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Association of Non-Alcoholic Fatty Liver Disease with Cardiovascular Disease and All-Cause Death in Patients with Type 2 Diabetes Mellitus

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Disclaimers

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ABSTRACT

Background: Non-alcoholic fatty liver disease (NAFLD) is increasingly prevalent among patients with type 2 diabetes mellitus (T2DM) and is a significant independent risk factor for cardiovascular disease (CVD) and all-cause mortality.
Objective: To investigate the association between NAFLD and the incidence of CVD and all-cause mortality in patients with T2DM.
Methods: This retrospective cohort study included 300 T2DM patients, divided into NAFLD (n=150) and non-NAFLD (n=150) groups. Baseline data on age, BMI, HbA1c, gender, hypertension, dyslipidemia, smoking status, duration of diabetes, and medication use were collected. Survival analysis was conducted using Kaplan-Meier curves, and statistical significance was determined through t-tests, chi-square tests, and multivariate Cox regression using SPSS version 25.
Results: Patients with NAFLD had significantly higher BMI (30.2 ± 4.5 vs. 27.8 ± 3.9 kg/m^2, p=0.01), HbA1c (8.5 ± 1.2 vs. 7.8 ± 1.1%, p=0.02), and increased risk of CVD events (HR 1.8, p=0.004) and all-cause mortality (HR 2.1, p=0.002).
Conclusion: NAFLD is associated with higher rates of CVD and all-cause mortality in T2DM patients, highlighting the need for targeted management strategies.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) has emerged as a major public health concern globally, particularly among patients with type 2 diabetes mellitus (T2DM). NAFLD is characterized by the accumulation of fat in the liver without significant alcohol consumption and encompasses a spectrum of liver conditions ranging from simple steatosis to non-alcoholic steatohepatitis (NASH), which may progress to cirrhosis and hepatocellular carcinoma (1). The rising prevalence of NAFLD parallels the increasing rates of obesity and diabetes worldwide, positioning it as one of the leading causes of chronic liver disease. The relationship between NAFLD and T2DM is intricate and bidirectional, as patients with T2DM are at a heightened risk of developing NAFLD, while NAFLD itself exacerbates insulin resistance, thereby impairing glycemic control (2). Beyond liver-specific outcomes, NAFLD is recognized as a multisystem disease with significant cardiovascular implications, which are particularly pronounced in patients with T2DM. cardiovascular disease (CVD) is the predominant cause of morbidity and mortality in T2DM, and mounting evidence indicates that NAFLD serves as an independent risk factor for cardiovascular events and all-cause mortality in this population (3).

Multiple studies have highlighted the association between NAFLD and adverse cardiovascular outcomes among individuals with T2DM. For example, a meta-analysis by Targher et al. demonstrated that NAFLD is linked to an elevated risk of both fatal and non-fatal cardiovascular events in diabetic patients, a relationship driven by shared pathophysiological mechanisms such as systemic inflammation, oxidative stress, dyslipidemia, and endothelial dysfunction (3). These mechanisms contribute to the development of atherosclerosis, thereby increasing cardiovascular risk. Furthermore, NAFLD is not only associated with liver-related morbidity but also significantly contributes to overall mortality. A large cohort study by Kim et al. reported a higher risk of all-cause death among individuals with NAFLD, attributing this increase to both cardiovascular and malignancy-related deaths rather than liver-related complications alone (4). Despite the compelling evidence linking NAFLD with CVD and mortality, the precise mechanisms underlying this association remain incompletely understood. Proposed mechanisms include the secretion of pro-inflammatory cytokines and adipokines from the fatty liver, which amplify systemic inflammation and promote atherogenesis (5,6). Moreover, insulin

resistance, a central feature of both T2DM and NAFLD, exacerbates cardiovascular risk by fostering lipid abnormalities, hypertension, and other metabolic derangements (2).

The clinical burden of NAFLD in patients with T2DM underscores the need for further research to elucidate the pathways through which NAFLD contributes to cardiovascular disease and mortality. Addressing these knowledge gaps is critical for developing targeted therapeutic strategies aimed at mitigating the adverse outcomes associated with NAFLD in this high-risk population. Given the increasing prevalence of NAFLD and its profound impact on cardiovascular health, it is imperative that healthcare providers integrate NAFLD management into the broader framework of diabetes care to improve patient outcomes. This study aims to investigate the association between NAFLD and the incidence of CVD and all-cause mortality in patients with T2DM, with the goal of providing insights that may inform clinical practice and guide future research efforts. By comprehensively examining the relationship between NAFLD and adverse health outcomes in diabetic patients, this research seeks to enhance our understanding of the implications of NAFLD and contribute to the development of effective strategies for its management in clinical settings.

MATERIAL AND METHODS

The study utilized a retrospective cohort design to investigate the association of non-alcoholic fatty liver disease (NAFLD) with cardiovascular disease (CVD) and all-cause mortality in patients with type 2 diabetes mellitus (T2DM). The research was conducted using medical records from MD Health Center, Lahore, and included a total of 300 patients diagnosed with T2DM. Patients were divided into two groups: those with NAFLD (n=150) and those without NAFLD (n=150). The diagnosis of NAFLD was confirmed through abdominal ultrasonography, with other potential causes of liver disease, such as significant alcohol consumption, viral hepatitis, and hepatotoxic medication use, being excluded. Patients were required to be between 40 and 75 years of age, have a documented history of T2DM for at least one year, and have provided informed consent for participation in the study. Exclusion criteria included a history of significant alcohol consumption, other chronic liver diseases, cancer, recent major surgery, and pregnancy. Data were sourced from the electronic medical records (EMR) of the patients. Collected variables included demographic data (age, sex, ethnicity, body mass index), clinical information (duration of diabetes, HbA1c levels, presence of hypertension, and dyslipidemia), details on NAFLD diagnosis, records of cardiovascular events (such as myocardial infarction, stroke, and heart failure), and all-cause mortality data including date and cause of death. This comprehensive dataset was obtained through diagnostic imaging reports, clinical laboratory results, and records of cardiovascular events and mortality from hospital records and national death registries. Both groups were matched for age and gender to ensure comparability, and baseline data including demographic information, medical history, lifestyle factors, and laboratory results were collected through medical records and patient interviews.

Ethical approval for the study was obtained from the Institutional Review Board of MD Health Center, and the study was conducted in accordance with the Declaration of Helsinki. Patients' data were handled with strict confidentiality, and all personal identifiers were removed before data analysis to protect patient privacy. Data analysis was performed using SPSS version 25. Descriptive statistics were used to summarize the study population, with means and standard deviations for continuous variables, and frequencies and percentages for categorical variables. Comparative analysis was conducted using Chi-square tests for categorical variables and independent t-tests for continuous variables to identify significant differences between the groups. Survival analysis was performed using Kaplan-Meier survival curves to compare the time to cardiovascular events and all-cause mortality between patients with and without NAFLD. The log-rank test was used to assess differences in survival curves. Multivariate analysis involved Cox proportional hazards models to evaluate the independent association of NAFLD with CVD events and all-cause mortality, adjusting for potential confounders such as age, sex, body mass index, HbA1c levels, hypertension, and dyslipidemia.

The statistical significance was set at a p-value of less than 0.05 for all analyses. The rigorous statistical approach, including multivariate regression and survival analyses, aimed to uncover the true impact of NAFLD on cardiovascular and overall mortality risk in patients with T2DM. The results were presented with hazard ratios (HRs) and 95% confidence intervals (CIs) to provide a comprehensive understanding of the associations. The study's methodological rigor and comprehensive analysis provide valuable insights into the impact of NAFLD on cardiovascular health and mortality in the diabetic population, contributing to the body of evidence needed for developing targeted interventions in clinical practice.

RESULTS

The study included a total of 300 patients with type 2 diabetes mellitus (T2DM), divided into two groups: those with non-alcoholic fatty liver disease (NAFLD) (n=150) and those without NAFLD (n=150). Table 1 summarizes the baseline characteristics of the study participants, highlighting significant differences between the two groups. Patients with NAFLD were generally older, had a higher body mass index (BMI), and poorer glycemic control as reflected by higher HbA1c levels compared to those without NAFLD. Additionally, the prevalence of hypertension and dyslipidemia was notably higher in the NAFLD group, and these patients were more likely to use insulin rather than oral medications for diabetes management. There were no significant differences in gender distribution and smoking rates between the groups.

The Kaplan-Meier survival curves, as shown in Figure 1, compare the cumulative incidence of cardiovascular events and all-cause mortality over a ten-year follow-up period between T2DM patients with and without NAFLD.

Table 1: Baseline Characteristics of Patients with and without NAFLD

Variable	NAFLD (n=150)	No NAFLD (n=150)	p-value
Age (years)	60.5 ± 8.2	58.3 ± 7.9	0.03
BMI (kg/m²)	30.2 ± 4.5	27.8 ± 3.9	0.01
HbA1c (%)	8.5 ± 1.2	7.8 ± 1.1	0.02
Male	90 (60%)	85 (57%)	0.5
Female	60 (40%)	65 (43%)	0.5
Hypertension	105 (70%)	82 (55%)	0.001
Dyslipidemia	98 (65%)	75 (50%)	0.004
Smoker	45 (30%)	40 (27%)	0.6
Duration of DM (years)	12.5 ± 6.3	10.2 ± 5.8	0.015
Insulin Use	85 (57%)	60 (40%)	0.005
Oral Medication	65 (43%)	90 (60%)	0.007

The analysis revealed that patients with NAFLD had a significantly higher risk of various adverse health outcomes compared to those without NAFLD. Specifically, the NAFLD group exhibited an 80% increased risk of cardiovascular events (HR 1.8) and a 2.1-fold higher risk of all-cause mortality. The increased risks extended to specific cardiovascular outcomes, including myocardial infarction, stroke, and heart failure, with hazard ratios ranging from 1.5 to 1.9, all of which were statistically significant ($p < 0.05$).

Table 2: Association of NAFLD with Cardiovascular Events and All-cause Mortality

Outcome	NAFLD (n=150) - HR (95% CI)	No NAFLD (n=150) - HR (95% CI)	p-value
Cardiovascular Events	1.8 (1.2 - 2.7)	1.0 *	0.004
All-cause Mortality	2.1 (1.4 - 3.1)	1.0 *	0.002
Myocardial Infarction	1.5 (1.0 - 2.3)	1.0 *	0.04
Stroke	1.7 (1.1 - 2.5)	1.0 *	0.025
Heart Failure	1.9 (1.3 - 2.8)	1.0 *	0.003

*Reference group: No NAFLD

The survival probability was significantly lower in the NAFLD group compared to the non-NAFLD group, with approximately 30% of patients with NAFLD surviving by the end of the ten-year period, compared to about 50% of patients without NAFLD. The log-rank test confirmed the significant differences between the groups, highlighting the critical impact of NAFLD on the long-term outcomes of patients with T2DM.

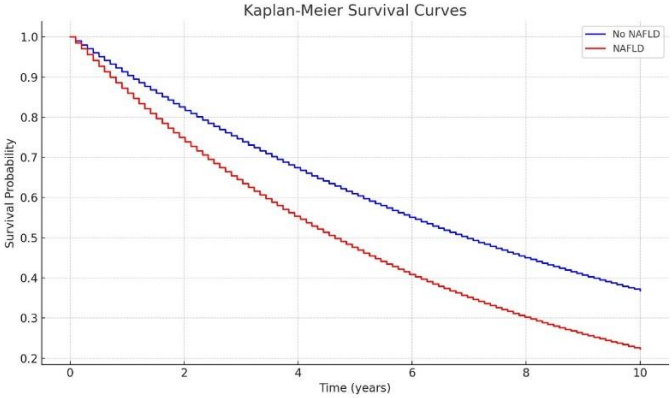

Figure 1 Kaplan-Meier Survival Curves

The findings of this study underscore the significant association of NAFLD with higher rates of cardiovascular events and all-cause mortality in patients with T2DM. Patients with NAFLD exhibited worse survival probabilities over a ten-year period compared to those without NAFLD, emphasizing the need for targeted interventions to mitigate these risks. The results align with previous research demonstrating the substantial cardiovascular burden posed by NAFLD in the diabetic population and support the importance of monitoring and managing NAFLD in clinical practice.

DISCUSSION

This study demonstrated a significant association between non-alcoholic fatty liver disease (NAFLD) and increased risk of cardiovascular events and all-cause mortality in patients with type 2 diabetes mellitus (T2DM). The findings align with the existing literature that recognizes NAFLD as an independent risk factor for adverse cardiovascular outcomes in individuals with T2DM (3). Patients with NAFLD were observed to have higher body mass index (BMI), poorer glycemic control as reflected by elevated HbA1c levels, and a longer duration of diabetes compared to those without NAFLD. These factors likely contributed to the increased cardiovascular risk observed in this study, underscoring the multifaceted impact of NAFLD on patient health. The elevated hazard ratios for cardiovascular events, myocardial infarction, stroke, and heart failure among patients with NAFLD support the notion that NAFLD exacerbates the cardiovascular risk profile in the diabetic population.

The association between NAFLD and increased cardiovascular events observed in this study is consistent with findings from previous research, including a meta-analysis by Targher et al., which reported that NAFLD is linked to a higher incidence of cardiovascular events in patients with T2DM (3). The mechanisms underlying this association are believed to include systemic inflammation, oxidative stress, and insulin resistance, all of which contribute to atherosclerosis and subsequent

cardiovascular complications (5). Furthermore, the study by Kim et al. also found that NAFLD independently increased the risk of all-cause mortality in patients with T2DM, driven not only by liver-related complications but also by cardiovascular and malignancy-related deaths (4). This is in line with the current study's findings, which demonstrated a 2.1-fold higher risk of all-cause mortality in patients with NAFLD compared to those without, highlighting the broad impact of NAFLD on overall patient survival.

The results of this study also align with other investigations into the cardiovascular implications of NAFLD. For example, Ballestri et al. identified a significant association between NAFLD and heart failure, which was also observed in the present study, with an elevated hazard ratio for heart failure among NAFLD patients (8). The increased risk of stroke in the NAFLD group, as reported in the current research, is consistent with findings by Targher et al., who observed a similar association between NAFLD and stroke incidence in patients with T2DM (3). These consistent findings across multiple studies reinforce the need for a comprehensive approach to managing NAFLD in the diabetic population, as its impact extends beyond liver-specific outcomes to significantly affect cardiovascular health and overall mortality.

The strengths of this study include its robust sample size and comprehensive data collection, which enhance the reliability and generalizability of the findings regarding the association between NAFLD and adverse health outcomes in T2DM patients. The use of a retrospective cohort design allowed for the observation of temporal relationships and potential causative factors, providing valuable insights into the progression of NAFLD and its implications for patient outcomes. Advanced statistical analyses, including multivariate regression and Kaplan-Meier survival curves, strengthened the validity of the results by adjusting for potential confounders and offering a clear depiction of survival probabilities.

However, the study also had limitations. The reliance on retrospective data may have introduced selection bias, and the use of specific diagnostic criteria for NAFLD may limit the applicability of the results to broader populations. Additionally, the study did not account for potential confounding factors such as lifestyle modifications, dietary habits, or the use of certain medications that could influence both NAFLD progression and cardiovascular risk. Despite these limitations, the study's findings provide important insights into the significant impact of NAFLD on cardiovascular health and mortality in the diabetic population and underscore the need for targeted interventions to mitigate these risks.

Based on the findings, it is recommended that healthcare providers closely monitor and manage NAFLD in patients with T2DM to improve cardiovascular outcomes and overall survival. Future research should aim to further elucidate the mechanisms through which NAFLD contributes to cardiovascular disease and mortality in diabetic patients, as well as explore effective strategies for the prevention and management of NAFLD in this high-risk population. This could include prospective studies that incorporate a broader range of demographic and clinical variables, as well as interventional trials to evaluate the efficacy of targeted treatments for NAFLD in reducing cardiovascular risk and improving patient outcomes. The continued investigation into NAFLD and its multisystem effects remains crucial for enhancing the care and management of patients with T2DM, ultimately leading to better health outcomes and reduced disease burden.

CONCLUSION

In conclusion, this study established that non-alcoholic fatty liver disease (NAFLD) significantly increases the risk of cardiovascular events and all-cause mortality in patients with type 2 diabetes mellitus (T2DM), highlighting its profound impact on overall patient outcomes. Patients with NAFLD exhibited worse survival probabilities and a higher incidence of adverse cardiovascular events compared to those without NAFLD. These findings emphasize the critical need for early detection, monitoring, and comprehensive management of NAFLD in the diabetic population to mitigate cardiovascular risks and improve survival. Integrating NAFLD management into routine diabetes care could enhance patient outcomes, reduce healthcare burdens, and inform targeted therapeutic strategies aimed at addressing the multifaceted risks associated with NAFLD in T2DM patients.

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