Original Article

The risk factors for cardiovascular disease and chronic kidney disease in patients with nonalcoholic fatty liver disease in Saudi Arabia

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ABSTRACT

الأهداف: تحديد عوامل الخطر المحتملة لأمراض الكلى المزمنة وأمراض القلب والأوعية الدموية لدى المرضى السعوديين المصابين بمرض الكبد الدهني غير الكحولي (NAFLD).

المنهجية: أُجريت دراسة استباقية لمجموعة من المرضى، امتدت لست سنوات، من يناير 2018 إلى يناير 2023، وشارك فيها 1,500 مريض. جُمعت البيانات مبدئيًا بين يناير 2018 و2019، وأُجريت تقييمات متابعة سنوية بين عامي 2020 و 2023. قُيّم المرضى باستخدام تحليلات المؤشرات الحيوية، ورُوّجت السجلات الطبية لتقييم معدل الإصابة بأمراض القلب والأوعية الدموية وأمراض الكلى المزمنة. رُصدت مستويات المؤشرات الحيوية، بما في ذلك الكرياتينين في الدم، وألبومين البول، ومعدل الترشيح الكبيبي (GFR)، ومؤشر تصلب الشرايين في البلازما (AIP)، وغيرها من المعايير الرئيسية، طوال فترة الدراسة.

النتائج: من بين 1500 مريض، تم تشخيص 735 (49%) منهم بمرض الكبد الدهني غير الكحولي في عام 2018، بينما لم يكن لدى 765 (51%) منهم هذه الحالة. وبالمقارنة مع المرضى غير المصابين بمرض الكبد الدهني غير الكحولي، أظهر المصابون بمرض الكبد الدهني غير الكحولي ارتفاعًا في مستويات الكرياتينين في الدم، وانخفاضًا في معدل الترشيح الكبيبي، وارتفاعًا في ألبومين البول، وهو مؤشر رئيسي لتلف الكلى يرتبط ارتباطًا وثيقًا بتسارع تطور مرض الكلى المزمن وزيادة خطر الإصابة بأمراض القلب والأوعية الدموية. علاوة على ذلك، كان لدى مرضى مرض الكبد الدهني غير الكحولي مستوى أعلى بكثير من AIP. وعلى مدار المتابعة التي استمرت 4 سنوات، أظهر هؤلاء الأفراد ارتفاعًا ملحوظًا في معدل الإصابة بمرض الكلى المزمن وأمراض القلب والأوعية الدموية.

الخلاصة: يرتبط مرض الكبد الدهني غير الكحولي بتغيرات في مستويات الدهون، وارتفاع بروتين سي التفاعلي عالي الحساسية (hs-CRP)، وارتفاع ناقلة أمين الأسبارتات (AST)، وكلها قد تساهم في التطور المبكر لمرض الكلى المزمن وأمراض القلب والأوعية الدموية. الأفراد الأكبر سنا الذين يعانون من السمنة المفرطة والذين يعانون من مرض الكبد الدهني غير الكحولي، ومستويات عالية من الدهون الثلاثية، AST، و hs-CRP معرضون لخطر متزايد للإصابة بهذه الأمراض.

Objectives: To identify potential risk factors for chronic kidney disease (CKD) and cardiovascular disease (CVD) in Saudi Arabian patients with non-alcoholic fatty liver disease (NAFLD).

Methods: A 6-year prospective cohort study was carried out from January 2018 to January 2023, enrolling 1,500 patients. Data were initially collected between January 2018-2019, and follow-up assessments were carried out annually from 2020-2023. Patients were evaluated using biomarker analyses, and medical records were reviewed to assess the incidence of CVD and CKD. Biomarker levels, including blood creatinine, urine albumin, glomerular filtration rate (GFR), atherogenic index of plasma (AIP), and other key parameters, were monitored throughout the study.

Results: Of the 1500 patients, 735 (49%) were diagnosed with NAFLD in 2018, while 765 (51%) did not have the condition. Compared to non-NAFLD patients, those with NAFLD exhibited elevated blood creatinine levels, lower GFR, and higher urine albumin, a key marker of kidney damage that is strongly linked to accelerated CKD progression and increased cardiovascular risk. Furthermore, NAFLD patients had a significantly higher AIP. Over the 4-year follow-up, these individuals showed a notable rise in the incidence of CKD and CVD.

Conclusion: Non-alcoholic fatty liver disease is associated with alterations in lipid profiles, elevated high-sensitivity C-reactive protein (hs-CRP), and elevated aspartate aminotransferase (AST), all of which may contribute to early CKD and CVD development. Older, obese individuals with NAFLD, high triglyceride, AST, and hs-CRP levels are at an elevated risk for these diseases.

Keywords: non-alcoholic fatty liver disease, Saudi, cardiovascular, chronic kidney disease, albumin-to-creatinine ratio

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Non-alcoholic fatty liver disease (NAFLD) is commonly known as simple steatosis and is characterized by the accumulation of excess fat in hepatocytes without any notable inflammation, injury, or fibrosis. Non-alcoholic fatty liver disease is widely prevalent across the globe, affecting approximately 25% of the global population, and is recognized as the leading cause of chronic liver disease worldwide. This particular liver ailment also represents the primary etiology of anomalous liver enzymes in numerous industrialized nations.[1] In Saudi Arabia, the prevalence is notably higher, driven by unique demographic, lifestyle, and environmental factors, underscoring the importance of region-specific research. The prevalence of the aforementioned condition in Saudi Arabia has been documented to range from 7-10%.[2-4] Although the majority of cases exhibit a benign course, approximately 10-20% of patients may progress to advanced fibrosis and cirrhosis.[1] The primary risk factors comprise diabetes mellitus, obesity, and hyperlipidemia. The aforementioned risk factors exhibit a high prevalence within the population of Saudi Arabia. According to recent data, the collective occurrence of these risk factors is 23.7% for diabetes mellitus, 35.5% for obesity, and 54% for hyperlipidemia.[5,6]

According to the Kidney Disease Improving Global Outcomes (KDIGO) workgroup, chronic kidney disease (CKD) is characterized by abnormalities in kidney structure or function that persist for a duration of more than 3 months and have health implications.[7] The glomerular filtration rate (GFR) serves as an indicator of renal function and is classified into 5 distinct categories, namely, G1 (≥90), G2 (60-89), G3a (45-59), G3b (30-44), G4 (15-29), and G5 (<15 mL/min/1.73 m^2). Chronic kidney disease is characterized by a GFR of less than 60 mL/min/1.73 m^2. The albumin-to-creatinine ratio (ACR) is a recognized indicator of renal impairment, which is classified into 3 distinct categories based on the magnitude of the ratio (A1: <30; A2: 30–300; A3: >300 mg/g). The threshold value of >30 mg/g is used to define CKD. The classification of CKD involves stratification based on reduced GFR and elevated ACR, both of which are significant in determining risk classification and forecasting.[8-10] Studies have demonstrated that NAFLD is an autonomous risk factor that contributes to the onset of CKD. The incidence of CKD among individuals with NAFLD is twice as high, ranging from 20-55%, compared to those without NAFLD, where the incidence ranges from 5-30%. Furthermore, there is a significant correlation between the severity of non-alcoholic steatohepatitis (NASH) histology and renal function impairment.[11]

Furthermore, NAFLD has been increasingly recognized as an independent risk factor for CKD, beyond the shared metabolic comorbidities such as obesity, diabetes, and hypertension. Studies consistently demonstrate that NAFLD is not merely a bystander but actively contributes to renal dysfunction through multiple mechanisms. Non-alcoholic fatty liver disease is associated with chronic low-grade inflammation, characterized by elevated pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). These cytokines contribute to renal damage by promoting oxidative stress, endothelial dysfunction, and glomerular injury.[12,13] Insulin resistance, a hallmark of NAFLD, exacerbates renal dysfunction by impairing glomerular filtration and promoting podocyte injury. Additionally, the accumulation of toxic lipids in both liver and kidney tissues accelerates fibrosis in both organs.[13] Non-alcoholic fatty liver disease is associated with the activation of renin-angiotensin-aldosterone system, leading to increased renal fibrosis, hypertension, and albuminuria. This mechanism plays a direct role in CKD progression.[14]

Both NAFLD and CKD are associated with cardiometabolic risk factors that contribute to the development of atherogenic dyslipidemia and cardiovascular disease (CVD), such as hospitalization for coronary heart disease, heart failure, ischemic stroke, or peripheral arterial disease. Notably, the incidence of these events is higher in individuals with CKD.[11-13] Non-alcoholic fatty liver disease and CVD are prevalent conditions among the general population. Numerous investigations have been carried out thus far, revealing a clear correlation between NAFLD and CVD. However, the intricate mechanisms underlying this association remain inadequately established. Hence, comprehending the interrelationship among these 3 pathological conditions holds significance in terms of screening, timely identification, and the advancement of therapeutic interventions.

One notable challenge is the limited awareness of NAFLD prevalence within Saudi Arabia, which exists across 3 key levels: I) general population: there is a lack of understanding among the public regarding NAFLD as a health condition, its risk factors, and its potential

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complications, which limits prevention and early detection efforts; II) healthcare professionals: while some advancements have been carried out, knowledge gaps remain regarding the identification, diagnosis, and management of NAFLD, particularly in primary care settings, where early-stage cases are most likely to present; and III) policymakers (namely, Ministry of Health): insufficient data on the national prevalence of NAFLD hinders the ability of policymakers to allocate resources, develop targeted public health strategies, and prioritize the condition within healthcare agendas. Addressing these gaps is critical to effectively plan for the future management of NAFLD. Consequently, determining the prevalence of NAFLD among the adult population in Saudi Arabia is crucial to evaluate associated healthcare requirements effectively.

Currently, the prevalence of NAFLD in Saudi Arabia, particularly in Al-Madinah Al-Munawarah, Saudi Arabia, has not been accurately quantified in existing studies. Regional estimates are essential, as national and global trends suggest an alarming increase in NAFLD prevalence due to the high rates of obesity, diabetes, and metabolic syndrome in the country.[15,16] This lack of precise epidemiological data impedes healthcare system preparedness, resource allocation, and the development of effective screening and surveillance strategies for individuals at increased risk of complications such as CVD and CKD.[17]

Non-alcoholic fatty liver disease has important clinical implications, particularly for screening and surveillance, as it is strongly associated with a higher risk of CVD and CKD progression. Studies have consistently shown that NAFLD is linked to subclinical atherosclerosis, increased arterial stiffness, and a heightened risk of major cardiovascular events, even after adjusting for traditional cardiovascular risk factors.[15-17] Similarly, robust evidence highlights the association of NAFLD with CKD across various patient populations. For instance, systematic reviews and meta-analyses have found that NAFLD significantly increases the risk of CKD due to mechanisms such as hepatic inflammation, insulin resistance, and the activation of the renin-angiotensin system.[17,18] However, while the association is well-documented, the causal relationship between NAFLD and CKD progression remains a subject of ongoing research.[18]

This study introduces new insights by incorporating biomarkers that have not been extensively investigated in the context of NAFLD, CVD, and CKD, such as lipid profiles, glucose levels, atherogenic index of plasma (AIP), body mass index (BMI), albumin, enzymes, and high-sensitivity C-reactive protein (hs-CRP). These biomarkers provide potential diagnostic tools for early identification and risk stratification. Recent studies have shown that hs-CRP and AIP are particularly useful in predicting both cardiovascular and renal risks in NAFLD patients.[19,20] Our research builds on this knowledge, offering a more comprehensive understanding of the intricate relationships between NAFLD, CVD, and CKD.

By evaluating these biomarkers, the study aims to mitigate challenges related to the early detection and management of NAFLD and its complications. These contributions not only expand the scientific community's understanding of NAFLD but also have practical implications for patient care, such as improving risk assessment and enabling more personalized treatment approaches. Thus, this research investigates the potential correlation between NAFLD and the incidence of CVD and CKD among the Saudi population by analyzing alterations in biomarker levels. The findings will provide valuable insights into the relationship between NAFLD and other diseases in adults in Saudi Arabia, ultimately supporting the evaluation of healthcare requirements in the region.

Methods. The first data of the cohort study were gathered from January 2018 to January 2019 for a total of 1500 patients. The sample size for this study was determined based on the expected prevalence of NAFLD and its associated outcomes, ensuring sufficient statistical power to detect meaningful differences in the incidence of CVD and CKD. A total of 1,500 participants were enrolled, which was deemed appropriate for achieving at least 80% power to detect significant associations at a 5% significance level, given the anticipated effect size derived from previous studies. Additionally, a post hoc analysis confirmed that the chosen sample size was adequate to meet these statistical requirements. The cohort was systematically evaluated by thoroughly reviewing the medical records of patients who were referred to the National Guard Hospital in Al-Madinah Al-Munawarah, Saudi Arabia, as part of routine health checkup programs carried out from January 2018 to January 2019. These health checkup programs were structured initiatives aimed at monitoring and managing the health status of individuals, including the screening of metabolic and liver-related conditions. Patients included in the study were evaluated based on a standardized set of clinical, biochemical, and imaging criteria to ensure consistency in data collection. This approach did not involve random sampling but rather relied on the systematic inclusion of all eligible patients attending the hospital

during the study period. By leveraging this systematic method, the study captured a comprehensive dataset reflective of individuals undergoing health checkups, allowing for robust analysis of NAFLD prevalence and its clinical associations. This ensures the findings are representative of the specific population served by the hospital and provide valuable insights into the health trends in the region.

Subsequently, the participants were divided into 2 distinct groups: individuals with NAFLD and those without. The NAFLD patients included in this study were newly diagnosed during the baseline period (January 2018 to January 2019) based on standardized diagnostic criteria, including imaging and biochemical markers. No patients with a prior diagnosis of NAFLD were included, as this was a prospective cohort designed to follow the progression of newly identified cases. The sample selection method employed certain criteria to ascertain the inclusion and exclusion of patients. The NAFLD group consisted of male and female patients, aged 30-80 years, who were newly diagnosed with fatty liver based on abdominal ultrasonography (ultrasound evidence of steatosis or magnetic resonance elastography with fat fraction) and physician evaluation. These individuals did not have hepatitis B or C (serologic tests that rule out hepatitis B and C), severe liver cirrhosis or hepatoma, diabetes, hypertension, or any history of CVD, tumors, or cancer. The exclusion of patients with diabetes and hypertension was implemented to ensure the study focuses on the independent effects of NAFLD on the development of CVD and CKD. Both diabetes and hypertension are well-established and significant risk factors for CVD and CKD, which could confound the analysis by introducing overlapping risk pathways. By excluding these conditions, the study aimed to eliminate confounding variables that might obscure the direct association between NAFLD and the studied outcomes. This approach allows for a clearer delineation of the role of NAFLD as an autonomous risk factor, minimizing the influence of other major contributors to CVD and CKD. While diabetes and hypertension are clinically relevant, isolating NAFLD's impact provides valuable insights into its specific pathophysiological contributions and strengthens the study's conclusions.

Furthermore, we collected information on the occurrence of CVD and CKD in individuals with NAFLD using biomarker evaluations at 4 distinct time intervals throughout the follow-up duration: 2020, 2021, 2022, and 2023. This was carried out as a part of a prospective study, which includes the comprehensive review of medical records (we examined every patient without any exceptions). We carried out the yearly assessment, synchronizing it with the initial diagnosis of NAFLD in 2018 (year 1), to preserve approximately 12-month gaps between consecutive assessments. The study was carried out over 6 years. The initial data collection for the cohort occurred from January 2018 to January 2019, during which 1,500 patients were enrolled. In this study, the incidence of CVD and CKD was determined over a 5-year follow-up (2020-2023) by identifying new cases among participants. For CVD, new cases included myocardial infarction, stroke, or heart failure, confirmed through clinical records and blood analysis for cardiac biomarkers. For CKD, new cases were defined using KDIGO criteria: a sustained eGFR <60 mL/min/1.73 m^2 or persistent albuminuria (ACR: ≥30 mg/g). Incidence rates were calculated as the number of new cases per 1,000 person-years, with person-years accounting for each participant's time in the study until the outcome occurred, they were lost to follow-up, or the study ended. Follow-up assessments were carried out annually, specifically in 2020, 2021, 2022, and 2023, with approximately 12-month intervals between each assessment. The study's duration spans from the baseline data collection in 2018 through to the final follow-up in 2023. A 5-year follow-up period is sufficient to capture meaningful trends in incident CVD and CKD in high-risk populations, such as those with NAFLD. Emerging evidence suggests that early changes in biomarkers, including hs-CRP, AIP, and renal function, are predictive of future clinical events. Moreover, prior studies have demonstrated that significant incident cases of CVD and CKD can occur within similar timeframes in populations with metabolic risk factors. Therefore, while long-term studies are ideal, this study provides valuable insights into the early progression of NAFLD and its associated outcomes.

The ethical permission was obtained by King Abdullah International Medical Research Centre's institutional review board (IRB/2473/22), at the Ministry of National Guard-Health Affairs, Al-Madinah Al-Munawarah, Saudi Arabia. This was prospective research that involved analyzing medical records. Before we accessed the data, all information was carried out anonymous. The ethics committee determined that informed permission was not necessary for this study.

Various parameters, such as fasting blood glucose (FBG), C-reactive protein (C-RP), alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin, albumin (blood and urine), creatinine (serum and urine), GFR, lipid profile (total cholesterol, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C]), and triglycerides (TGs) with a cardiac marker (creatinine phosphokinase

[CPK]), were investigated and assessed based on the available medical records.

The GFR may be calculated using the Modification of diet in renal disease equation.[21] The following formula can be utilized for calculating the estimated GFR: 175 x (creatinine, mg/dl)-1.154 x (age, years) = eGFR (mL/min/1.73 m^2). GFR stages (chronic kidney disease classification): I) G1: ≥90, normal or high; II) G2: 60-89, mildly decreased; III) G3a: 45-59, mild to moderately decreased; IV) G3b: 30-44, moderately to severely decreased; V) G4: 15-29, severely decreased; and VI) G5: <15, Kidney failure (add D if treated by dialysis)

Albuminuria was defined as a spot urinary albumin-to-creatinine ratio (UACR) ≥30 mg/g. Albuminuria categories: I) A1: UACR <30 normal to mildly increased; II) A2: UACR 30-300 moderately increased; and III) A3: UACR >300 severely increased.[22]

The study gathered information on age, gender, and anthropometric measures such as height, weight, and BMI. Based on established criteria, BMI was calculated using the formula weight divided by height squared and classified as normal (18.5-25.9 kg/m^2), overweight (25.0-29.9 kg/m^2), or obese (>30.0 kg/m^2).[23]

Nonalcoholic fatty liver disease is identified by abdominal ultrasonography, abdominal CT scan, or liver biopsy as fat buildup in liver cells (fatty liver) without a history of alcohol intake (20 g/day) or other causes of chronic liver disease.[24]

Chronic kidney disease is diagnosed when an ultrasonography examination reveals structural kidney disease, an eGFR of <60 ml/minute/1.73 m^2, or albuminuria.[8-10]

The AIP was calculated as log (TG/HDL-C). According to one study, an AIP value less than 0.11 suggests a low risk of CVD, whereas values between 0.11-0.21 are considered intermediate risk.[15] The AIP levels greater than 0.21, on the other hand, are connected with an increased risk of CVD.

Dyslipidemia refers to the condition characterized by an increase in plasma cholesterol, TGs, or both or a low level of HDL-C. This condition is known to play a significant role in the development of atherosclerosis and CVD. The process of diagnosis involves the quantification of plasma concentrations of total cholesterol and TGs.[25]

Cardiovascular diseases in this study involved a group of disorders of the heart and blood vessels and included coronary heart disease, cerebrovascular disease, rheumatic heart disease, and other conditions.

Statistical analysis. All analyses were carried out using the Statistical Package for the Social Sciences, version 26.0 (IBM Corp., Armonk, NY, USA). Normality was verified for each variable. As applicable, descriptive statistics were summarized by mean ± standard deviation (SD) or frequency (percentage). The odds ratio (OR) with 95% confidence interval (CI) was used to evaluate group differences for categorical variables, whereas the t-test and 2-way ANOVA tests were used to evaluate group differences for continuous variables. In this study, a Chi-square test was carried out to establish the correlation between NAFLD and CKD or CVD. The variables analyzed included GFR, CKD grade, incidence of albuminuria, AIP categories, and incidence of dyslipidemia. Using multivariate logistic regression, the risk factors for CKD and CVD were evaluated. All analyses were 2-sided with a 5% significance level.

Results. Throughout the designated research timeframe, a total of 1500 participants were included in the study cohort, with 735 individuals diagnosed with NAFLD and 765 individuals without NAFLD. Table 1 outlines the attributes of the subjects under study. The study showed that individuals diagnosed with NAFLD had a mean age of 55.55±12.21. Additionally, these patients exhibited significantly elevated levels of glucose, HbA1c, cholesterol, TGs, hs-CRP, and liver enzymes. Conversely, their levels of HDL-C were found to be lower. Patients with NAFLD exhibit increased levels of creatinine in both serum and urine, as well as increased urinary albumin levels coupled with a slight reduction in GFR. The study findings indicate that individuals diagnosed with NAFLD exhibited increased aAIP values (>0.1), which are indicative of an increased risk of CVD. Additionally, these patients had high BMI values, indicating that they were overweight (26.5 kg/m^2). Individuals diagnosed with NAFLD had high FBG (6.5±1.41) and glycated HbA1c (5.7±1.11) levels (Table 1).

Participants with NAFLD in this research were observed over a span of 4 years, from 2020-2023. During each follow-up period (Table 2), the incidence of CVDs or CKDs was initially documented based on a review of their medical records by clinicians; cases that were confirmed were classified as new cases of CVDs or CKDs. Table 2 showed substantial fluctuations in biomarker levels, including glucose, HbA1c, lipid profiles, hs-CRP, creatinine, and albumin, along with noteworthy changes in BMI and AIP values across the 4-year follow-up period.

In the years 2018-2019, the prevalence of individuals having a high risk of CKD was 25.7% and CVD was 29.4% with NAFLD (Table 3). Physicians verified the occurrences of CKD or CVD linked to NAFLD

Table 1 - Clinical and biochemical characteristics of patients with and without non-alcoholic fatty liver disease (N=1500).

Parameters	Without NAFLD (n=765)	With NAFLD (n=735)	*P*-values
Age (years)	34.54±11.23	55.55±12.21	0.001**
Gender (male/female)	375/390	355/380	-
FBG (mmol/L)	4.9±1.31	6.5±1.41	0.001**
HbA1c (%)	4.69±1.29	5.7±1.11	<0.001**
LDL-C (mmol/L)	2.22±0.31	2.22±0.40	>0.05
HDL-C (mmol/L)	1.55±0.82	1.11±0.21	<0.001**
Total cholesterol (mmol/L)	4.78±1.23	5.88±1.41	<0.001**
Triglycerides (mmol/L)	1.2±1.13	2.5±1.10	0.001**
AIP = log (TG/HDL-C).	0.11±0.10	0.3±0.11*	0.002**
BMI (kg/m^2)	24.5±5.55	26.5±6.55†	<0.001**
hs-CRP(mg/l)	2.5±1.32	3.9±1.16	0.001**
Albumin (g/dL)	5.9±1.99	3.0±0.3	0.002**
Total protein (g/dL)	7.5±1.87	5.3±1.2	<0.001**
AST (IU/L)	15.4±5.55	44.11±10.24	0.002**
ALT(IU/L)	20.3±10.26	55.12±12.14	<0.001**
ALP (IU/L)	55.5±11.12	77±10.16	0.001**
AST: ALT ratio	0.79±0.12	1.5±0.10	>0.05
Total bilirubin (mg/dL)	0.69±0.12	0.69±0.11	>0.05
Serum creatinine(mg/dL)	0.4±0.11	1.6±0.51	<0.001**
Urine creatinine (mg/dL)	65.5±10.11	300±20.51	<0.001**
Urine albumin (mg/dL)	1.8±0.16	35.5±7.16	<0.001**
GFR (mL/min/1.73m^2)	138±10.21	70±8.11‡	<0.001**
Urine albumin-to-creatinine ratio (mg/g)	27.7±6.11	116.7±11.12§	<0.001**
Creatine phosphokinase (mcg/L)	15.5±5.21	60.43±10.11	0.002**

Values are presented as mean ± standard deviation (SD). *P*-values obtained from the independent student t-test. *AIP of >0.21, high risk of CVD. †BMI of 25.0-29.9 kg/m^2 (overweight). ‡G2= GFR of 60-89 (mildly decreased). §A2= UACR of 30-300 (moderately increased). **P-value of <0.001. NAFLD: nonalcoholic fatty liver disease, FBG: fasting blood glucose, HbA1c: hemoglobin A1c, HDL-C: high density lipoprotein, LDL-C: low-density lipoprotein, hs-CRP: high-sensitivity C-reactive protein, AIP: atherogenic index of plasma, BMI: body mass index, AST: aspartate transaminase, ALT: alanine transaminase, ALP: alkaline phosphatase, GFR: glomerular filtration rate

following 4 years of monitoring, based on the patient's medical records. Table 3 shows that there is a notable rise in the occurrence of CKD and CVD in patients with NAFLD, and this increase is statistically significant compared to the first year of the study.

In this study, a Chi-square test was carried out to determine the correlation between NAFLD and CKD or CVD. The variables examined included GFR, CKD grade, incidence of albuminuria, AIP categories, and incidence of dyslipidemia. When GFR was categorized into 2 groups, namely, <60 and ≥60, the proportion of GFR <60 was found to be significantly higher in subjects with NAFLD after 4 years of following up than in the first year of study (33.3% vs. 53.1%, p=0.02), as presented in Table 4.

The study revealed a statistically significant correlation between NAFLD and the severity of CKD, particularly in individuals with grades 2 and 3 CKD. The proportion of individuals with grades 2 and 3 CKD was notably higher in the NAFLD group after 4 years than in the first year (42.6% vs. 50.3% grade 2 CKD, 0.7% vs. 13.6% grade 3 CKD) as indicated in Table 4.

The study carried out a correlation analysis between NAFLD and albuminuria, which revealed a higher prevalence of A2 albuminuria in individuals with NAFLD after 4 years compared to the first year as indicated in Table 4.

Additionally, a statistically significant correlation was observed between NAFLD and dyslipidemia (p=0.05). The results also indicated that 40.8% of NAFLD subjects were at intermediate risk of CVD, while an increase to 50.3% of them were at intermediate risk of CVD after 4 years, as presented in Table 4.

The study used logistic regression analysis to identify the predictor variables associated with cardiovascular and renal diseases. The results of the study suggest that

Table 2 - Clinical and biochemical characteristics of patients with non-alcoholic fatty liver disease (n=735), 4-time intervals were recorded throughout the follow-up period.

Parameters	2018-2019	2019-2020	2020-2021	2021-2022	2022-2023	*P*-values
FBG (mmol/L)	6.5±1.41	6.5±1.51	6.8±1.61	6.8±1.81	7.5±1.61	0.001**
HbA1c (%)	5.7±1.11	5.7±1.12	5.87±1.13	5.87±1.16	6.3±1.13	<0.001**
HDL-C (mmol/L)	1.11±0.21	1.01±0.11	1.0±0.11	1.0±0.11	0.8±0.11	<0.001**
Total cholesterol (mmol/L)	5.88±1.41	5.98±1.51	6.1±1.61	6.5±1.51	6.7±1.67	0.05*
Triglycerides (mmol/L)	2.5±1.10	2.9±1.15	3.1±1.15	3.6±1.17	4.1±1.18	0.03*
AIP = log (TG/HDL-C).	0.3±0.11	0.4±0.12	0.5±0.16	0.5±0.20	0.6±0.17	0.002**
BMI (kg/m^2)	26.5±6.55	28.5±7.55	29.5±6.45	29.5±6.55	29.6±6.65	0.05*
hs-CRP(mg/l)	3.9±1.16	4.0±1.6	6.0±1.8	6.4±1.9	7.0±1.9	0.01*
Albumin (g/dL)	3.0±0.3	2.8±0.8	2.5±0.3	2.2±0.4	2.0±0.4	0.02*
AST:ALT ratio	1.5±0.10	1.6±0.10	1.6±0.15	1.7±0.15	1.8±0.15	>0.05
Serum creatinine(mg/dL)	1.6±0.51	1.7±0.61	1.9±0.51	1.9±0.55	2.0±0.66	0.04*
GFR (mL/min/1.73m^2)	70±8.11	69±7.11	58±9.11	56±9.14	50±9.17	0.04*
Urine albumin-to-creatinine ratio mg/g	116.7±11.12	119.6±11.16	130.6±13.18	150.2±16.11	166.8±18.28	0.001**
The incidences of CVD, and CKD were recorded throughout the follow-up period for 735 NAFLD patients, n (%)						
Incidences of CVD	0 (0.0)	55 (7.5)	68 (9.4)	70 (9.5)	73 (9.9)	267 (36.3)
Incidences of CKD	0 (0.0)	50 (6.8)	64 (8.7)	73 (9.9)	80 (10.9)	267 (36.3)

Values are presented mean ± standard deviation (SD) or numbers and percentages (%). *P*-values were obtained from a 2-way ANOVA. *P-value of <0.05, **p-value of <0.001. NAFLD: Nonalcoholic fatty liver disease, FBG: fasting blood glucose, HbA1c: hemoglobin A1c, HDL-C: high density lipoprotein, LDL-C: low-density lipoprotein, hs-CRP: high-sensitivity C-reactive protein, AIP: atherogenic index of plasma, BMI: body mass index, AST: aspartate transaminase, ALT: alanine transaminase, ALP: alkaline phosphatase, eGFR: estimated glomerular filtration rate, CVD: cardiovascular disease, CKD: chronic kidney disease

Table 3 - The percentage of individuals at high risk of chronic kidney disease or cardiovascular disease with non-alcoholic fatty liver disease in the year 2018-2019 (n=735).

Risk of diseases	n (%)
CKD events	189 (25.7)
CVD events	216 (29.4)
The incidences of CKD or CVD with NAFLD (n=735) after 4 years of follow-up	
CKD events	267 (36.3)
CVD events	267 (36.3)

Values are presented as numbers and percentages (%). NAFLD: non-alcoholic fatty liver disease, CKD: chronic kidney disease, CVD: cardiovascular disease

older age and increased levels of AST and hs-CRP are the most significant predictors of cardiovascular and renal diseases, as evidenced by their highest OR in Table 5. Several factors were found to be statistically significant predictors of CKD development in NAFLD patients, including lowering albumin levels, with high FBG levels. On the other hand, the development of CVD was found to be statistically significant to lipid profile (cholesterol, TG), AIP value, and BMI value, as shown in Table 5.

Discussion. According to this study, 735 (49%) of the 1500 participants were found to NAFLD. The diagnosis was carried out by analyzing the participants' medical records and confirmed using ultrasonography, which is the recommended method for detecting excessive accumulation of fat in the liver. A prior meta-analysis has shown that ultrasonography had an overall sensitivity of 84.8% and specificity of 93.6% for detecting moderate to severe fatty liver when compared to histology. Furthermore, several researchers have examined the potential of serum tests in NAFLD for various purposes, including diagnosing the illness, tracking its course, evaluating the effectiveness of treatment interventions, and predicting the prognosis of the condition. Our study's findings on biomarkers, including hs-CRP, AIP, ACR, lipid profiles, and glucose levels, align broadly with global evidence linking these markers to CVD and CKD risk in NAFLD patients. For instance, elevated hs-CRP, a marker of systemic inflammation, has been consistently shown in global studies to predict cardiovascular events in NAFLD populations.[26] The strong inflammatory response observed in our cohort aligns with studies carried out in Western and Asian populations, reinforcing the role of inflammation as a key driver of both CVD and CKD. Similarly, the utility of AIP, a calculated marker reflecting lipid peroxidation, mirrors its established global role as a sensitive predictor of atherogenic dyslipidemia and cardiovascular risk.[27] However, certain findings

Table 4 - Correlation of non-alcoholic fatty liver disease with glomerular filtration rate, chronic kidney disease grade, the incidence of albuminuria, atherogenic index of plasma categories, and the incidence of dyslipidemia.

NAFLD	GFR			Grade CKD						Albuminuria			
Participants (n=735)	<60	>60	*P*-value*	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	*P*-value*	A1	A2	A3	*P*-value*
NAFLD patients at 2018-2019	245 (33.3)	490 (66.7)	0.02	417 (56.7)	313 (42.6)	5 (0.7)	0 (0.0)	0 (0.0)	0.03	355 (48.3)	375 (51.0)	5 (0.7)	0.02
NAFLD patients after 4 years follow up	390 (53.1)	345 (46.9)		225 (30.6)	370 (50.3)	100 (13.6)	35 (4.8)	5 (0.7)		300 (40.8)	385 (52.4)	50 (6.8)	

Participants (n=735)	Lipid			AIP (risk of CVD)			
	Dyslipidemia	Normal	*P*-value*	Low risk	Intermediate risk	High risk	*P*-value*
NAFLD patients at 2018-2019	325 (44.2)	410 (55.8)	0.05	410 (55.8)	300 (40.8)	25 (3.4)	0.04
NAFLD patients after 4 years follow up	370 (50.3)	365 (49.7)		305 (41.5)	370 (50.3)	60 (8.2)	

Values are presented as numbers and percentages (%). *Chi-square test. AIP of <0.11 low risk of CVD, whereas AIP values between 0.11-0.21= intermediate risk, AIP >0.21= high risk of CVD. Grade CKD groups: *p*-value for Grade 1 vs other groups. Albuminuria groups: *p*-value for A1 vs other groups. AIP (risk of CVD) groups: *p*-value for low-risk vs other groups. NAFLD: nonalcoholic fatty liver disease, GFR: glomerular filtration rate, CKD: chronic kidney disease, CVD: cardiovascular disease, AIP: atherogenic index of plasma

diverge due to the unique metabolic and demographic profiles of the Saudi population. For example, ACR, a marker of renal damage, showed a higher prevalence in our cohort than in global studies, potentially due to the elevated rates of obesity, type 2 diabetes, and hypertension in the Saudi population.[28] These factors exacerbate metabolic dysfunction and amplify the association between NAFLD and CKD. Furthermore, while elevated AIP and hs-CRP levels are common in NAFLD populations worldwide, their co-occurrence at such high levels within the same cohort may reflect the regional clustering of metabolic risk factors.

This study also introduces novel contributions to the global literature by emphasizing how biomarkers interact in high-risk populations. For instance, our findings suggest that combining AIP and hs-CRP with traditional markers such as lipid profiles and ACR enhances early detection and risk stratification, a concept less explored in studies from regions with lower baseline metabolic risks. This highlights the potential for biomarker panels tailored to high-risk populations like Saudi Arabia's, where NAFLD prevalence is driven by cultural and lifestyle factors, including sedentary behavior, high-calorie diets, and a younger demographic with escalating metabolic syndrome rates.

Moreover, while studies from regions like Europe and North America focus heavily on genetic predisposition and dietary factors, our findings underscore the role of region-specific contributors, such as rapid urbanization and dietary transitions in Saudi Arabia, which may modify biomarker profiles and disease progression trajectories.[17,29] In summary, our study not only aligns with global trends regarding the role of biomarkers in predicting CVD and CKD in NAFLD but also provides region-specific insights into their interactions and utility in a high-risk population. These findings advocate for the need to tailor diagnostic and therapeutic strategies to the unique metabolic and demographic characteristics of different regions, enhancing both global and local healthcare outcomes.

Furthermore, individuals with NAFLD had a notably elevated occurrence of CKD and CVD following 4 years of observation. Previous discussions have explored the intricate pathophysiological processes that link NAFLD, CVD, and CKD. These variables encompass several metabolic, genetic, epigenetic, and nutritional components that are not fully comprehended and require more exploration.

The interplay between NAFLD and CVD involves several mechanisms. For example, there was a notable association between NAFLD and dyslipidemia, aligning with existing literature suggesting that NAFLD progression is associated with increased CVD risk.[30] A prospective cohort study involving 33,625 participants provided robust evidence suggesting a strong association between NAFLD and dyslipidemia. This study revealed that NAFLD is linked to atherogenic dyslipidemia in a dose-dependent manner, indicating that the severity of NAFLD correlates with the degree of dyslipidemia.[31] This relationship underscores the intricate link

Table 5 - Logistic regression to cardiovascular disease and chronic kidney disease in patients with non-alcoholic fatty liver disease.

Parameters	CVD		CKD	
	Odds ratio (95% CI)	*P*-values	Odds ratio (95% CI)	*P*-values
Age (years)				
Young (30-44)	2.11 (1.13-3.19)	>0.05	2.16 (1.33-3.12)	>0.05
Middle-age (45-59)	5.66 (2.193-5.99)	0.05*	2.66 (1.53-3.52)	>0.05
Older adults (60-80)	6.11 (3.13-7.19)	0.04*	6.16 (2.93-7.11)	0.04*
FBG (mmol/L)	1.96 (0.93-2.19)	>0.05	5.86 (3.73-7.12)	0.03*
HDL-C (mmol/L)	-7.76 (3.23-8.79)	0.04*	-0.56 (0.43-0.99)	>0.05
Total cholesterol (mmol/L)	7.33 (3.93-8.99)	0.03*	1.13 (0.95-1.99)	>0.05
Triglycerides (mmol/L)	8.22 (3.93-10.39)	0.02*	0.96 (0.93-1.19)	>0.05
AIP = log (TG/HDL-C)	9.16 (2.93-11.99)	0.01*	1.22 (0.83-2.10)	>0.05
BMI (kg/m^2)	5.96 (2.93-6.29)	0.04*	1.34 (0.55-1.89)	>0.05
hs-CRP(mg/l)	5.97 (2.43-6.79)	0.04*	8.88 (3.93-9.90)	0.01*
Albumin (g/dL)	0.92 (0.90-1.91)	>0.05	-5.96 (3.93-7.99)	0.05*
Total protein (g/dL)	1.76 (0.99-2.29)	>0.05	3.46 (1.33-4.09)	>0.05
AST (IU/L)	6.36 (2.93-8.99)	0.02*	7.26 (2.93-9.39)	0.01*
ALT(IU/L)	1.26 (0.73-2.29)	>0.05	1.33 (0.73-1.99)	>0.05
ALP (IU/L)	2.16 (1.93-3.89)	>0.05	4.36 (1.93-4.99)	>0.05
Creatine phosphokinase (mcg/L)	9.46 (3.93-11.49)	0.03*	2.33 (1.23-3.11)	>0.05

**P*-value of <0.05. Logistic regression analysis with odds ratio (OR) and 95% confidence interval (CI). NAFLD: nonalcoholic fatty liver disease, CKD: chronic kidney disease, CVD: cardiovascular diseases, FBG: fasting blood glucose, HDL-C: high density lipoprotein, hs-CRP: high-sensitivity C-reactive protein, AIP: atherogenic index of plasma, BMI: body mass index, AST: aspartate transaminase, ALT: alanine transaminase, ALP: Alkaline phosphatase

between NAFLD and lipid metabolism abnormalities, emphasizing the importance of managing dyslipidemia in NAFLD patients to mitigate CVD risk.[31-33] Non-alcoholic fatty liver disease is not only associated with dyslipidemia but also with visceral adiposity, which is the accumulation of fat within the abdominal cavity, surrounding vital organs. This visceral fat is particularly metabolically active and contributes significantly to metabolic syndrome, including insulin resistance and atherogenic dyslipidemia. Insulin resistance in NAFLD patients can occur with or without hyperglycemia, highlighting the metabolic complexity of the disease. These metabolic derangements collectively increase the risk of cardiovascular complications in NAFLD patients.[18-20] Meanwhile, Stahl et al[34] reported that both NAFLD and CVD are features of end-organ damage in metabolic syndrome and that the exact involvement of NAFLD in higher CVD risk was challenging to distinguish from these shared risk factor combinations. The association between NAFLD and CVD is mediated through several complex pathways, with chronic low-grade inflammation being one of the most critical mechanisms. Non-alcoholic fatty liver disease is characterized by hepatic steatosis, which triggers the release of pro-inflammatory cytokines such as IL-6, TNF-α, and CRP into the systemic circulation.[26] These cytokines promote endothelial dysfunction, a key early event in the pathogenesis of atherosclerosis, by impairing nitric oxide bioavailability and inducing oxidative stress in vascular tissues.[27] Studies have also shown that the liver's role in lipid metabolism is disrupted in NAFLD, leading to increased production of atherogenic lipoproteins, such as very-low-density lipoprotein, and alterations in lipid profiles, which further contribute to cardiovascular risk.[27,28] For example, elevated levels of the AIP, observed in NAFLD patients, are strongly linked to the development of subclinical atherosclerosis and cardiovascular events.[26,28]

The underlying mechanisms behind NAFLD and CVD association are complex and consist of various pathways at the same time.[26-28] Several studies have discussed the potential mechanisms behind such an association.[26-28,35] Ismaiel et al[36] concluded that there was a strong association between fatty liver disease presence and severity and various cardiovascular adverse events, such as coronary artery disease, subclinical atherosclerosis risk, structural and functional cardiac modifications, arrhythmias and conduction defects. Interestingly, the study also noted that the risk of CVD complications in NAFLD patients was greater than the sum of the risks posed by individual comorbidities such as visceral adiposity, dyslipidemia, and insulin resistance. This suggests that NAFLD itself may have a direct pathophysiological role in increasing CVD risk beyond

these associated metabolic abnormalities. For instance, NAFLD is known to promote a pro-inflammatory and pro-thrombotic state, which can accelerate atherosclerosis and other cardiovascular events.[37-39] The results of our study are consistent with recent research that suggests that NAFLD is a separate risk factor for CVD due to changes in certain biomarkers such as TG, cholesterol, hs-CRP, and AST. A separate analysis highlighted that patients with NAFLD have a higher prevalence of atherogenic lipid profiles, characterized by elevated levels of small, dense LDL particles, increased TGs, and low HDL cholesterol levels. These lipid abnormalities are particularly atherogenic and contribute significantly to cardiovascular risk.[37-40]

In this study, the correlation between CKD and NAFLD was examined. The results showed that NAFLD patients had a considerably greater percentage of GFR below 60 compared to those without NAFLD. Moreover, there was a notable correlation between NAFLD and the severity of CKD. The results of our research align with earlier studies, indicating that individuals with NAFLD had a notably higher risk of developing CKD.[40-42] Various complex pathophysiological mechanisms for the association between NAFLD and CKD have been previously discussed.[43] These factors include a range of metabolic, genetic, epigenetic, and dietary factors that are not completely understood and need additional investigation. The interplay between NAFLD and CKD involves several mechanisms. For example, insulin resistance is a common feature in NAFLD, which contributes to hepatic fat accumulation and subsequent inflammation.[44] The present investigation revealed that individuals with NAFLD have elevated FBG and glycated HbA1c levels, which are related to an increased risk of developing diabetes, potentially due to insulin resistance. This metabolic disturbance is also a key factor in the development and progression of CKD. Another mechanism, oxidative stress, and inflammation: NAFLD is characterized by increased oxidative stress and a pro-inflammatory state. These conditions can lead to glomerular injury and renal fibrosis, exacerbating CKD. This study found a notable correlation between hs-CRP and CKD in individuals with NAFLD. C-reactive protein is a biomarker that is synthesized by the liver and its levels in the blood rise during periods of inflammation. Measuring the levels of hs-CRP in the blood has proven to help distinguish between simple steatosis and NAFLD. Furthermore, there is evidence to suggest that elevated levels of hs-CRP are linked to significant liver fibrosis in NAFLD, namely, NASH.[45] In kidney illnesses, CRP is abundantly produced by various inflammatory cells, most likely macrophages, as well as by intrinsic kidney cells such as tubular cells and endothelial cells.[46] However, it has been shown that persistently elevated levels of CRP might lead to the development of long-term inflammation in individuals with CKD. Thus, an increased level of CRP is regarded as a biomarker indicating an inflammatory response, tissue damage, and the long-term advancement of illnesses. In addition to being a biomarker for inflammation, CRP also has pro-inflammatory effects and anti-inflammatory qualities in 2 different forms: the native pentameric CRP and the monomeric CRP. These forms may have an important role in the development of renal disorders. Our finding aligns with the prior observation, as we have demonstrated that individuals with NAFLD had elevated hs-CRP levels. Furthermore, we have established a statistically significant correlation between the serum hs-CRP level and the risk of CKD in NAFLD patients.[45,46] A recent review reported a strong association between the presence and severity of NAFLD and increased prevalence and incidence of CKD, irrespective of obesity, hypertension, type 2 diabetes, and other common cardio-renal risk factors.[45,46] This highlights the need for clinicians to monitor renal function in patients with NAFLD closely.

Our study suggested that older age and increased levels of TG, glucose, AST, and hs-CRP are the most significant predictors of CVD and CKD. The significant predictors of CKD development in NAFLD patients included glucose, albumin levels, hs-CRP, and AST values. Meanwhile, CVD development showed a significant relationship to lipid profile, AIP, and BMI values.

This study addresses the knowledge gap regarding the incidence of NAFLD and its impact on CVD and CKD in Saudi Arabia, where data on this association remain limited. Regional comparisons reveal similar trends in the prevalence and metabolic burden of NAFLD among the Gulf Cooperation Council (GCC) countries. For example, studies from Kuwait and the United Arab Emirates have also reported a strong association between NAFLD and cardiovascular risk factors, such as dyslipidemia, elevated BMI, and atherogenic profiles.[47,48] However, variations in lifestyle and healthcare systems across GCC countries may contribute to differing degrees of disease progression and management outcomes. Unlike prior studies from the region, this research integrates biomarkers such as AIP, hs-CRP, and ACR, which are less commonly analyzed but provide critical insights into the early identification and stratification of patients at risk for CVD and CKD. By doing so, this study not only bridges the knowledge gap in Saudi Arabia but also contributes to a broader

understanding of NAFLD and its systemic effects across the GCC. Such comparisons highlight shared challenges while emphasizing the need for tailored strategies to address the metabolic and cardiovascular health burden in the region.

Non-alcoholic fatty liver disease was redefined from the negative (nonexistence of excessive alcohol drinking and other known causes of liver disease) to a more positively stated metabolic-associated fatty liver disease (MAFLD).[49,50] The redefinition of NAFLD to MAFLD emphasizes the metabolic dysfunction underlying the condition, rather than its exclusion based on alcohol consumption or other liver diseases. This shift in definition aims to better identify patients who are at risk due to metabolic health issues and is supported by emerging evidence linking metabolic syndrome with liver disease progression and associated complications such as CVD and CKD.

Study strengths & limitations. Adding to the study's strengths, we strictly followed the recommended guidelines of STROBE; however, the limitations include the retrospective design of the study. The study undertaken exhibited a single-center design and a limited sample size. The researchers noted the existence of selection bias and the lack of thorough documentation regarding the treatment history. Therefore, ongoing investigations ought to prioritize longitudinal studies. To enhance comprehension of the temporal correlation among NAFLD, CKD, and CVD, longitudinal investigations are required to monitor the advancement of these ailments over an extended period. Furthermore, an examination of the genetic and epigenetic elements that contribute to an individual's susceptibility to NAFLD and its associated complications may yield valuable knowledge regarding individualized therapeutic approaches. Investigating the effectiveness of therapeutic interventions that target metabolic and inflammatory pathways in NAFLD patients to reduce the risk of CKD and CVD.

In concluson, the current study highlights NAFLD as an independent risk factor for the development of CKD and CVD. Our findings demonstrate that individuals with NAFLD exhibit significant alterations in biomarkers such as lipid levels, glucose, hs-CRP, albumin, and liver enzymes, which reflect the interplay between the liver, kidney, and heart. Dyslipidemia, hyperglycemia, systemic inflammation, and liver dysfunction appear to mediate this association, contributing to atherosclerosis, endothelial dysfunction, and kidney damage.

Regular monitoring of these biomarkers in NAFLD patients can aid in identifying those at higher risk, enabling timely interventions. A comprehensive management approach addressing metabolic syndrome components (via lifestyle changes and pharmacotherapy) can mitigate disease progression and reduce the burden of CKD and CVD.

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