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Association between Nonalcoholic Fatty Liver Disease Severity Assessed by Fibroscan and Atherosclerotic Cardiovascular Disease Risk Score

Kaleem Ullah, Shahid Kareem, Abeer Sarfaraz, Wasiq Anwar, Nida Batool, Sadia Abubakar
Department of Cardiology, Liaqat National Hospital, Karachi

ABSTRACT

Objective: The purpose of this study was to investigate the association between the 10-year atherosclerotic cardiovascular disease (ASCVD) risk score and the severity of nonalcoholic fatty liver disease (NAFLD), as determined by Fibroscan.

Methodology: Patients with NAFLD who had Fibroscan to measure liver stiffness and steatosis presenting at the cardiology department of Liaquat National Hospital in Karachi, Pakistan were included in this cross-sectional investigation. Lipid profiles, waist circumference, liver enzyme levels, and 10-year ASCVD risk scores were among the demographic, clinical, and biochemical data gathered.

Results: Of the 217 patients in the study, 62.2% had steatosis, and 99.1% were obese, indicating significant prevalence of liver disease and metabolic disorders. Most were older than 45 (75.1%) and female (62.2%). Low risk for ASCVD was 42.9%, moderate risk was 30.4%, intermediate risk was 11.5%, and high risk was 15.2%. Significant risk variables for ASCVD included advanced liver fibrosis ($p<0.05$), higher blood cholesterol ($p<0.01$), older age ($p<0.01$), and the LDL to HDL ratio ($p<0.01$). Males dominated higher ASCVD risk categories ($p<0.001$), and the high-risk group had the highest prevalence of dyslipidemia, especially with metabolic syndrome ($p<0.001$). There was a significant correlation between ASCVD risk and NAFLD severity as determined by fibroscopy ($p=0.035$).

Conclusion: In conclusion, the study demonstrates a strong association between advanced NAFLD and increased ASCVD risk. Key risk factors, including age, serum cholesterol, LDL to HDL ratio, and liver fibrosis severity, were significantly linked to higher ASCVD risk ($p<0.05$). Males and individuals with dyslipidemia, particularly those with metabolic syndrome, were more likely to be at higher risk.

Keywords: Atherosclerosis, Cardiovascular Risk, Liver Fibrosis, Metabolic Syndrome, Nonalcoholic Fatty Liver Disease (NAFLD).

Authors' Contribution:
[1,2]Conception; Literature research; manuscript design and drafting; [2,3]Critical analysis and manuscript review; [5,6]Data analysis; Manuscript Editing.

Correspondence:
Kaleem Ullah Sheikh
Email: kshaikh72@gmail.com

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Introduction

NAFLD has emerged as a global public health concern because of its rising incidence, progressive nature and strong association with metabolic disorder. It is defined as a condition where excessive fat is accumulated in the liver and when it is not caused by alcohol, it is referred to as NASH; NASH is considered an important feature of Mets, a grouping of risk factors that include; insulin resistance, hypertension, increased levels of lipids in the blood, and obesity, especially abdominal obesity. It is thought to affect around 25% of the adult

population globally[1], increasing in those with obesity, type 2 diabetes and other features of the metabolic syndrome where it can affect up to 75%[2]. In Pakistan, studies indicate a prevalence ranging from 14% to 47% in the general population, with a pooled estimate of 29.82%[3,4]. The prevalence is higher among individuals with metabolic disorders, reaching 58.47% in diabetics and 74.08% in hypertensive patients[4]. NAFLD is strongly associated with obesity, diabetes, and metabolic syndrome[5]. Despite its increasing prevalence, awareness and understanding of NAFLD remain low among patients. A study found that only 26.4% of NAFLD patients knew about their condition, and merely 14.5% were aware of its cardiovascular risks[5]. The rising trends of obesity and diabetes in Pakistan contribute to the increasing NAFLD prevalence[4]. There is a pressing need for population-based studies and initiatives to raise public awareness about NAFLD.

Extrahepatic complications are tremendously challenging since NAFLD has a critical long-term health issue as it is a leading cause of liver morbidity and mortality[4]. In addition to the liver specific mortality, new research evidence reveals that NAFLD is related with an elevated risk of several cancers, including hepatocellular carcinoma[6]. Moreover, NAFLD also plays a vital role in the development and progression of CVD, as it is indicative of subclinical arteriosclerosis and cardiovascular risk. Several studies prove that NAFLD patients have higher lifetime cumulative incidence of fatal and non-fatal ASCVD due to shared atherothrombotic processes in NAFLD and ASCVD.

It also established that NAFLD and ASCVD have common features, indicated by their association with metabolic disorder characterized by insulin resistance, hyperglycemia, dyslipidemia, hypertension, and obesity[7]. Such factors cause atherosclerosis and vascular injury that enhance the prevalence of cardiovascular events. NAFLD, with its interference into liver metabolic pathways, may increase inflammation and oxidative stress processes which contribute to endothelial dysfunction, vascular remodeling related to atherogenesis in individuals with NAFLD[7]. These overlapping risk factors naturally lead to many questions regarding the connection of NAFLD and cardiovascular disease, especially regarding individuals with different levels of fibrosis. The NAFLD fibrosis score which is employed to predict the degree of fibrosis in patients with NAFLD using non-invasive methodology, has a relationship with the following; cardiovascular risk markers[8]. The score uses age, serum albumin, platelet count, hyperglycemia, ALT, AST, and BMI, all of which offers great implications for the prognosis of the severity of liver fibrosis, which is one of the main factors affecting the progression of HCV.

Significantly higher NAFLD fibrosis scores have been positively correlated with CIMT, which signifies subclinical atherosclerosis, and LVH, for increased risk of cardiovascular events[9]. Furthermore, higher NAFLD fibrosis score is associated with worse cardiovascular events and all-cause mortality in patients with known cardiovascular disease[10]. This suggests that liver fibrosis, as assessed by the NAFLD fibrosis score, may serve as an independent predictor of cardiovascular risk and could potentially be used to stratify patients at risk for adverse cardiovascular outcomes.

While it is well established that both NAFLD and ASCVD share common risk factors, the impact of different stages of liver fibrosis on the long-term cardiovascular risk profile is not fully elucidated. Specifically, the relationship between the degree of liver fibrosis, as measured by Fibroscan, and the 10-year atherosclerotic cardiovascular disease (ASCVD) risk remains unclear. Understanding this link is essential for enhancing risk assessment and creating focused therapies for people at high risk of both liver and cardiovascular disease, given the significant prevalence of both NAFLD and ASCVD in the global population. Thus, the main goal of this study was to investigate the relationship between the 10-year

ASCVD risk in people with NAFLD and the severity of NAFLD as determined by Fibroscan.

Methodology

This cross-sectional study was carried out in the cardiology department of Liaquat National Hospital in Karachi, Pakistan, between September 2024 and February 2025. The primary objective was to evaluate the correlation between the projected ASCVD risk score and the severity of NAFLD as determined by Fibroscan.

Using particular inclusion and exclusion criteria, participants were gathered from the inpatient and outpatient departments. Participants who were 20 years of age or older, male or female, and had received a diagnosis of nonalcoholic fatty liver disease (NAFLD) by imaging, biochemical, or clinical means were eligible. Pregnancy, hepatitis B or C, cirrhosis or advanced fibrosis as determined by computed tomography or ultrasonography, splenectomy, and inadequate medical information or lack of permission were therefore among the exclusion criteria used in the study. A standardized questionnaire was used to gather data related to demographics and other study parameters. To obtain thorough information, clinical evaluations and diagnostic instruments were also used. Participants underwent a non-invasive Fibroscan evaluation to gauge liver steatosis and stiffness. Four groups including no substantial fibrosis, mild fibrosis, severe fibrosis, and advanced fibrosis were created based on the Fibroscan results. The degree of hepatic steatosis was evaluated using the Control Attenuation Parameter (CAP) values, where higher CAP values denoted a larger liver fat content. Individual patient characteristics, such as age, gender, blood pressure, cholesterol, smoking status, and history of diabetes, were used to create the 10-year ASCVD risk score. Low risk (<5%), intermediate risk (5-7.5%), moderate risk (>7.5-20%), and high risk (>20%) were the four categories into which this score was divided. Participants were measured barefoot and wearing light clothing, and anthropometric data, including height and weight, were used to determine Body Mass Index (BMI). Following an overnight fast, blood samples are taken for biochemical testing in order to evaluate liver function and lipid profiles. Lastly, as part of standard diagnostic procedures, imaging methods such as liver CT scans and abdominal ultrasonography were carried out to evaluate liver steatosis using the Liver Attenuation Index (LAI) and validate the NAFLD diagnosis. The required sample size was calculated using the formula:

$$n = \frac{Z^2 \cdot p(1-p)}{d^2}$$

The sample size was calculated using the single population proportion formula with a 95% confidence level, 5% margin of error, and an anticipated NAFLD prevalence of 51%, based on findings from a local study[11]. This yielded a minimum required sample of 196 participants. To enhance statistical power and accommodate potential exclusions, a final sample of 217 participants was recruited.

Data analysis was performed using SPSS version 22.0. Descriptive statistics were computed for all continuous variables (mean ± SD) and categorical variables (frequency and percentages). Normality of the continuous variables was first tested using the Shapiro-Wilk test. For not normally distributed continuous variables, the Kruskal-Wallis test was applied to assess differences across ASCVD risk categories. Categorical variables were compared using the chi-square test or Fisher's exact test where appropriate. A p-value of less than 0.05 was considered statistically significant. The study adhered strictly to ethical standards in compliance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to data collection, ensuring that they fully understood the purpose of the study, their involvement, and any potential risks. The study protocol was approved by the **Institutional Review Board (IRB) and Medical**

Ethics Committee at Liaquat National Hospital (LNH), Karachi [Ref #1091-2024-LNH-ERC; Dated 25/09/2024]. Participant confidentiality was maintained throughout the study, and all data were anonymized before analysis.

Results

Table I summarizes the demographic and clinical characteristics of the 217 participants. The majority were female (62.2%) and over 45 years old (75.1%). Diabetes was present in 54.8% of participants, and 45.2% had hypertension. Most were non-smokers (69.6%). Dyslipidemia was prevalent, with 62.7% having low HDL cholesterol and 22.6% having dyslipidemia with metabolic syndrome. Obesity affected 99.1% of participants. Fibroscan results showed that 35.9% had no significant fibrosis, while 6.5% had advanced fibrosis. CAP scores indicated severe steatosis in 47.5% of participants. Steatosis was present in 62.2%, reflecting a cohort with high rates of metabolic disorders and liver disease. Figure 1 illustrates the distribution of atherosclerotic cardiovascular disease (ASCVD) risk among the study participants. The majority of participants (42.9%) fell into the low-risk category, indicating a relatively lower likelihood of developing cardiovascular events. A smaller proportion (11.5%) were classified as having an intermediate ASCVD risk. Approximately one-third of the participants (30.4%) were categorized as having moderate ASCVD risk, suggesting a higher risk of future cardiovascular issues. Finally, 15.2% of participants were identified as having high ASCVD risk, representing the group most vulnerable to cardiovascular events. Table II shows that several variables were significantly associated with ASCVD risk categories. Age, serum cholesterol, LDL to HDL ratio, fibro scan score, hemoglobin levels, lifetime risk, gender, dyslipidemia subtypes, and NAFLD severity by fibro scan were all significantly linked to ASCVD risk ($p<0.05$), with older age, higher cholesterol, and more advanced fibrosis observed in higher-risk groups

Table I: Demographic and Clinical Characteristics of Study Participants (n = 217).

Variables		n (%)
Gender	Male	82 (37.8)
	Female	135 (62.2)
Age Groups	≤45 years	54 (24.9)
	>45 years	163 (75.1)
Co-morbid	Diabetes	119 (54.8)
	Hypertension	98 (45.2)
Smoking Status	Smoker	66 (30.4)
	Non-Smoker	151 (69.6)
Dyslipidaemia	Normolipidemia	15 (6.9)
	Combined hyperlipidemia	10 (4.6)
	Hyperlipidemia	3 (1.4)
	Dyslipidemia with MetS	49 (22.6)
	Low HDLc	136 (62.7)
	Hypertriglyceridemia	4 (1.8)
Obesity	Yes	215 (99.1)
	No	2 (0.9)
NAFLD severity by fibro scan	No significant fibrosis (≤6.5 kPa)	78 (35.9)
	Mild (6.6-8.2 kPa)	64 (29.5)
	Significant (8.3-9.6 kPa)	61 (28.1)
	Advance (>9.6 kPa)	14 (6.5)
NAFLD severity by CAP score	Nil Significance (<248 dB/m)	89 (41)
	Mild (248-280 dB/m)	18 (8.3)
	Moderate (281-319 dB/m)	7 (3.2)
	Severe (>319 dB/m)	103 (47.5)
Steatosis	Yes	135 (62.2)
	No	82 (37.8)

Notably, males and those with dyslipidemia with metabolic syndrome were more prevalent in high-risk categories. In contrast, variables such as HbA1c, creatinine, ALT, BMI, blood pressure, diabetes, hypertension, smoking, steatosis, and NAFLD by CAP score were not significantly associated with ASCVD risk.

Table II. ASCVD Risk Factors and Clinical Parameters.						
		ASCVD Risk				p-value
		Low	Intermediate	Moderate	High	
Age (years)		46.00 (44.00-50.00)	48.00 (45.00-58.00)	56.00 (48.00-60.00)	59.00 (56.00-65.00)	<0.01*
HbA1c (%)		6.70 (5.30-7.60)	7.50 (5.30-7.80)	7.10 (5.30-7.90)	7.60 (5.50-8.50)	0.07
Creatinine (mg/dL)		1.00 (0.70-1.20)	1.10 (0.90-1.20)	1.00 (0.80-1.27)	1.00 (0.90-1.50)	0.67
ALT (IU/L)		47.00 (30.00-67.00)	45.00 (36.00-67.00)	50.00 (32.00-70.00)	57.00 (37.00-70.00)	0.73
Serum Cholesterol(mg/dL)		171.00 (153.00-180.00)	170.00 (160.00-180.00)	194.00 (172.00-250.00)	250.00 (230.00-320.00)	<0.01*
LDL to HDL ratio		4.79 (3.70-6.36)	3.17 (2.74-4.07)	2.88 (2.57-3.25)	3.46 (2.95-5.17)	<0.01*
Fibro scan score		7.80 (4.20-8.20)	8.00 (4.60-8.40)	8.20 (6.50-8.50)	6.90 (4.20-9.60)	<0.05*
Hemoglobin (g/dL)		11.10 (10.70-12.50)	11.20 (10.50-11.80)	11.95 (11.30-13.67)	12.50 (11.50-13.70)	<0.01*
CAP score		248.00 (215.00-341.00)	325.00 (240.00-335.00)	325.00 (216.00-340.00)	322.00 (228.00-351.00)	0.21
Body Mass Index (kg/m²)		30.84 (28.50-32.50)	29.00 (28.30-31.20)	30.40 (28.70-32.30)	29.70 (28.20-31.60)	0.26
Waist circumference (cm)		105.00 (94.00-110.00)	106.00 (94.00-110.00)	108.00 (95.00-111.00)	105.00 (94.00-114.00)	0.31
Hip circumference (cm)		110.00 (98.00-115.00)	110.00 (100.00-114.00)	113.00 (99.00-117.75)	110.00 (98.00-119.00)	0.38
Waist to Hip ratio		0.96 (0.95-0.96)	0.96 (0.95-0.97)	0.96 (0.95-0.97)	0.96 (0.95-0.97)	0.35
Systolic Blood pressure		127.00 (116.00-147.00)	122.00 (120.00-140.00)	128.00 (120.00-147.00)	120.00 (115.00-145.00)	0.61
Lifetime risk (%)		69.00 (69.00-69.00)	50.00 (41.75-64.25)	39.00 (39.00-39.00)	69.00 (50.00-69.00)	<0.01*
Gender	Male	6(6.5)	9(36)	38(57.6)	29(87.9)	<0.001*
	Female	87(93.5)	16(64)	28(42.4)	4(12.1)	
Diabetes	Yes	47(50.5)	15(60)	36(54.5)	21(63.6)	0.573
	No	46(49.5)	10(40)	30(45.5)	12(36.4)	
Hypertension	Yes	46(49.5)	10(40)	30(45.5)	12(36.4)	0.573
	No	47(50.5)	15(60)	36(54.5)	21(63.6)	
Smoking Status	Smoker	34(36.6)	8(32)	15(22.7)	9(27.3)	0.297
	Non-Smoker	59(63.4)	17(68)	51(77.3)	24(72.7)	
Dyslipidemia	Normolipidemia	3(3.2)	2(8)	8(12.1)	2(6.1)	<0.001*
	Combined hyperlipidemia	1(1.1)	1(4)	8(12.1)	0(0)	
	Hyperlipidemia	1(1.1)	1(4)	1(1.5)	0(0)	
	Dyslipidemia with MetS	9(9.7)	6(24)	21(31.8)	13(39.4)	
	Low HDLc	79(84.9)	15(60)	26(39.4)	16(48.5)	
	Hypertriglyceridemia	0(0)	0(0)	2(3)	2(6.1)	
Steatosis	Yes	51(54.8)	18(72)	43(65.2)	23(69.7)	0.256
	No	42(45.2)	7(28)	23(34.8)	10(30.3)	
NAFLD severity by fibro scan	No significant fibrosis (≤6.5 kPa)	38(40.9)	10(40)	19(28.8)	11(33.3)	0.035*
	Mild (6.6-8.2 kPa)	34(36.6)	8(32)	15(22.7)	7(21.2)	
	Significant (8.3-9.6 kPa)	20(21.5)	6(24)	24(36.4)	11(33.3)	
	Advance (>9.6 kPa)	1(1.1)	1(4)	8(12.1)	4(12.1)	
NAFLD severity by CAP score	Nil Significance (<248 dB/m)	46(49.5)	8(32)	25(37.9)	10(30.3)	0.379
	Mild (248-280 dB/m)	6(6.5)	3(12)	4(6.1)	5(15.2)	
	Moderate (281-319 dB/m)	4(4.3)	0(0)	2(3)	1(3)	
	Severe (>319 dB/m)	37(39.8)	14(56)	35(53)	17(51.5)	

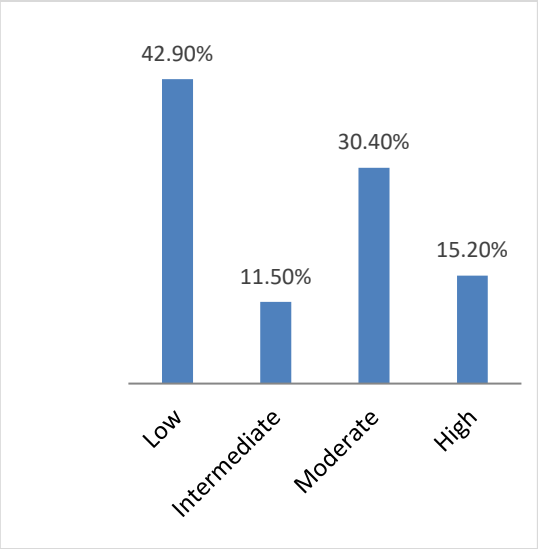

Figure 1. ASCVD risk distribution

Discussion

As NAFLD has emerged as a significant public health concern due to its association with MetS and CVD, it has become crucial to understand the interplay between NAFLD severity and ASCVD risk for tailoring preventive and therapeutic strategies. In the present study, the participants had a mean age of 51.87 ± 8.59 years, focused on individuals with moderate to high ASCVD risk scores, and examined the cross-sectional relationship between the severity of NAFLD as determined by Fibroscan and ASCVD risk scores. A majority of the patients (65.4%) were classified as having mild to moderate NAFLD, while 34.6% had advanced NAFLD. Although severe cases were less frequent in our cohort, our findings align with those of Sen et al., who observed a similar distribution of NAFLD severity[12], although Bhusal et al. reported a predominance of moderate over severe cases[13]. Differences in patient demographics, as well as diagnostic criteria and methodologies, could account for these discrepancies.

Our results revealed that the moderate to high ASCVD risk group tended to be older and exhibited higher total cholesterol levels, with a notable increase in abdominal obesity, as evidenced by greater waist circumference. Additionally, as the severity of the ASCVD score worsened, there were significant associations with lipid abnormalities, including elevated total cholesterol, low-density lipoprotein cholesterol (LDL-C), triglycerides, and lower high-density lipoprotein cholesterol (HDL-C). In line with earlier research that connected the severity of NAFLD to dyslipidemia and atherosclerotic risk factors[14], elevated liver enzyme levels (AST and ALT) were also noted in the current study among those with higher ASCVD scores.

Patients with higher overall 10-year ASCVD risk scores also had greater levels of fatty plaques, arterial wall thickening, stenosis, and elevated Agatston scores, a crucial indicator of coronary artery calcification (CAC), according to the results of our cohort. This bolsters the body of research that has shown how NAFLD and subclinical atherosclerosis are related. Nearly one-third of our patients had severe types of non-alcoholic fatty liver disease (NAFLD), which is frequently associated with metabolic abnormalities such atherogenic dyslipidemia[15], which is typified by raised triglyceride levels, high LDL-C, and low HDL-C. This emphasizes even more how metabolic syndrome (MetS), cardiovascular disease, and non-alcoholic fatty liver disease interact.

The presence of comorbidities, particularly MetS, was found to significantly increase the risk of developing atherosclerosis in our cohort. Patients with NAFLD and MetS are known to be at an elevated risk for atherosclerosis and cardiovascular complications, a finding consistent with prior studies[16]. This metabolic cluster, including insulin resistance, obesity, dyslipidemia, and hypertension, accelerates the development of atherosclerotic plaques and the progression of vascular calcification, as measured by coronary artery calcification (CAC), carotid intima-media thickness (CIMT), and aortic stiffness. These pathological changes are further amplified by oxidative stress and inflammation, which are common in individuals with MetS and contribute to endothelial dysfunction. Interestingly, our study found no significant gender-based

differences in the severity of NAFLD, which is consistent with some studies but contradicts others that have reported gender differences in the prevalence and severity of NAFLD. However, we observed that as NAFLD severity increased, both liver steatosis scores and control attenuation parameter (CAP) values also increased, indicating a correlation with obesity. These findings align with previous research, which highlights the strong association between NAFLD, obesity, and metabolic abnormalities such as insulin resistance and lipid dysregulation[17]. A significant proportion of our cohort had type diabetes and metabolic syndrome, both of which are known to cause reduced insulin sensitivity in the liver, skeletal muscle, and adipose tissue. This diminished insulin sensitivity enhances inflammation, oxidative stress, and disruptions in lipid and glucose metabolism. Additionally, it contributes to visceral adiposity and glucose intolerance, conditions commonly associated with the development of subclinical atherosclerosis, as indicated by measurements of coronary artery calcification (CAC), carotid intima-media thickness (CIMT), and aortic stiffness[18-21]. Previous studies have demonstrated that NAFLD is independently linked to vascular atherosclerosis, including increased CAC and CIMT, further confirming the role of NAFLD as a predictor of cardiovascular risk[22,23].

A meta-analysis comparing patients with type 2 diabetes (T2DM) with and without NAFLD found that the two conditions synergistically elevated cardiovascular risk[24]. Even in patients without metabolic syndrome, the presence of NAFLD independently increases cardiovascular risk, and this risk appears to escalate as liver fibrosis progresses[25]. However, our study did not find the same results, suggesting that the relationship between liver fibrosis and cardiovascular risk may vary depending on the population and other confounding factors.

Our study's cross-sectional design, which restricts the capacity to make causal inferences, is its primary limitation. Furthermore, the study was only carried out at a single center, which can have an impact on study generalizability. Longitudinal studies, larger and more diverse cohorts, and more thorough evaluations of the numerous factors influencing both liver and cardiovascular disease are ways that future research should try to overcome these constraints. Future research can improve patient outcomes and lessen the burden of both liver disease and cardiovascular consequences by gaining a knowledge of the mechanisms that link the severity of NAFLD and cardiovascular risk. This will help guide efforts for early identification and risk stratification.

Conclusion

In conclusion, this study offers significant new information about the connection between atherosclerotic cardiovascular disease (ASCVD) risk, metabolic problems, and non-alcoholic fatty liver disease (NAFLD). The study discovered a strong correlation between the degree of liver fibrosis and an elevated risk of ASCVD, as well as high prevalence rates of obesity, dyslipidemia, and NAFLD among the individuals. The LDL to HDL ratio, age, serum cholesterol levels, and the severity of NAFLD were found to be important determinants of ASCVD risk. It was discovered that higher ASCVD risk categories were more likely to contain males. The results emphasize the significance of early screening and care by indicating that metabolic disorders and severe liver disease are important predictors of cardiovascular risk.

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