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10-YEAR RISK OF CVD IN PATIENTS WITH METABOLIC SYNDROME WITH AND WITHOUT NAFLD

Original Research (ID: 1700)

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ABSTRACT

Background: Metabolic syndrome is a major cardiometabolic disorder that increases the likelihood of future cardiovascular disease through clustered abnormalities such as central obesity, hypertension, dyslipidemia, and impaired glucose regulation. Non-alcoholic fatty liver disease commonly coexists with metabolic syndrome and may further increase cardiovascular risk through inflammation, insulin resistance, and endothelial dysfunction. However, liver status is not routinely included in conventional cardiovascular risk prediction tools, which may underestimate risk in affected patients.

Objective: To compare the estimated 10-year cardiovascular disease risk among patients with metabolic syndrome with and without non-alcoholic fatty liver disease and to determine whether non-alcoholic fatty liver disease independently predicts higher cardiovascular risk.

Methods: This cross-sectional observational study included 100 patients with metabolic syndrome, divided equally into two groups: metabolic syndrome with ultrasound-confirmed non-alcoholic fatty liver disease and metabolic syndrome without fatty liver on ultrasound. Demographic, clinical, and biochemical variables were recorded, including age, sex, waist circumference, blood pressure, triglycerides, high-density lipoprotein cholesterol, and fasting glucose. The 10-year cardiovascular disease risk was estimated using the Framingham Risk Score and ASCVD Risk Estimator. Group comparisons, correlation analysis, and multivariable regression analysis were performed.

Results: The mean Framingham Risk Score was significantly higher in patients with non-alcoholic fatty liver disease than in those without it (22.4 ± 8.2% versus 16.3 ± 7.6%, $p = 0.03$). Similarly, the mean ASCVD risk was higher in the non-alcoholic fatty liver disease group (24.1 ± 9.1% versus 18.9 ± 7.5%, $p = 0.04$). High cardiovascular risk was observed in 60% of patients with non-alcoholic fatty liver disease compared with 36% without it ($p = 0.01$). Fatty liver grade showed a positive correlation with Framingham Risk Score ($r = 0.45$, $p = 0.01$) and ASCVD risk ($r = 0.42$, $p = 0.02$). Multivariable regression showed that non-alcoholic fatty liver disease independently predicted higher Framingham Risk Score ($\beta = 0.32$, $p = 0.02$) and ASCVD risk ($\beta = 0.29$, $p = 0.03$).

Conclusion: Non-alcoholic fatty liver disease was associated with higher estimated 10-year cardiovascular disease risk among patients with metabolic syndrome. Routine liver assessment may improve cardiovascular risk stratification and help identify patients who may benefit from earlier preventive intervention.

Keywords: Atherosclerosis; Cardiovascular Diseases; Fatty Liver; Framingham Study; Metabolic Syndrome; Risk Assessment; Ultrasonography.

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INTRODUCTION

Metabolic syndrome is a clinically important cluster of interrelated metabolic abnormalities that substantially increases the risk of cardiovascular disease and type 2 diabetes. It is commonly characterized by central obesity, hypertension, dyslipidemia, impaired glucose regulation, and insulin resistance. Because these risk factors often occur together and reinforce one another, metabolic syndrome has become a major contributor to the growing burden of non-communicable diseases worldwide. Its prevalence is estimated to affect nearly one-fifth to one-third of adults globally, although rates vary according to age, sex, ethnicity, lifestyle patterns, and geographic region. Individuals with metabolic syndrome are more likely to develop myocardial infarction, stroke, peripheral arterial disease, and diabetes-related complications, making early cardiovascular risk identification a key priority in this population (1). The association between metabolic syndrome and cardiovascular disease is well established, but risk prediction in these patients remains an evolving area of clinical research. Conventional tools such as the Framingham Risk Score and the Atherosclerotic Cardiovascular Disease risk estimator are widely used to estimate the 10-year probability of cardiovascular events. These models generally rely on traditional variables such as age, sex, blood pressure, cholesterol levels, diabetes status, and smoking history. Although these tools provide useful guidance, they may not fully capture the broader metabolic and inflammatory burden present in patients with metabolic syndrome. This limitation has encouraged growing interest in additional conditions that may refine cardiovascular risk assessment and help identify patients who require earlier or more intensive preventive care (2).

Non-alcoholic fatty liver disease has emerged as one such condition of increasing clinical relevance. It is defined by excessive fat accumulation in the liver in the absence of significant alcohol intake and is now considered one of the most common chronic liver disorders worldwide. Non-alcoholic fatty liver disease shares several pathogenic features with metabolic syndrome, particularly insulin resistance, visceral adiposity, atherogenic dyslipidemia, and low-grade systemic inflammation. In many patients, it remains clinically silent for years and is often detected incidentally on liver ultrasound or during evaluation for abnormal liver enzymes. Despite its apparently hepatic origin, its implications extend beyond the liver, as accumulating evidence suggests that cardiovascular disease is a leading cause of morbidity and mortality among individuals with non-alcoholic fatty liver disease (3,4). The relationship between non-alcoholic fatty liver disease and cardiovascular risk appears to be more than a simple coexistence of shared risk factors. Several biological mechanisms may explain its contribution to vascular injury, including chronic inflammation, oxidative stress, endothelial dysfunction, altered lipid metabolism, and worsening insulin resistance. These mechanisms can accelerate atherosclerosis and may amplify cardiovascular risk in patients who already have metabolic syndrome. Therefore, the presence of non-alcoholic fatty liver disease may identify a subgroup of patients with metabolic syndrome who carry a higher long-term cardiovascular risk than would be expected from conventional risk factors alone (5).

Although metabolic syndrome is already recognized as a high-risk clinical state, the incremental effect of non-alcoholic fatty liver disease on estimated 10-year cardiovascular risk is not routinely considered in everyday practice. This creates an important gap in clinical risk stratification. If patients with both metabolic syndrome and non-alcoholic fatty liver disease have a higher predicted cardiovascular risk than those with metabolic syndrome alone, then screening for fatty liver may provide additional value in preventive cardiometabolic care. Liver ultrasound, being non-invasive, accessible, and relatively inexpensive, may serve as a practical tool for identifying such high-risk individuals in routine clinical settings (6,7). Given the rising prevalence of both metabolic syndrome and non-alcoholic fatty liver disease, understanding their combined impact on cardiovascular risk has direct clinical importance. A clearer assessment of this relationship may support earlier lifestyle modification, stricter control of metabolic risk factors, and more individualized cardiovascular prevention strategies. Therefore, the present study is designed to compare the 10-year risk of cardiovascular disease among patients with metabolic syndrome with and without non-alcoholic fatty liver disease. The study hypothesizes that patients with metabolic syndrome and coexisting non-alcoholic fatty liver disease have a higher estimated 10-year cardiovascular disease risk than patients with metabolic syndrome alone, thereby supporting the potential role of non-alcoholic fatty liver disease as an additional marker in cardiovascular risk assessment (8).

METHODS

This cross-sectional observational comparative study was conducted at a tertiary care hospital in Peshawar, Pakistan, from January 2025 to June 2025. The study was designed to compare the estimated 10-year cardiovascular disease risk among patients with metabolic syndrome with and without non-alcoholic fatty liver disease. Ethical approval was obtained from the Institutional Review Board/Ethical Review Committee of the hospital before the start of data collection. Written informed consent was obtained from all participants after explaining the purpose of the study, the procedures involved, confidentiality of data, and the voluntary nature of participation. A total of 100 adult participants were enrolled who fulfilled the diagnostic criteria for metabolic syndrome according to the National Cholesterol

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Education Program Adult Treatment Panel III criteria. Participants aged 30 to 74 years were considered eligible for inclusion. Metabolic syndrome was defined by the presence of at least three of the following components: waist circumference greater than 102 cm in men or greater than 88 cm in women, serum triglyceride level of 150 mg/dL or above, high-density lipoprotein cholesterol less than 40 mg/dL in men or less than 50 mg/dL in women, blood pressure of 130/85 mmHg or above, and fasting plasma glucose of 100 mg/dL or above. Patients with a history of established cardiovascular disease, significant alcohol intake, viral hepatitis B or C, autoimmune liver disease, drug-induced liver disease, or any other known chronic liver disorder were excluded from the study. Significant alcohol intake was defined as alcohol consumption greater than 20 g/day in women and greater than 30 g/day in men.

After eligibility assessment, participants were divided into two equal groups on the basis of abdominal ultrasonography findings. Group A included 50 patients with metabolic syndrome and ultrasound-confirmed non-alcoholic fatty liver disease, whereas Group B included 50 patients with metabolic syndrome without evidence of fatty liver on ultrasound. Abdominal ultrasonography was performed by a senior radiologist using standard sonographic criteria. Non-alcoholic fatty liver disease was identified by increased hepatic echogenicity in comparison with the renal cortex, reduced visualization of intrahepatic vessels, and attenuation of the ultrasound beam, after excluding secondary causes of hepatic steatosis. The severity of hepatic steatosis was graded as mild, moderate, or severe according to liver echogenicity, visualization of intrahepatic vascular structures, and clarity of the diaphragm and posterior hepatic parenchyma. Demographic, clinical, and biochemical data were collected using a structured data collection form. The recorded variables included age, sex, waist circumference, systolic and diastolic blood pressure, fasting plasma glucose, triglyceride level, high-density lipoprotein cholesterol, smoking status, diabetes status, antihypertensive medication use, and lipid profile parameters required for cardiovascular risk estimation. Waist circumference was measured using a non-stretchable measuring tape at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest. Blood pressure was recorded in the sitting position after an adequate period of rest, and laboratory parameters were measured from fasting venous blood samples according to standard hospital laboratory procedures.

The primary outcome of the study was the estimated 10-year cardiovascular disease risk calculated using the Framingham Risk Score and the Atherosclerotic Cardiovascular Disease Risk Estimator. Participants were categorized into low, intermediate, and high cardiovascular risk groups according to the standard cut-off values recommended for each risk prediction tool. The secondary outcome was the relationship between ultrasound-based fatty liver grade and estimated cardiovascular risk scores among patients with metabolic syndrome and non-alcoholic fatty liver disease. Data were analyzed using the Statistical Package for the Social Sciences version 26. Continuous variables were presented as mean and standard deviation for normally distributed data, while non-normally distributed variables were summarized using median and interquartile range where appropriate. Categorical variables were presented as frequencies and percentages. The Shapiro-Wilk test was used to assess normality of continuous variables. Independent sample t-tests were applied for comparison of normally distributed continuous variables between the two groups, whereas the Mann-Whitney U test was used for non-normally distributed variables. Categorical variables were compared using the chi-square test or Fisher's exact test where applicable. Pearson correlation analysis was used to assess the relationship between fatty liver grade and cardiovascular risk scores when assumptions of normality were met, while Spearman correlation was considered for ordinal or non-normally distributed variables. Multivariable linear regression analysis was performed to determine whether non-alcoholic fatty liver disease was independently associated with 10-year cardiovascular risk after adjusting for conventional cardiovascular risk factors. A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 100 participants with metabolic syndrome were included in the study and were equally distributed into two groups. Group A included 50 participants with metabolic syndrome and ultrasound-confirmed non-alcoholic fatty liver disease, while Group B included 50 participants with metabolic syndrome without sonographic evidence of fatty liver. The mean age was 55.2 ± 8.4 years in Group A and 56.1 ± 7.9 years in Group B, with no statistically significant difference between the groups ($p = 0.58$). The sex distribution was also comparable, with 30 males and 20 females in Group A and 32 males and 18 females in Group B ($p = 0.79$). Baseline metabolic parameters were generally similar between both groups. The mean waist circumference was 104.3 ± 12.6 cm in Group A and 102.7 ± 11.2 cm in Group B ($p = 0.47$). Mean systolic blood pressure was 142 ± 18 mmHg in Group A and 141 ± 17 mmHg in Group B ($p = 0.85$). The mean triglyceride level was 180 ± 25 mg/dL among participants with non-alcoholic fatty liver disease and 170 ± 24 mg/dL among those without non-alcoholic fatty liver disease ($p = 0.42$). Mean high-density lipoprotein cholesterol was 38 ± 6 mg/dL in Group A and 39 ± 7 mg/dL in Group B ($p = 0.61$), while mean fasting plasma glucose was 110 ± 15 mg/dL and 108 ± 16 mg/dL, respectively ($p = 0.64$).

The estimated 10-year cardiovascular disease risk was higher in participants with non-alcoholic fatty liver disease. The mean Framingham Risk Score was 22.4 ± 8.2% in Group A compared with 16.3 ± 7.6% in Group B, showing a statistically significant difference between the groups ($p = 0.03$). The absolute mean difference in Framingham Risk Score was 6.1 percentage points. Similarly, the mean 10-year risk calculated by the ASCVD Risk Estimator was 24.1 ± 9.1% in Group A and 18.9 ± 7.5% in Group B, with a statistically significant difference of 5.2 percentage points between the groups ($p = 0.04$). The calculated effect size was 0.77 for the Framingham Risk Score and 0.63 for the ASCVD Risk Estimator. When participants were categorized according to Framingham cardiovascular risk groups, a greater proportion of participants with non-alcoholic fatty liver disease fell into the high-risk category. In

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Group A, 12% of participants were classified as low risk, 28% as intermediate risk, and 60% as high risk. In comparison, Group B had 24% of participants in the low-risk category, 40% in the intermediate-risk category, and 36% in the high-risk category. The difference between groups was statistically significant for the high-risk category, with 60% of participants in Group A and 36% in Group B classified as high risk ($p = 0.01$). According to the ASCVD Risk Estimator, elevated cardiovascular risk was observed in 84% of participants in Group A compared with 70% of participants in Group B ($p = 0.02$).

Correlation analysis showed a statistically significant positive relationship between ultrasound-based fatty liver grade and estimated cardiovascular risk scores. Fatty liver grade demonstrated a moderate positive correlation with the Framingham Risk Score ($r = 0.45$, $p = 0.01$) and with the ASCVD Risk Estimator ($r = 0.42$, $p = 0.02$). Higher grades of hepatic steatosis were associated with higher estimated cardiovascular risk scores. Multivariable linear regression analysis was performed to assess whether the presence of non-alcoholic fatty liver disease was associated with estimated cardiovascular risk after adjustment for conventional cardiovascular risk factors. In the Framingham Risk Score model, age ($\beta = 0.41$, $p < 0.001$), male sex ($\beta = 0.28$, $p = 0.01$), systolic blood pressure ($\beta = 0.33$, $p = 0.002$), high-density lipoprotein cholesterol ($\beta = -0.29$, $p = 0.02$), triglycerides ($\beta = 0.26$, $p = 0.01$), fasting glucose ($\beta = 0.22$, $p = 0.02$), and the presence of non-alcoholic fatty liver disease ($\beta = 0.32$, $p = 0.02$) were statistically significant predictors. The overall model was statistically significant ($F = 9.72$, $p < 0.001$) and explained 48% of the variance in Framingham Risk Score, with an adjusted R^2 value of 0.44.

A similar pattern was observed in the ASCVD risk model. Age ($\beta = 0.44$, $p = 0.001$), male sex ($\beta = 0.31$, $p = 0.01$), systolic blood pressure ($\beta = 0.30$, $p = 0.003$), high-density lipoprotein cholesterol ($\beta = -0.27$, $p = 0.02$), triglycerides ($\beta = 0.24$, $p = 0.02$), fasting glucose ($\beta = 0.21$, $p = 0.02$), and the presence of non-alcoholic fatty liver disease ($\beta = 0.29$, $p = 0.03$) were statistically significant predictors of estimated ASCVD risk. The model was statistically significant ($F = 8.95$, $p = 0.001$), with an R^2 value of 0.46 and an adjusted R^2 value of 0.42.

Table 1. Cardiovascular Risk Category Distribution (FRS)

Risk Category	Group A	Group B	p-value
Low (<10%)	12%	24%	0.04
Intermediate (10–20%)	28%	40%	0.03
High (>20%)	60%	36%	0.01

Table 2. Correlation Between Liver Fat Grade and Risk Scores

Variable	r-value	p-value
Liver grade vs FRS	0.45	0.01
Liver grade vs ASCVD	0.42	0.02

Table 3. Multivariate Regression Analysis

Predictor	β (FRS)	p-value	β (ASCVD)	p-value
Age	0.41	<0.001	0.44	<0.001
Male Gender	0.28	0.01	0.31	0.01
Systolic BP	0.33	0.002	0.30	0.003
HDL Cholesterol	-0.29	0.02	-0.27	0.02
Triglycerides	0.26	0.01	0.24	0.02
Fasting Glucose	0.22	0.02	0.21	0.02
NAFLD (Presence)	0.32	0.02	0.29	0.03

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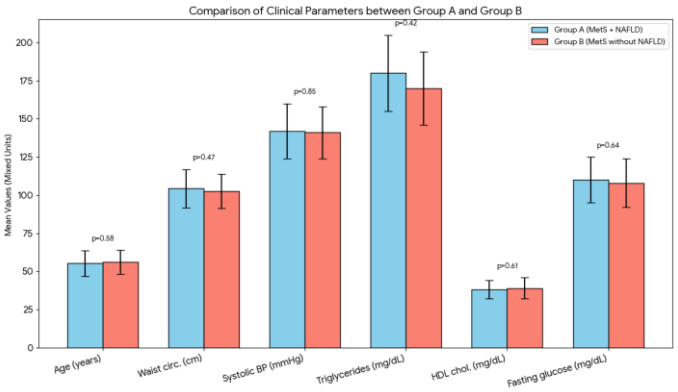

Figure.1. Baseline Characteristics of Study Participants

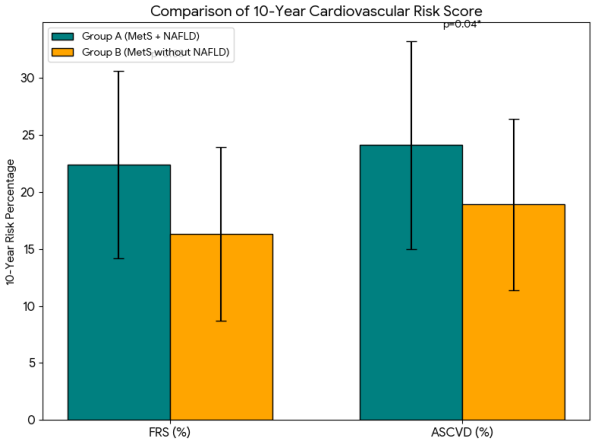

Figure.2. Comparison of 10-Year Cardiovascular Risk

DISCUSSION

The present study demonstrated that patients with metabolic syndrome and coexisting non-alcoholic fatty liver disease had higher estimated 10-year cardiovascular disease risk than patients with metabolic syndrome alone. Although both groups were broadly comparable in terms of baseline metabolic parameters, the group with non-alcoholic fatty liver disease showed significantly higher Framingham Risk Score and ASCVD risk estimates. This finding suggested that fatty liver disease may add to the overall cardiovascular risk burden in patients who already have metabolic syndrome. The persistence of this association after adjustment for conventional risk factors further supported the view that non-alcoholic fatty liver disease was not merely a coincidental finding, but may represent an additional marker of adverse cardiometabolic status (9-11). These findings were consistent with the growing body of literature indicating that non-alcoholic fatty liver disease was closely linked with cardiovascular morbidity and mortality. Earlier studies had shown that cardiovascular disease was among the leading causes of adverse outcomes in patients with non-alcoholic fatty liver disease, even when liver-related complications were not clinically advanced. This relationship appeared particularly important in individuals with metabolic syndrome, where hepatic steatosis, insulin resistance, dyslipidemia, hypertension, and central obesity often existed as interconnected abnormalities. The present findings therefore added support to the concept that non-alcoholic fatty liver disease may reflect a more advanced or more diffuse metabolic disturbance in patients with metabolic syndrome (12-14).

The biological relationship between non-alcoholic fatty liver disease and cardiovascular risk was supported by several plausible mechanisms. Hepatic steatosis had been associated with chronic low-grade inflammation, oxidative stress, endothelial dysfunction, altered adipokine secretion, and impaired lipid metabolism. The liver has a central role in glucose regulation, lipoprotein synthesis, and inflammatory signaling; therefore, accumulation of fat within the liver may contribute to systemic metabolic imbalance. Increased production of pro-inflammatory cytokines, including tumor necrosis factor-alpha and interleukin-6, may promote vascular inflammation and accelerate atherogenesis. In addition, worsening insulin resistance may contribute to endothelial injury, plaque formation, and progression of subclinical atherosclerosis (15-17). A notable finding of the study was the positive correlation between fatty liver grade and estimated cardiovascular risk scores. Participants with higher grades of hepatic steatosis had higher Framingham and ASCVD risk estimates, indicating a graded relationship between liver fat severity and cardiovascular risk. This pattern supported the possibility that ultrasound-detected hepatic steatosis may serve as a practical clinical indicator of cumulative cardiometabolic burden. However, this relationship should be interpreted cautiously because ultrasound grading is semi-quantitative and may be influenced by operator experience, body habitus, and the degree of liver fat accumulation. Despite these limitations, the observed trend remained clinically relevant, particularly in resource-limited settings where ultrasound is widely available and relatively inexpensive (18,19).

The regression analysis further indicated that non-alcoholic fatty liver disease remained significantly associated with higher estimated cardiovascular risk after adjustment for age, sex, systolic blood pressure, HDL cholesterol, triglycerides, and fasting glucose. This finding suggested that the presence of fatty liver may help identify a subgroup of patients with metabolic syndrome who require closer cardiovascular assessment. Standard cardiovascular risk calculators do not directly include liver-related variables, and this may lead to under-recognition of risk in patients whose metabolic dysfunction is accompanied by hepatic steatosis. Incorporating liver assessment into cardiometabolic evaluation may therefore improve clinical awareness and encourage earlier preventive interventions, such as lifestyle modification, weight reduction, glycemic control, blood pressure optimization, and lipid management (20-22). The findings also had relevance for South Asian populations, where metabolic syndrome, diabetes, visceral adiposity, and non-alcoholic fatty liver disease are increasingly common. In such populations, cardiovascular disease often develops at relatively younger ages and may occur even in individuals who do not appear severely obese by conventional body mass index criteria. The presence of non-alcoholic fatty

liver disease in patients with metabolic syndrome may therefore represent an under-recognized contributor to cardiovascular risk in this region. These results supported the need for greater clinical attention to fatty liver disease as part of routine metabolic and cardiovascular risk evaluation (23-25).

The study had several strengths. It directly compared two clinically relevant groups of patients with metabolic syndrome, with and without ultrasound-confirmed non-alcoholic fatty liver disease. Both groups were similar in baseline demographic and metabolic characteristics, which reduced the likelihood that the observed difference in cardiovascular risk was driven only by traditional metabolic syndrome components. The use of two established cardiovascular risk prediction tools also strengthened the assessment by allowing comparison across commonly used scoring systems. In addition, grading of hepatic steatosis provided an opportunity to examine whether cardiovascular risk increased with increasing severity of fatty liver (26,27). Several limitations also needed to be considered. The cross-sectional design limited the ability to establish a causal relationship between non-alcoholic fatty liver disease and cardiovascular outcomes. The study assessed predicted 10-year cardiovascular risk rather than actual cardiovascular events, so the findings should be interpreted as risk-estimation data rather than evidence of future event rates. The sample size was relatively small, and participants were recruited from a single tertiary care hospital, which may limit the generalizability of the findings to broader community populations. Ultrasound was practical and non-invasive, but it was less sensitive than magnetic resonance imaging or liver biopsy for quantifying hepatic fat, particularly in mild steatosis. In addition, some variables required for cardiovascular risk estimation, such as smoking status, total cholesterol, diabetes status, and treatment status for hypertension, should be consistently documented to ensure accurate risk calculation (28).

Another methodological consideration was that regression models used risk scores as outcome variables while including several predictors that were already components of those same risk scores. This may introduce mathematical overlap and should be addressed in future analyses. Larger prospective cohort studies are needed to determine whether non-alcoholic fatty liver disease independently predicts actual cardiovascular events beyond established risk calculators. Future research should also evaluate whether adding liver-related markers, ultrasound grade, fibrosis scores, or advanced imaging parameters improves cardiovascular risk prediction among patients with metabolic syndrome. Such work may help determine whether non-alcoholic fatty liver disease should be incorporated into routine cardiovascular risk stratification models (29). Overall, the study indicated that non-alcoholic fatty liver disease was associated with higher estimated 10-year cardiovascular disease risk among patients with metabolic syndrome. The findings supported the clinical value of recognizing fatty liver disease as a potential marker of increased cardiometabolic risk, while also emphasizing the need for longitudinal evidence before making firm conclusions about causality or risk prediction improvement.

CONCLUSION

Non-alcoholic fatty liver disease was associated with a higher estimated 10-year cardiovascular disease risk among patients with metabolic syndrome. The findings suggest that the presence and severity of fatty liver may reflect an added cardiometabolic burden beyond conventional risk factors. Incorporating assessment for non-alcoholic fatty liver disease into routine cardiovascular risk evaluation may help identify high-risk patients earlier and support timely preventive strategies, including lifestyle modification and stricter control of metabolic risk factors, to reduce future cardiovascular morbidity and mortality.

AUTHOR CONTRIBUTION

Author	Contribution
Dr Muhammad Hassan	Conceptualization, Methodology, Formal Analysis, Writing - Original Draft, Validation, Supervision
Dr Zeeshan Ali Junejo	Methodology, Investigation, Data Curation, Writing - Review & Editing
Dr Shayan Rehmani	Investigation, Data Curation, Formal Analysis, Software
Dr Ghulam Qadir Memon	Software, Validation, Writing - Original Draft
Dr Sameeullah	Formal Analysis, Writing - Review & Editing

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