early weight reduction can reverse the disease and decrease the risk of liver fibrosis as well as risk of developing CKD or CKD progression. The figure below (William N, et al. 2016) shows how weight reduction is effective.



Laboratory monitoring:

- AST AND ALT three and six months after patients with NAFLD implement lifestyle interventions for weight loss.
- AST AND ALT three and six months after patients with NAFLD implement lifestyle interventions for weight loss.
- For patients who achieve their weight loss goals and have normal serum aminotransferases, obtain a noninvasive assessment every four years.

When patients should be referred to hepatologist?

- Aminotransferases (alanine aminotransferase and aspartate aminotransferase) that remain elevated despite loss of ≥5 percent of body weight (to evaluate for other etiologies of liver disease)
- Aminotransferases (alanine aminotransferase and aspartate aminotransferase) that remain elevated despite loss of ≥5 percent of body weight (to evaluate for other etiologies of liver disease)
- Steatohepatitis on liver biopsy
- Steatohepatitis on liver biopsy

Recommendations:

- The use of the new definition MAFLD, compared to NAFLD, offers numerous advantages in clinical, epidemiological, risk stratification of CKD and research terms in the future.
- Patients diagnosed with NAFLD and at considerable risk of CKD should be managed by a multidisciplinary approach and motivated to change lifestyle and reduce weight.
- Future prospective studies involving different ethnicities to further explore the association between MAFLD, and CKD progression should be encouraged
- Based on the evidence from the current and recent literature about the strong correlation of MAFLD and CKD regardless of the existence of proteinuria, we suggest that MAFLD should be added to the KDIGO table of CKD stages and albumin to creatinine ratio to better stratify patients at risk of CKD and CVD. This can enable concerned physicians to put effective preventive measures in place.

Conclusion:

The entanglement between MAFLD and CKD incidence and progression seems to be more than just a simple correlation as evidenced in the current literature, however more randomized controlled studies should be encouraged in the future to explore the causal relationship between them. Meanwhile it is important to set forward early management and preventive measures in patients with CKD and MAFLD to avoid rapid decline of kidney function and CKD progression.

References:

1. Mantovani, A.; Scorletti, E.; Mosca, A.; Alisi, A.; Byrne, C.D.; Targher, G. Complications, morbidity and mortality of nonalcoholic fatty liver disease. Metabolism 2020, 111, 154170. [CrossRef] [PubMed]
2. Younossi, Z.M.; Koenig, A.B.; Abdelatif, D.; Fazel, Y.; Henry, L.; Wymer, M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016, 64, 73–84. [CrossRef] [PubMed]
3. Le, M.H.; Yeo, Y.H.; Li, X.; Li, J.; Zou, B.; Wu, Y.; Ye, Q.; Huang, D.Q.; Zhao, C.; Zhang, J.; et al. 2019 Global NAFLD Prevalence: A Systematic Review and Meta-analysis. Clin. Gastroenterol. Hepatol. 2021. [CrossRef] [PubMed]
4. Younossi, Z.M.; Golabi, P.; de Avila, L.; Paik, J.M.; Srishord, M.; Fukui, N.; Qiu, Y.; Burns, L.; Afendy, A.; Nader, F. The global epidemiology of NAFLD and NASH in patients with

type 2 diabetes: A systematic review and meta-analysis. J. Hepatol. 2019, 71, 793–801. [CrossRef] [PubMed]
5. Lonardo, A.; Mantovani, A.; Lugari, S.; Targher, G. Epidemiology and pathophysiology of the association between NAFLD and metabolically healthy or metabolically unhealthy obesity. Ann. Hepatol. 2020, 19, 359–366. [CrossRef]
6. Byrne, C.D.; Targher, G. NAFLD: A multisystem disease. J. Hepatol. 2015, 62, S47–S64. [CrossRef]
7. Mantovani, A.; Csermely, A.; Petracca, G.; Beatrice, G.; Corey, K.E.; Simon, T.G.; Byrne, C.D.; Targher, G. Non-alcoholic fatty liver disease and risk of fatal and non-fatal cardiovascular events: An updated systematic review and meta-analysis. Lancet Gastroenterol. Hepatol. 2021, 6, 903–913. [CrossRef]
8. Mantovani, A.; Petracca, G.; Beatrice, G.; Tilg, H.; Byrne, C.D.; Targher, G. Non-alcoholic fatty liver disease and risk of incident diabetes mellitus: An updated meta-analysis of 501 022 adult individuals. Gut 2021, 70, 962–969. [CrossRef]
9. Mantovani, A.; Petracca, G.; Beatrice, G.; Csermely, A.; Lonardo, A.; Schattenberg, J.M.; Tilg, H.; Byrne, C.D.; Targher, G. Non-alcoholic fatty liver disease and risk of incident chronic kidney disease: An updated meta-analysis. Gut 2022, 71, 156–162. [CrossRef]
10. Younossi, Z.M.; Rinella, M.E.; Sanyal, A.J.; Harrison, S.A.; Brunt, E.M.; Goodman, Z.; Cohen, D.E.; Loomba, R. From NAFLD to MAFLD: Implications of a Premature Change in Terminology. Hepatology 2021, 73, 1194–1198. [CrossRef]
11. Wong, V.W.; Lazarus, J.V. Prognosis of MAFLD vs. NAFLD and implications for a nomenclature change. J. Hepatol. 2021, 75, 1267–1270. [CrossRef] [PubMed]
12. Fouad, Y.; Dufour, J.F.; Zheng, M.H.; Bollipo, S.; Desalegn, H.; Gronbaek, H.; Gish, R.G. The NAFLD-MAFLD debate: Is there a Consensus-on-Consensus methodology? Liver Int. 2022, 42, 742–748. [CrossRef] [PubMed]
13. Eslam, M.; Newsome, P.N.; Sarin, S.K.; Anstee, Q.M.; Targher, G.; Romero-Gomez, M.; Zelber-Sagi, S.; Wai-Sun Wong, V.; Dufour, J.F.; Schattenberg, J.M.; et al. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. J. Hepatol. 2020, 73, 202–209. [CrossRef]
14. Eslam, M.; Sanyal, A.J.; George, J.; International Consensus, P. MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease. Gastroenterology 2020, 158, 1999–2014.e1. [CrossRef]
15. Mantovani, A. MAFLD vs NAFLD: Where are we? Dig. Liver Dis. 2021, 53, 1368–1372. [CrossRef] [PubMed] 16. Mantovani, A.; Dalbeni, A. NAFLD, MAFLD and DAFLD. Dig. Liver Dis. 2020, 52, 1519–1520. [CrossRef] [PubMed]
16. Ayada, I.; van Kleef, L.A.; Alferink, L.J.M.; Li, P.; de Knegt, R.J.; Pan, Q. Systematically comparing epidemiological and clinical features of MAFLD and NAFLD by meta-analysis: Focusing on the non-overlap groups. Liver Int. 2022, 42, 277–287. [CrossRef]
17. Kalantar-Zadeh, K.; Jafar, T.H.; Nitsch, D.; Neuen, B.L.; Perkovic, V. Chronic kidney disease. Lancet 2021, 398, 786–802. [CrossRef]
18. Lv, J.C.; Zhang, L.X. Prevalence and Disease Burden of Chronic Kidney Disease. Adv. Exp. Med. Biol. 2019, 1165, 3–15. [CrossRef] Int. J. Mol. Sci. 2022, 23, 7007 10 of 11
19. Hounkpatin, H.O.; Harris, S.; Fraser, S.D.S.; Day, J.; Mindell, J.S.; Taal, M.W.; O'Donoghue, D.; Roderick, P.J. Prevalence of chronic kidney disease in adults in England: Comparison of nationally representative cross-sectional surveys from 2003 to 2016. BMJ Open 2020, 10, e038423. [CrossRef]
20. Mantovani, A.; Zusi, C.; Dalbeni, A.; Grani, G.; Buzzetti, E. Risk of Kidney Dysfunction IN Nafld. Curr. Pharm. Des. 2020, 26, 1045–1061. [CrossRef] [PubMed]
21. Byrne, C.D.; Targher, G. NAFLD as a driver of chronic kidney disease. J. Hepatol. 2020, 72, 785–801. [CrossRef]
22. Wang, T.Y.; Wang, R.F.; Bu, Z.Y.; Targher, G.; Byrne, C.D.; Sun, D.Q.; Zheng, M.H. Association of metabolic dysfunction-associated fatty liver disease with kidney disease. Nat. Rev. Nephrol. 2022, 18, 259–268. [CrossRef] [PubMed]
23. Cheung, A.; Ahmed, A. Nonalcoholic Fatty Liver Disease and Chronic Kidney Disease: A Review of Links and Risks. Clin. Exp. Gastroenterol. 2021, 14, 457–465. [CrossRef] [PubMed]
24. Tao, Z.; Li, Y.; Cheng, B.; Zhou, T.; Gao, Y. Influence of Nonalcoholic Fatty Liver Disease on the Occurrence and Severity of Chronic Kidney Disease. J. Clin. Transl. Hepatol. 2022, 10, 164–173. [CrossRef]
25. Musso, G.; Gambino, R.; Tabibian, J.H.; Ekstedt, M.; Kechagias, S.; Hamaguchi, M.; Hultcrantz, R.; Hagstrom, H.; Yoon, S.K.; Charatcharoenwitthaya, P.; et al. Association of non-alcoholic fatty liver disease with chronic kidney disease: A systematic review and meta-analysis. PLoS Med. 2014, 11, e1001680. [CrossRef]
26. Mantovani, A.; Zaza, G.; Byrne, C.D.; Lonardo, A.; Zoppini, G.; Bonora, E.; Targher, G. Nonalcoholic fatty liver disease increases risk of incident chronic kidney disease: A systematic review and meta-analysis. Metabolism 2018, 79, 64–76. [CrossRef]
27. Sinn, D.H.; Kang, D.; Jang, H.R.; Gu, S.; Cho, S.J.; Paik, S.W.; Ryu, S.; Chang, Y.; Lazo, M.; Guallar, E.; et al. Development of chronic kidney disease in patients with non-alcoholic fatty liver disease: A cohort study. J. Hepatol. 2017, 67, 1274–1280. [CrossRef]
28. Mahmoodi, B.K.; Matsushita, K.; Woodward, M.; Blankestijn, P.J.; Cirillo, M.; Ohkubo, T.; Rossing, P.; Sarnak, M.J.; Stengel, B.; Yamagishi, K.; et al. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without hypertension: A meta-analysis. Lancet 2012, 380, 1649–1661. [CrossRef]
29. Mantovani, A.; Turino, T.; Lando, M.G.; Gjini, K.; Byrne, C.D.; Zusi, C.; Ravaioli, F.; Colecchia, A.; Maffeis, C.; Salvagno, G.; et al. Screening for non-alcoholic fatty liver disease using liver stiffness measurement and its association with chronic kidney disease and cardiovascular complications in patients with type 2 diabetes. Diabetes Metab. 2020, 46, 296–303. [CrossRef]
30. Cacoub, P.; Desbois, A.C.; Isnard-Bagnis, C.; Rocatello, D.; Ferri, C. Hepatitis C virus infection and chronic kidney disease: Time for reappraisal. J. Hepatol. 2016, 65, S82–S94. [CrossRef] [PubMed]
31. Fabrizi, F.; Donato, F.M.; Messa, P. Association between hepatitis B virus and chronic kidney disease: A systematic review and meta-analysis. Ann. Hepatol. 2017, 16, 21–47. [CrossRef] [PubMed]

32. Lai, Y.J.; Chen, Y.Y.; Lin, Y.K.; Chen, C.C.; Yen, Y.F.; Deng, C.Y. Alcohol Consumption and Risk of Chronic Kidney Disease: A Nationwide Observational Cohort Study. Nutrients 2019, 11, 2121. [CrossRef] [PubMed]
33. Cheungpasitporn, W.; Thongprayoon, C.; Kittanamongkolchai, W.; Brabec, B.A.; O'Corragain, O.A.; Edmonds, P.J.; Erickson, S.B. High alcohol consumption and the risk of renal damage: A systematic review and meta-analysis. QJM 2015, 108, 539–548. [CrossRef]
34. Li, Y.; Zhu, B.; Song, N.; Shi, Y.; Fang, Y.; Ding, X. Alcohol consumption and its association with chronic kidney disease: Evidence from a 12-year China health and Nutrition Survey. Nutr. Metab. Cardiovasc. Dis. 2022, 32, 1392–1401. [CrossRef]
35. Bianco, C.; Romeo, S.; Petta, S.; Long, M.T.; Valenti, L. MAFLD vs NAFLD: Let the contest begin! Liver Int. 2020, 40, 2079–2081. [CrossRef]
36. Jung, C.Y.; Koh, H.B.; Park, K.H.; Joo, Y.S.; Kim, H.W.; Ahn, S.H.; Park, J.T.; Kim, S.U. Metabolic Dysfunction-Associated Fatty Liver Disease and Risk of Incident Chronic Kidney Disease: A Nationwide Cohort Study. Diabetes Metab. 2022, 48, 101344. [CrossRef]
37. Sun, D.Q.; Jin, Y.; Wang, T.Y.; Zheng, K.I.; Rios, R.S.; Zhang, H.Y.; Targher, G.; Byrne, C.D.; Yuan, W.J.; Zheng, M.H. MAFLD and risk of CKD. Metabolism 2021, 115, 154433. [CrossRef]
38. Hashimoto, Y.; Hamaguchi, M.; Okamura, T.; Nakanishi, N.; Obora, A.; Kojima, T.; Fukui, M. Metabolic associated fatty liver disease is a risk factor for chronic kidney disease. J. Diabetes Investig. 2022, 13, 308–316. [CrossRef]
39. Deng, Y.; Zhao, Q.; Gong, R. Association Between Metabolic Associated Fatty Liver Disease and Chronic Kidney Disease: A Cross-Sectional Study from NHANES 2017–2018. Diabetes Metab. Syndr. Obes. 2021, 14, 1751–1761. [CrossRef]
40. Zhang, H.J.; Wang, Y.Y.; Chen, C.; Lu, Y.L.; Wang, N.J. Cardiovascular and renal burdens of metabolic associated fatty liver disease from serial US national surveys, 1999–2016. Chin. Med. J. 2021, 134, 1593–1601. [CrossRef] [PubMed]
41. Liang, Y.; Chen, H.; Liu, Y.; Hou, X.; Wei, L.; Bao, Y.; Yang, C.; Zong, G.; Wu, J.; Jia, W. Association of MAFLD With Diabetes, Chronic Kidney Disease, and cardiovascular disease: A 4.6-Year Cohort Study in China. J. Clin. Endocrinol. Metab. 2022, 107, 88–97. [CrossRef] [PubMed]
42. Okamura, T.; Hashimoto, Y.; Hamaguchi, M.; Obora, A.; Kojima, T.; Fukui, M. Effect of alcohol consumption and the presence of fatty liver on the risk for incident type 2 diabetes: A population-based longitudinal study. BMJ Open Diabetes Res. Care 2020, 8, e001629. [CrossRef] [PubMed]
43. Jang, H.R.; Kang, D.; Sinn, D.H.; Gu, S.; Cho, S.J.; Lee, J.E.; Huh, W.; Paik, S.W.; Ryu, S.; Chang, Y.; et al. Nonalcoholic fatty liver disease accelerates kidney function decline in patients with chronic kidney disease: A cohort study. Sci. Rep. 2018, 8, 4718. [CrossRef] Int. J. Mol. Sci. 2022, 23, 7007 11 of 11
44. Vilar-Gomez, E.; Calzadilla-Bertot, L.; Friedman, S.L.; Gra-Oramas, B.; Gonzalez-Fabian, L.; Villa-Jimenez, O.; Lazo-Del Vallin, S.; Diago, M.; Adams, L.A.; Romero-Gomez, M.; et al. Improvement in liver histology due to lifestyle modification is independently associated with improved kidney function in patients with non-alcoholic steatohepatitis. Aliment Pharmacol. Ther. 2017, 45, 332–344. [CrossRef] [PubMed]
45. Mantovani, A. Time to revise the definition of NAFLD: A purist vision. Dig. Liver Dis. 2019, 51, 457–458. [CrossRef]
46. Eslam, M.; Valenti, L.; Romeo, S. Genetics and epigenetics of NAFLD and NASH: Clinical impact. J. Hepatol. 2018, 68, 268–279. [CrossRef]
47. Xia, M.; Zeng, H.; Wang, S.; Tang, H.; Gao, X. Insights into contribution of genetic variants towards the susceptibility of MAFLD revealed by the NMR-based lipoprotein profiling. J. Hepatol. 2021, 74, 974–977. [CrossRef]
48. Mantovani, A.; Taliento, A.; Zusi, C.; Baselli, G.; Prati, D.; Granata, S.; Zaza, G.; Colecchia, A.; Maffeis, C.; Byrne, C.D.; et al. PNPLA3 I148M gene variant and chronic kidney disease in type 2 diabetic patients with NAFLD: Clinical and experimental findings. Liver Int. 2020, 40, 1130–1141. [CrossRef]
49. Polyzos, S.A.; Kang, E.S.; Tsochatzis, E.A.; Kechagias, S.; Ekstedt, M.; Xanthakos, S.; Lonardo, A.; Mantovani, A.; Tilg, H.; Cote, I.; et al. Commentary: Nonalcoholic or metabolic dysfunction-associated fatty liver disease? The epidemic of the 21st century in search of the most appropriate name. Metabolism 2020, 113, 154413. [CrossRef]
50. Lee, H.; Lee, Y.H.; Kim, S.U.; Kim, H.C. Metabolic Dysfunction-Associated Fatty Liver Disease and Incident Cardiovascular Disease Risk: A Nationwide Cohort Study. Clin. Gastroenterol. Hepatol. 2021, 19, 2138–2147.e10. [CrossRef] [PubMed]
51. Byrne, C.D.; Targher, G. Non-alcoholic fatty liver disease is a risk factor for cardiovascular and cardiac diseases: Further evidence that a holistic approach to treatment is needed. Gut 2021. [CrossRef] [PubMed]
52. Mantovani, A.; Valenti, L. A call to action for fatty liver disease. Liver Int. 2021, 41, 1182–1185. [CrossRef] [PubMed] 54. Mantovani, A.; Dalbeni, A. Treatments for NAFLD: State of Art. Int. J. Mol. Sci. 2021, 22, 2350. [CrossRef] [PubMed]
53. Mantovani, A.; Byrne, C.D.; Targher, G. Efficacy of peroxisome proliferator-activated receptor agonists, glucagon-like peptide-1 receptor agonists, or sodium-glucose cotransporter-2 inhibitors for treatment of non-alcoholic fatty liver disease: A systematic review. Lancet Gastroenterol. Hepatol. 2022, 7, 367–378. [CrossRef]

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