REVIEW ARTICLE

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# Chronic kidney disease and the severity of non-alcoholic fatty liver disease: a systematic review

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## INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) has emerged as the leading cause of liver disease in developed countries, affecting more than one-third of the adult population[1]. NAFLD encompasses a spectrum of diseases, ranging from simple hepatic steatosis to non-alcoholic steatohepatitis (NASH), which can progress to liver cirrhosis and hepatocellular carcinoma[2].

NAFLD is now recognized as a multisystemic disease with extrahepatic involvement that affects the cardiovascular, endocrine, pulmonary, and renal systems. In the United States, NAFLD is expected to become the leading cause of liver transplantation in the next few years.

NAFLD is also associated with an increase in the incidence and prevalence of chronic kidney disease (CKD), which is defined as a glomerular filtration rate (GFR) <60 mL/min/1.73 m². These two diseases share several cardiometabolic risk factors, as well as profibrotic and proinflammatory molecular mechanisms[3]. Recent studies have reported CKD in 20–25% of individuals with NAFLD[4] essential to establish primary prevention strategies for CKD and to implement appropriate interventions to manage this condition in patients with NAFLD.

This systematic review aims to contribute to the ongoing discussion of the relationship and impact of NAFLD severity on the development of CKD.

## METHODS

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements. The study protocol was registered on the PROSPERO platform under the number CRD42022307980 and followed a predefined protocol based on the systematic reviews guideline[5].

To select articles, we conducted a literature search using the PUBMED, Web of Science, Scopus, Literatura Latino-americana e do Caribe em Ciências da Saúde (LILACS), and EMBASE databases. The search was conducted between May 2021 and September 2021.

The initial search was performed on PubMed to access the MEDLINE database, using the strategy defined below by the following descriptors (Non-alcoholic Fatty Liver Disease OR (non-alcoholic AND Fatty Liver AND disease) OR Nonalcoholic Steatohepatitis) AND "Renal Insufficiency, Chronic" OR "Chronic Renal Insufficiency."

The entire process was conducted by two independent authors, who searched the databases, read the titles and abstracts of the articles, and applied the inclusion and exclusion criteria. Disagreements were resolved through consensus, and when necessary, a third reviewer was consulted.

Based on the articles found, we conducted the study according to the PECOS strategy (Participants, Exposure, Comparison, and Outcomes) and followed the inclusion criteria described below:

Inclusion criteria: prospective and retrospective cohort and cross-sectional studies assessing the association between NAFLD and CKD in patients aged 18 years, and the studies that evaluated renal dysfunction in adult patients with NAFLD fibrosis progression with the risk of CKD.

Exclusion criteria: review articles, clinical trials, case reports, editorials, and experimental studies; studies in specific populations such as diabetics and individuals with CKD from dialysis centers; and studies in patients with NAFLD diagnosis by non-invasive markers such as the fatty liver index (FLI)[6] or by the parametric attenuation coefficient (PAC)[7].

To assess the quality of the selected studies, we used the Newcastle-Ottawa Scale, which employs a scoring system from

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0 to 9 in three domains: selection, comparability, and results. The higher score indicated better study quality, and a minimum score of 7 was established for the inclusion of the studies. The Rayyan Qari software was used to confirm the accuracy of the included articles.

CKD was diagnosed by estimating the GFR using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) method.

We conducted a sensitivity analysis of the studies based on several factors, including the research site, length of stay in the study, methodology used in NAFLD follow-up, and NAFLD severity assessed by non-invasive methods, such as the FIB-4[8-10] and NAFLD score[11,12], liver elastography, or histological analysis.

## RESULTS

A PRISMA flowchart (Figure 1) shows the studies evaluated in this review. Initially, 431 articles were identified during the literature search, of which 52 duplicated articles were excluded. Based on the title and abstract, 365 articles were reviewed, and 19 studies were selected for full text assessment.

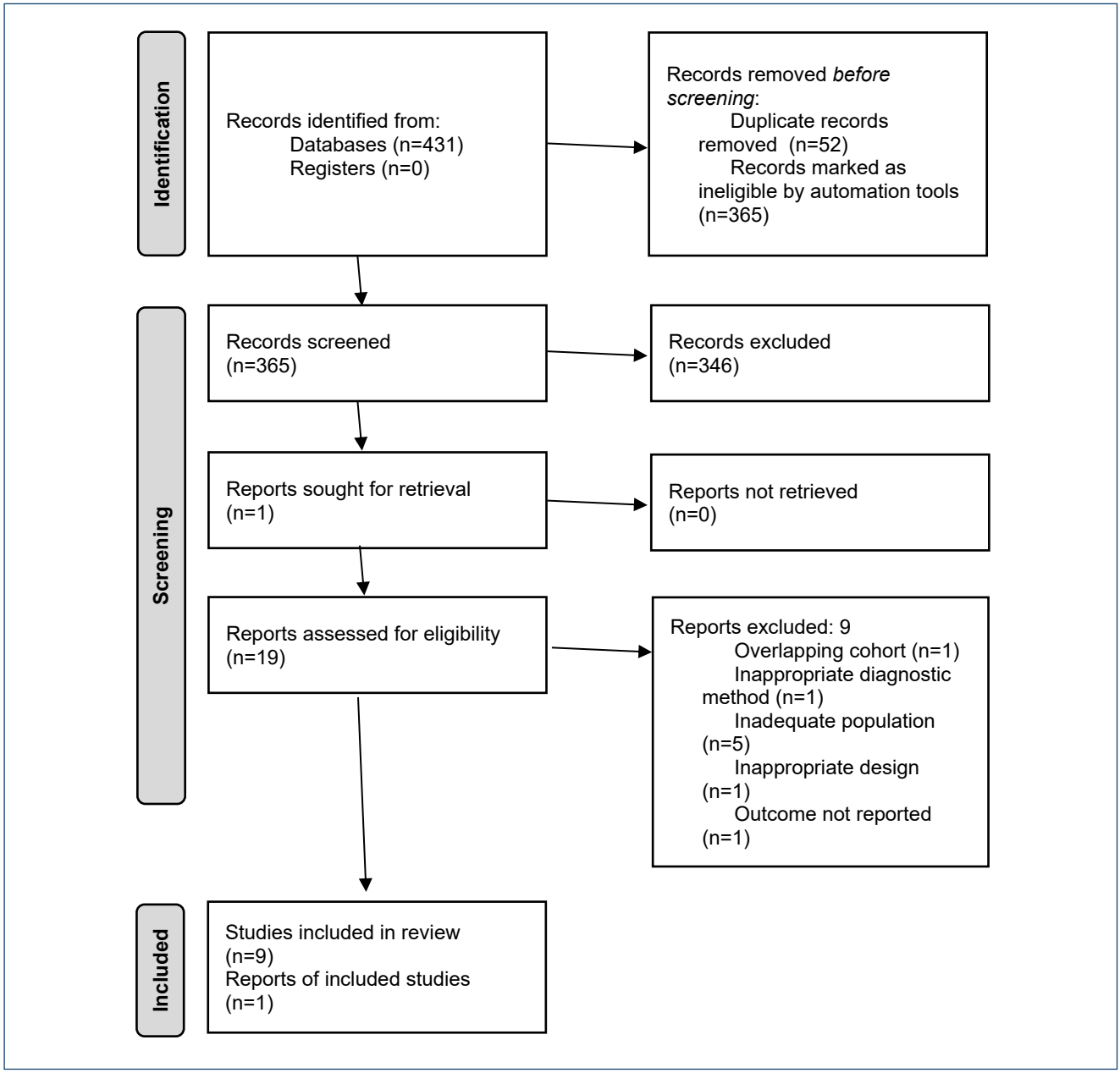


**Figure 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of the studies evaluated.

After excluding articles with an inadequate population (n=5), inadequate diagnostic method of steatosis (n=1), overlapping cohort (n=1), unreported outcome of interest (n=1), and inadequate study design (n=1), a total of 10 articles were included in the final analysis, and their quality was assessed.

Table 1 presents the main characteristics of the included studies. The presence of NAFLD was found to be associated with the presence of CKD in four studies[13-16], and the development of NAFLD was found to increase the risk of CKD incidence in four additional studies[17-20]. In these eight studies[13-20], the severity of liver disease was associated with a reduction in kidney function, regardless of known risk factors. Two studies did not find an association between NAFLD and CKD nor an increase in the incidence of CKD after adjusting for metabolic syndrome elements.

Table 2 presents the studies that were excluded after evaluation. Three studies were excluded because they focused on a cohort of individuals with pre-existing CKD. Two studies focused solely on the molecular mechanisms involved in the condition being studied. Seven studies evaluated only specific populations of individuals. One study had a small sample size. One study examined only the effect of fibrosis. In one study, the outcome was not of interest to the researchers. Finally, one study used a non-imaging or biopsy-based diagnosis of steatosis, which may not be sufficiently reliable for this investigation.

## DISCUSSION

In this systematic review of 10 observational longitudinal studies, comprising a total of 165,246 participants from different countries, we found a positive association between the presence of NAFLD and CKD stage ≥3, defined as the occurrence of eGFR <60 mL/min/1.73 $m^2$, with or without accompanying overt proteinuria. Moreover, the prevalence of CKD increased with the severity of NAFLD.

This systematic review is relevant because less is still known about the relationship between the evolution of NAFLD and the incidence of CKD. In recent years, this association has aroused increasing scientific interest, mainly due to the knowledge that NAFLD, in its broad spectrum, is associated with the development and progression of cardiovascular diseases.

There is now increasing evidence that the severity of NAFLD predicts the development and progression of CKD, suggesting that NAFLD-associated CKD might involve some unique mechanisms. Indeed, the hepatic and systemic vaso-regulatory changes seen in NAFLD may evoke the hepatorenal reflex and impair renal function[21].

According to the literature, the study developed by Targher et al.[15] demonstrated for the first time that individuals with NASH confirmed by liver biopsy had a moderate decrease in GFR and more frequent albuminuria than controls without NASH. This study was carried out with 80 non-obese patients, and adjustments were made for the main confounding factors such as age, gender, waist circumference, Homeostases Model Assessment-Insulin Resistance (HOMA-IR) score, systolic blood pressure, and triglycerides. Thus, it is possible to speculate that NASH is not associated with CKD because of shared cardiovascular risk factors, but NASH itself may contribute to the development of CKD.

Yasui et al.[16] studied 92 individuals with NASH and found a high prevalence of CKD (21%) in those with NASH when compared to control without NASH. The study also identified obesity and NASH as risk factors for CKD in NASH.

In addition, a cohort study by Sinn et al.[18] assessed the longitudinal association between NAFLD and the incidence of CKD over a 10-year period. The study concluded that CKD developed more frequently in participants with NAFLD compared to those without NAFLD. This association was not explained by the emergence of systemic arterial hypertension (SAH) and type 2 diabetes mellitus (T2DM) and persisted after adjustments for risk factors and potential metabolic mediators.

These findings further support the association between NAFLD and CKD and highlight the need for early detection and management of NAFLD to prevent the development and progression of CKD.

This cohort also observed the strong association between NAFLD and CKD in individuals with more advanced fibrosis, indicated by the high NAFLD fibrosis score (NFS) score[9], and that fibrosis markers bring additional risk stratification, being used to identify the patients with NAFLD at increased risk of renal complications.

The European Association for the Study of the Liver recommends the evaluation of serum markers of fibrosis in hepatic steatosis[22]. The NFS can identify patients at low risk of advanced fibrosis and has been externally validated in ethnically diverse populations with NAFLD[23].

Despite the literature being likely to understand that NAFLD would act directly in the pathogenesis of CKD, other divergent studies in the literature have emerged. Sirota et al.[24] developed a large cross-sectional study with 11,469 adults who participated in the National Health and Nutrition Examination Survey, 1988–1994 (NHANES III). The hypothesis was that NAFLD was associated with CKD and that the severity of NAFLD would bring a greater chance of CKD. They concluded that there is a positive association between the presence and severity of NAFLD and CKD, but this association was attenuated after adjusting for confounding factors.

There are multiple possibilities for such discordant results found in studies examining the association between NAFLD and CKD. Some studies did not adjust for important confounding factors,

**Table 1.** Overview of the included studies investigating the association between renal dysfunction in individuals with nonalcoholic fatty liver disease.

| Author, year of publication | Country | Design of study | Number of subjects | Diagnosis of NAFLD | Setting | Definition of DRC | Statistical adjustment | NOS score |
|---|---|---|---|---|---|---|---|---|
| Targher, 2010[15] | Japan | Cross-sectional Case-control | 160 | Liver biopsy | 01 medical center | GFR <60 mL/min or albumin-to-creatinine ratio >3 mg/mmol | Age, gender, BMI, waist circumference, smoking, systolic BP, HOMA-IR score, and TG | 08 |
| Yasui, 2011[16] | Japan | Cross-sectional Case-control | 174 | Liver biopsy | 02 medical center | GFR <60 mL/min (Japanese Society of Nephrology) | BMI, SAH, age, sex, the presence of T2DM or dyslipidemia, levels of AST, ALT, or γ-GTP | 08 |
| Sinn, 2017[18] | South Korea | Cohort | 41430 | Ultrasonography | Samsung Medical Center | CKD-EPI <60 mL/min | Smoking, alcohol consumption, BMI, and estimated GFR at baseline, systolic blood pressure, HbA1c, LDL-C, use of diabetes, lipid lowering, and antihypertensive medications | |
| Sirota, 2012[24] | USA | Cross-sectional Case-control | 11469 | Ultrasonography | NHANES program | GFR <60 mL/min or GFR >60 mL/min with albuminuria | Model adjusted for age, sex and race (Model 1); and a model adjusted for history of hypertension, history of diabetes, systolic BP, waist circumference, TG, HDL-C, and HOMA-IR score | 08 |
| Wilechansky, 2019[25] | USA | Cohort | 987 | Tomography | Framingham Heart Study | CKD-EPI GFR <60 mL/min/1.73 m² and/or microalbuminuria (sex-specific urinary albumin-creatinine ratio) | Age, sex, smoking status, drinks per week, systolic blood pressure, diastolic blood pressure, use of antihypertensive medications, HDL-C, total cholesterol, regular aspirin use, and T2DM | 08 |
| Zhang, 2020[20] | USA and China | Cross-sectional | 65087 | Ultrasonography | NHANES and dataset chinese | CKD-EPI GFR <60 mL/min/1.73 m² and/or abnormal albuminuria and/or overt proteinuria | Age, sex, BMI, history of T2DM, and history of SAH | 08 |
| Liu, 2020[14] | Taiwan | Cross-sectional Case-control | 37825 | Ultrasonography | Taipei Tzu Chi Hospital | Proteinuria or GFR ≤60 mL/min/1.73 m² | Sex, age, current smoking, T2DM, SAH, low HDL-C, high TG, ALT, and systolic BP | 07 |
| Kaps, 2020[17] | Germany | Cohort | 48057 | | Disease Analyzer Database | | Diabetes, obesity, SAH, and ischaemic heart diseases | 08 |
| Zuo, 2021[19] | China | Cohort | 4402 | Ultrasonography | Medical center | Albumin-to-creatinine ratio >3 mg/mmol or GFR <60 mL/min/1.73 m² | Age, sex, smoking status, drinks, physical activity BMI, SBP, HbA1c, white blood cell count, UACR, eGFR, use of antidiabetic medications, antihypertensive, and use of lipid lowering medications | 08 |
| Cao, 2021[13] | China | Cross-sectional Case-control | 3872 | Ultrasonography | Medical center | Albumin-to-creatinine ratio >3 mg/mmol or GFR <60 mL/min/1.73 m² | Age, sex, and T2DM | 07 |

CKD was defined as a urinary albumin-to-creatinine ratio (UACR) ≥30 mg/g, an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² or both. BMI: body mass index; HOMA-IR: homeostatic model of insulin resistance; HDL-C: high-density lipoprotein cholesterol; TG: triglycerides; LDL-C: low-density lipoprotein cholesterol; NOS: Newcastle Ottawa Scale; SAH: systemic arterial hypertension; T2DM: Type 2 diabetes mellitus; SBP: systemic blood pressure; HbA1c: hemoglobin A1C.

**Table 2.** Studies that were evaluated in full text and were excluded.

| No. | First author | Year | Title | Reason for exclusion |
|---|---|---|---|---|
| 1 | Chinnadurai | 2019 | Non-alcoholic fatty liver disease and clinical outcomes in chronic kidney disease | Cohort of individuals who already had CKD |
| 2 | Mikolasevic | 2013 | Chronic kidney disease and nonalcoholic fatty liver disease proven by transient elastography | Cohort of individuals with CKD |
| 3 | Musso | 2015 | Emerging liver-kidney interactions in nonalcoholic fatty liver disease | Molecular study |
| 4 | Kasim | 2019 | Correlation between non-alcoholic fatty liver and chronic kidney disease | Small number of subjects in the study |
| 5 | Li | 2014 | Association between non-alcoholic fatty liver disease and chronic kidney disease in population with prediabetes or diabetes | Specific population with diabetes |
| 6 | Paik | 2019 | Chronic kidney disease is independently associated with increased mortality in patients with nonalcoholic fatty liver disease | Outcome was not of interest |
| 7 | Targher | 2014 | Nonalcoholic fatty liver disease is independently associated with an increased incidence of chronic kidney disease in patients with type 1 diabetes | Specific population with diabetes |
| 8 | Xu | 2016 | High FIB-4 index as an independent risk factor of prevalent chronic kidney disease in patients with nonalcoholic fatty liver disease | Associates only the effect of fibrosis |
| 9 | Targher | 2008 | Increased risk of CKD among type 2 diabetics with nonalcoholic fatty liver disease | Specific population |
| 10 | Aubert | 2021 | Role of non-alcoholic fatty liver disease in the evolution of renal function in patients with diabetes mellitus | Specific population |
| 11 | Targher | 2012 | Increased prevalence of chronic kidney disease in patients with Type 1 diabetes and non-alcoholic fatty liver | Specific population |
| 12 | Lu | 2020 | Non-alcoholic fatty liver disease increases the prevalence of maintenance haemodialysis in patients with chronic kidney disease | Specific population with chronic kidney disease |
| 13 | Machado | 2012 | Impaired renal function in morbid obese patients with nonalcoholic fatty liver disease | Specific population with obesity |
| 14 | Zeng | 2017 | Association between non-invasively diagnosed hepatic steatosis and chronic kidney disease in Chinese adults on their health check-up | Non-imaging or biopsy diagnosis of steatosis |
| 15 | Musso | 2016 | Fatty liver and chronic kidney disease: novel mechanistic insights and therapeutic opportunities | Molecular study |
| 16 | Chon | 2020 | Decrease in waist-to-hip ratio reduced the development of chronic kidney disease in non-obese non-alcoholic fatty liver disease | Specific population without obesity |

such as antihypertensive drug use and smoking. Additionally, studies conducted in hospitals may have selected individuals with more advanced liver disease, including NASH and fibrosis[25]. It is possible that only those with more advanced NAFLD, particularly with NASH or liver fibrosis, may be at increased risk for CKD.

More recently, cross-sectional studies with a large number of individuals[20,14] and long-term cohorts[17] have confirmed that NAFLD is an independent risk factor for CKD. Zuo et al.[19] confirmed this hypothesis but suggested that the progression of liver fibrosis in individuals with NAFLD is a more significant predictor for the development of CKD than baseline levels of metabolic diseases.

The biological mechanisms underlying this association are still not well understood. Possible factors include the activation of the renin-angiotensin system, hepatic insulin resistance, atherogenic dyslipidemia, proinflammatory, procoagulants, and pro-oxidants mediators, as well as alterations in the intestinal microbiota[13].

This review has certain limitations inherent to the design of the studies included. First, the observational design of the

eligible studies prevents us from establishing causality. Second, although most of the eligible studies adjusted the results for age, sex, obesity, hypertension, and diabetes, residual confounding due to some unmeasured factors cannot be excluded. Additionally, none of the eligible studies provide a histological characterization of NAFLD-associated kidney disease.

## CONCLUSIONS

This systematic review suggests a positive association between the presence and severity of NAFLD and CKD. However, further follow-up studies are needed to confirm these findings.

## ETHICAL STATEMENT

The authors declare that all experiments were conducted in accordance with the Declaration of Helsinki.

## AUTHORS' CONTRIBUTIONS

**KSDC**: Visualization, Writing – original draft. **CHCD**: Formal Analysis, Funding acquisition, Methodology, Project administration, Validation, Visualization, Writing – review & editing. **VAA**: Data curation, Investigation,. **RRS**: Investigation, Resources. **HPC**: Conceptualization, Methodology, Project administration, Supervision, Writing – review & editing.

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