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LIVER DYSFUNCTION IN DIABETICS: RECOGNIZING AND MANAGING NAFLD IN GENERAL PRACTICE

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is newly defined as metabolic dysfunction–associated steatotic liver disease (MASLD) and has been revealed as a common and critical complication of type 2 diabetes mellitus (T2DM). The objective of this study was to assess the magnitude of NAFLD among patients with T2DM who were seen at the endocrinology and general practice clinics at Jinnah Postgraduate Medical Centre (JPMC), Karachi, from January 2024 to June 2025. This cross-sectional analytical research design study included 350 adult T2DM patients, calculated based on assumed 70% prevalence of NAFLD, 95% confidence and 5% margin of error. Demographic, anthropometric, biochemical & clinical parameters were evaluated in the study participants. All patients had Fibrosis-4 (FIB-4) scores calculated and those with indeterminate or high-risk scores went on to vibration-controlled transient elastography (VCTE). SPSS 28.0 was used for data analysis, and independent predictors of fibrosis presence were identified through logistic regression. NAFLD was observed in 68.3% of patients (high-risk: 14%, indeterminate: 25.1%). Factors significantly associated with fibrosis risk included age, duration of diabetes, BMI, poor glycemic control (HbA1c ≥8%), and dyslipidemia (higher triglycerides and lower HDL-C levels). Intermediate or high fibrosis risk was independently predicted by age ≥50 years, HbA1c ≥8, obesity (BMI ≥30 kg/m²), diabetes duration ≥10 years, and triglycerides ≥150 mg/dL, as confirmed by logistic regression. In conclusion, these findings emphasize that NAFLD represents an important source of morbidity amongst patients with diabetes, and that non-invasive fibrosis assessment tools can be used in primary and specialty care to assess the risk of liver-related morbidity.

INTRODUCTION

Metabolic dysfunction–associated steatotic liver disease is still frequently termed non-alcoholic fatty liver disease (NAFLD) in clinical routine and has become one of the most relevant comorbidities in type 2 diabetes mellitus (T2DM). In T2DM patients, hepatic fat is not a benign epiphenomenon but rather a continuous disease spectrum that progresses from simple steatosis to inflammatory steatohepatitis and fibrosis, with a minority of cases progressing to cirrhosis and hepatocellular carcinoma (HCC) (Liver & Diabetes, 2024). Several recently published guidance documents from hepatology, diabetology, and metabolic societies now provide a unified and clear call to action to proactively pursue detection and risk stratification of NAFLD/MASLD on the background of diabetes care as a top priority of either general practice (in most settings, where diabetes is followed long-term) and its management as a fundamental responsibility. However, even though we have simple, validated non-invasive tools such as FIB-4, as well as stepwise pathways supported by society guidance documents to encourage case-finding, in routine primary care the majority of patients at-risk are still not identified until they develop advanced disease or extrahepatic complications (Liver & Diabetes, 2024).Diabetes is a very big problem. Various population-based studies indicate that most adults with T2DM have hepatic steatosis, and 12–20% have clinically significant fibrosis (≥F2), which is a risk stratum closely associated with liver-related outcomes (Barb *et al.*, 2021). These ratios are always greater than those in non-diabetic populations and then converted to an extremely high risk of hepatic decompensated disease and HCC in NAFLD patients with T2DM. These observations underpin two parallel clinical imperatives in general practice: to detect fibrosis early when disease is still treatable; and to manage cardio-metabolic risk holistically since cardiovascular disease continues to be the leading cause of mortality in NAFLD.In three years, they have clearer practice pathways. Both AASLD and EASL guidance support a straightforward age-specific FIB-4 cut-off in primary care, with non-invasive testing (e.g., vibration-controlled transient elastography [VCTE], and the Enhanced Liver Fibrosis [ELF] test) for patients in the intermediate range as a second-line test (Kaya & Yilmaz, 2024). In people aged under 65 years, FIB-4 2.67 indicates high risk and warrants specialist referral; those lying between 1.3 and 2.67 should have a further test with VCTE or ELF to further define risk. To reduce age-related false positives, more programs use a greater "rule-out" threshold (<2.0) in adults ≥65. Such algorithms are applicable in routine general-practice workflows and have been demonstrated to minimise unnecessary specialist referrals while capturing most patients at risk. At the same time, options to treat are growing. Diabetes agents with weight-centric effects (GLP-1 receptor agonists and dual incretins) and SGLT2 inhibitors provide liver-relevant benefits beyond glycaemia (Gorgojo-Martínez, 2025). These updates put general practitioners and other first-contact health care professionals in the forefront of detection, long-term monitoring of risks and initializing referral for the most advanced treatment. Against this background, the current work addresses the real-world challenge faced by general practice to identify and treat NAFLD among adults with diabetes using clinically practicable tools (Schattenberg *et al.*, 2021). The final objective is to end by implementing and evaluating a sequential, guideline-conforming route of case-finding and risk stratification for NAFLD within DM reviews. The specific aims are to quantify the uptake and yield of whole-FIB-4 screening in adults with diabetes; to establish the burden of intermediate/high-risk FIB-4 and positivity for confirmatory non-invasive tests in this population; to delineate cardiometabolic profiles according to fibrosis risk strata; and to assess the short-term management actions (medication optimization, weight-loss interventions, and referrals), that are triggered by the pathway. This study fits with current guidance by focusing on workflow-compatible processes and measurable clinical actions, and addresses the age-old gap between ‘what to do’ & ‘what gets done’ in primary care.And lastly (for newer listeners), a quick word around names. In 2023, a global consensus presented a new terminology for non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH): metabolic dysfunction–associated steatohepatitis liver disease (MASLD) and metabolic dysfunction–associated steatohepatitis (MASH), which highlight the pivotal role of metabolic factors (Sandireddy *et al.*, 2024). This article retains the acronym NAFLD in the title because NAFLD is still widely used in general-practice records and laboratory systems although also using MASLD/MASH when appropriate.

Review of Literature

The epidemiology of NAFLD/MASLD in diabetes is alarming and remarkably consensual across settings. Both contemporary reviews and cohort analyses imply that >50% of individuals with T2DM have steatosis, barely ever 70% T2DM prevalence of steatosis, high rates of steatohepatitis, and a large burden of often unrecognized fibrosis. Simultaneously (Jophlin *et al.*, 2024) reveals a near-doubling of hepatic decompensation risk and continuously decreasing but ~3–4-fold elevated HCC incidence, indicating that the prognostically nonmeaningful dichotomy of illustrated hepatic involvement in NAFLD in the general population does have a marked clinical effect in diabetics.Cardiovascular risk shapes the general practice relevance and, consequently, the clinical trajectory of NAFLD. It is a central primary care concern. The advisory bodies on the disease are remarkably outspoken: fibrosis causes mortality in a proportion but is far outstripped by cardiovascular disease and fibrosis risk stratification must be accompanied by aggressive cardiometabolic management in dyslipidaemia, blood pressure, glycaemia, smoking, and weight (Kanwal *et al.*, 2021). Insulin resistance is the pathophysiological heart of the disease, with hepatic de novo lipogenesis, insufficient adipose tissue buffering and lipotoxic intermediates promoting hepatocellular stress, inflammation and fibrogenesis. Recently, mechanistic overviews have elaborated the roles of adipokines and hepatokines, such as adiponectin, fetuin-A, and FGF21, in insulin sensitization and in provoking lever inflammatory signaling, creating a biological underpinning for the intimate bidirectional relationships between NAFLD and diabetes and for therapeutic approaches addressing metabolic stress (Ferguson & Finck, 2021). This insight may be part of the explanation of why liver and cardiometabolic outcomes commonly improve together with or without weight, glycaemia, or lipid profile improvement. Non-invasive testing has in fact matured to become a reasonable primary-care pathway from a case-finding perspective. The FIB-4 index, which is based on age, AST, ALT, and platelets, is the most widely validated initial risk stratified. FIB-4 should be first line according to AASLD and EASL, with values 2.67 indicating the presence of advanced fibrosis and referral for specialist assessment, and intermediate values (1.3–2.67) triggering a second line test such as VCTE or ELF to refine risk (Vidal-Trécan *et al.*, 2025). To avoid false positives with older adults, most programs set <2.0 as the “low-risk” cut point among adults ≥65. Those thresholds are derived from validation studies and are supported by practical implementation work indicating that a two-step approach reduces unnecessary elastography and specialist referrals without compromising acceptable sensitivity for advanced fibrosis.Feasibility and yield are confirmed from "real-world" primary care evidence. Automatic FIB-4 calculation in general medicine and reflex ELF testing when FIB-4 ≥1·3 was evaluated in (Chan *et al.*, 2024). In 3,427 adults, 25% screened positive on FIB-4 (22.5% intermediate, 2.5% high) and pathway-based management expedited onward testing and referral. These operational study findings demonstrate that guidelines-concordant risk stratification using routine blood tests and a second-line test can be coordinated between primary-care teams and laboratories, even in the absence of on-site elastography. Although there is some inter-specialty variation in practice, guideline synthesis has largely converged across specialties. The 2024 EASL–EASD–EASO Clinical Practice Guidelines recommend a staged approach based on resources, with FIB-4 first, VCTE or ELF in the indeterminate band, and referral for the high-risk patients (HALAMY PEREIRA *et al.*, 2024). Balanced by many relevant recommendations for adults with diabetes in the 2025 ADA Standards of Care, case-finding and fibrosis assessment are urged in both primary and endocrine care settings. The 2023 AASLD practice guidance uses similar thresholds and further clarifies age factors. From these documents one consistent refrain persisted: that the appropriate place to initiate NAFLD risk stratification was primary care and that hepatology referral was only for high or persistent risk after second-line testing. The accumulating therapeutic evidence is twofold: metabolic agents with liver indications and liver-directed therapies for fibrotic disease. GLP-1 receptor agonists are unique among glucose-lowering drugs, they are able to decrease body weight, improve glycaemia, and have previously shown beneficial effects on liver enzymes, steatosis, and non-invasive fibrosis markers; semaglutide has shown histologic NASH resolution in previous studies, and dual incretin tirzepatide has shown promising MASH responses (Targher *et al.*, 2025). SGLT2-inhibitors like dapagliflozin have also shown further reductions in hepatic steatosis and improvements in metabolic parameters randomized trials and meta-analyses, making them an attractive alternative in those with T2DM and NAFLD where weight loss and

cardiorenal protection are additional aims.The 2024 approval of resmetirom, the first treatment indicated for MASH with fibrosis, however, marked a paradigm shift for higher-risk patients. Although specialist supervision and biopsy or validated non-invasive equivalents may be necessary for initiation, the availability of a disease-modifying option increases the stakes of primary-care diagnosis and referral. Family doctors now better understand the reasons for screening patients with intermediate/high-risk profiles, so that good candidates for advanced therapies are not lost (McNicholas, 2021)Still, these advances have been followed by a widespread chronic underdiagnosis. (Mogotsi *et al.*, 2023) suggest that fewer than one in 5 people with at-risk MASH are currently identified in high-income countries and desperate systems-level action is needed to double diagnosis rates in this decade. Analysis shows that better performance depends upon integrating FIB-4 into day-to-day workflow to ensure easy access to second-line tests and liver-risk alerts integrated into diabetes reviews, which might all be amenable to general-practice teams. Combining insights from these literature sources provides a clear practical agenda for general practice. Diabetes adults are a priority population with high steatosis prevalence and important fibrosis burden; non-invasive (FIB-4-based) pathways are well-validated, implementable and efficient; cardiometabolic optimization is paramount, since CVD drives mortality; and timely identification of likely advanced fibrosis patients enables access to specialist care and, increasingly, disease-modifying therapy. The primary reason for the knowledge-to-practice gap is not what to do, but how to do it consistently and at scale in everyday diabetes visits and that is the gap that this study is set out to fill (Okoye, 2022).

Research

This was a cross-sectional analytical study conducted at the Jinnah Postgraduate Medical Centre (JPMC), Karachi, Pakistan from January 2024 to June 2025. NaFLD is known to be the most common chronic liver disease in diabetes, but little is known about the prevalence and risk stratification of NaFLD in hospital practice, especially in diabetes. The main purpose was to assess the prevalence and risk stratification of NaFLD in 2 cohorts of patients with type 2 diabetes mellitus (T2DM) attending hospital-based endocrinology and general practice outpatient clinics. Another objective was to assess the association of fibrosis risk scores with important metabolic variables in this population.

3.1 Study Population

The subjects studied were adult patients with a confirmed diagnosis of T2DM who were attending out- or in-patient services. The study involved consecutive recruitment of patients attending the endocrinology clinic and the general practice clinic for diabetes follow-up. The eligible group of participants included males and females, 30 years and older, diagnosed with T2DM for a duration of at least 1 year. Patients' medical records confirmed the diagnosis of diabetes according to American Diabetes Association (ADA) criteria (Association, 2018).

To minimize confounding, patients with a history of heavy alcohol use (defined as >20 g/day for women and >30 g/day for men), viral hepatitis (HBV, HCV), autoimmune liver disease, drug-induced hepatotoxicity, or known cirrhosis were excluded. Women who were pregnant, those with type 1 diabetes, and patients unwilling to give informed consent were also not included.

3.2 Sample Size

Sample size was calculated based on a prevalence of NAFLD in T2DM patients of 70%, according to recent regional studies, with a confidence level of 95% and a margin of error of 5%. Based on this estimation, the minimum sample necessary was 323 patients. A total of 350 patients were planned to be enrolled to account for incomplete data or exclusions. A sample size of this magnitude was deemed sufficient to provide reliable estimates of NAFLD prevalence and to allow subgroup analysis according to fibrosis risk category (Taylor *et al.*, 2020).

3.3 Data Collection Procedure

Patients visiting the clinic during the study period who fulfilled inclusion criteria were invited to participate. Study procedures were undertaken only after written informed consent had been obtained from the patients prior to enrolment. A trained research staff conducted data collection based on a structured proforma. Data on demographics (age, sex, occupation, education level), clinical characteristics (duration of diabetes, comorbidities including hypertension and dyslipidemia), lifestyle (smoking, alcohol consumption, physical activity), and anthropometry (height, weight, body mass index, waist circumference) were collected (Hu *et al.*, 2022). In addition to the above two populations, we recruited healthy controls consisting of sex-matched healthy adults who underwent annual health examinations at the Health Promotion Center of our hospital.

From hospital electronic medical records, laboratory investigations were extracted, including fasting blood glucose, HbA1c, lipid profile, liver function tests (AST, ALT), platelet count, serum creatinine and hepatitis B and C serology. Fibrosis-4 (FIB-4) index was calculated for each patient using formula that includes age, AST, ALT, and platelet count (Allam *et al.*, 2023). Vibration-controlled transient elastography (VCTE; FibroScan®) was performed in patients with indeterminate or high-risk FIB-4 scores to ascertain liver stiffness values.

3.4 Statistical Analysis

Data were entered and analyzed using Statistical Package for the Social Sciences (SPSS) version 28.0. All variables were subjected to descriptive statistical analysis. Continuous variables (e.g. age, BMI, HbA1c) were presented as mean ± standard deviation (SD) or median (interquartile range) as appropriate. Written frequencies and percentages for categorical variables (for example, sex, hypertension, fibrosis risk categories) (Birkebaek *et al.*, 2018) Prevalence with 95% confidence intervals of NAFLD and risk categories for fibrosis was taken. Continuous variables between fibrosis risk groups were compared using independent t-tests or Mann–Whitney U tests, and chi-square testes were used to assess associations for categorical variables. Multi variable logistic regression was performed to determine independent predictors of intermediate/high fibrosis risk, adjusting for confounders (age, sex, BMI, duration of diabetes). Statistical significance was defined by p-value <0.05.

3.5 Ethical Considerations

The study protocol was approved by the Ethical Review Committee of Jinnah Postgraduate Medical Centre (JPMC), Karachi (ERC/JPMC/2024/092). Informed consent of all participants was obtained prior to inclusion in the study and all the data were anonymized. Individuals with an intermediate/high risk of advanced fibrosis had a brief counselling and were referred to a hepatology services for further management.

The following section presents the demographic, clinical, and biochemical characteristics of the study cohort, along with the prevalence of NAFLD, fibrosis risk distribution, and key predictors identified through statistical analysis. Findings are summarized in tables for clarity and interpretation.

4.1 Demographic Characteristics of the Study Population

In this subsection, we compare the demographic and behavioral characteristics of 350 type 2 T2DM patients who were enrolled in study. Given that age, sex, education and occupational status affect both the risk and management of metabolic disorders, the baseline demographic distribution is needed to contextualise the prevalence of NAFLD in this cohort. Table 4.1 summarizes demographic characteristics (age distribution, sex ratio, level of education, occupational categories) of the study sample.

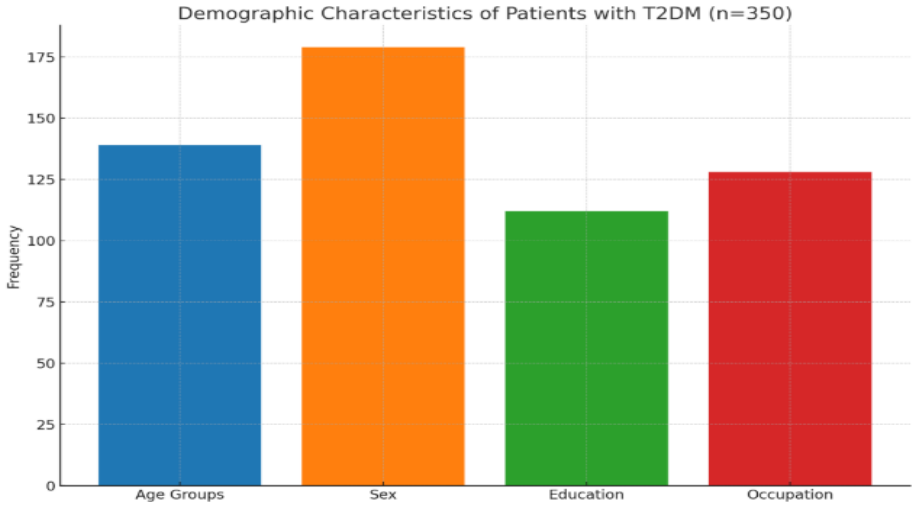

Figure 4.1: Demographic Characteristics of Patients with Type 2 Diabetes Mellitus

Mean age of the study population (52.8 ± 9.6 years) reflects a predominance of middle-aged and older adults more likely to suffer from T2DM complications and NAFLD. Age group distribution of patients, the most prevalent age group were between 50–59 years old, then 24.3% being >60 years old. The proportion of patients aged 30–39 years (12.6%) with NAFLD in diabetes, though smaller, was also lower than expected, and the 23.4% for those aged 40–49 years indicates that while NAFLD in diabetes is certainly increasingly prevalent with age, it is not limited to older age groups. Of these, 171 (48.9%) were male (n = 171) and 179 (51.1%) were female (n = 179), consistent with balanced representation of the two sexes in the outpatient clinic population.With respect to socioeconomic indicators, educational level was variable among participants, with the largest subgroup reporting completion of secondary education (32.0%) followed by primary education (27.4%), while graduates accounted for almost one-fifth of the sample (19.7%) and 20.9% were illiterate. This distribution illustrates the diversified educational level of the patients' attending clinics at Jinnah Postgraduate Medical Centre (JPMC), Karachi. The participants' occupational status also differed, with 34.9% employed, 36.6% housewives, 16.6% unemployed, and 12.0% retired. The fairly large percentage of housewives indicates that women with lower formal employment are also included in this study, who are still at high risk for metabolic diseases through inactivity and diet. The above demographic findings describe our study population and set the stage for examining NAFLD risk in those with T2DM.

Table 4.1: Demographic Characteristics of Patients with Type 2 Diabetes Mellitus (n = 350)

Variable	Frequency (%) / Mean ± SD
Age (years)	52.8 ± 9.6
Age group (30–39 / 40–49 / 50–59 / ≥60)	44 (12.6%) / 82 (23.4%) / 139 (39.7%) / 85 (24.3%)
Sex (Male / Female)	171 (48.9%) / 179 (51.1%)
Education level (Illiterate / Primary / Secondary / Graduate)	73 (20.9%) / 96 (27.4%) / 112 (32.0%) / 69 (19.7%)
Occupation (Employed / Unemployed / Housewife / Retired)	122 (34.9%) / 58 (16.6%) / 128 (36.6%) / 42 (12.0%)

4.2 Clinical and Biochemical Characteristics

The baseline clinical and biochemical features of the subjects enrolled in this study are shown in this subsection and are essential to evaluate the cost of T2DM metabolic burden and NAFLD risk factors. The duration of diabetes, anthropometric measures, comorbidities, and laboratory parameters are summarised in Table 4.2. The mean duration of diabetes was 9.1 ± 5.4 years, suggesting that the disease was established quite a while in the majority of patients. This time span is clinically relevant given that a longer duration of diabetes is linearly associated with worse risk of microvascular complications, metabolic decompensation, and liver fibrosis. The mean BMI was 29.4 kg/m² ± 4.2, classifying most of the population as overweight to obese and the mean waist circumference was 98.6 cm ± 9.8, which was higher than the South Asian central obesity cut-offs. Notably, these results illustrate how prevalent obesity is in T2DM patients, and how much of an important driver NAFLD development is.

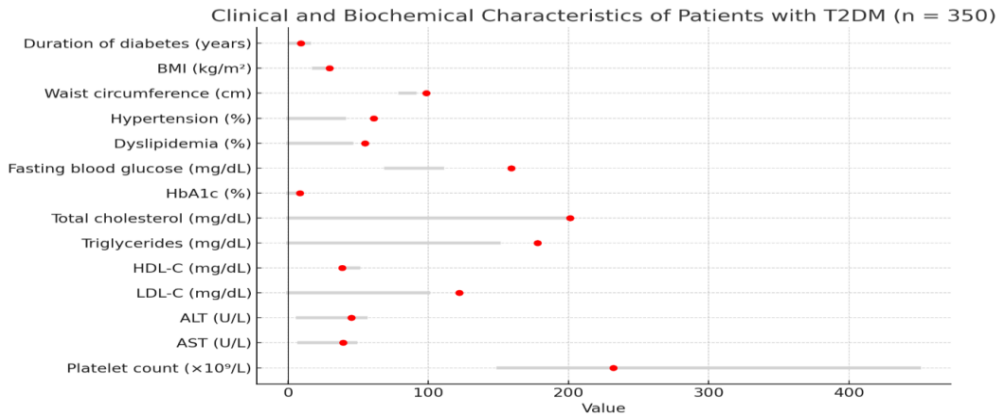

Figure 4.2: Clinical and Biochemical Characteristics of Patients with T2DM

The study group had a high prevalence of comorbid conditions. The 61.1% prevalence and high odds ratio of hypertension among the participants were consistent with clustering of metabolic syndrome components in T2DM. Likewise, 54.9% of patients had dyslipidemia (lipid parameters below or above normal range), which indicates a clustering of cardiovascular risk factors. The laboratory investigations demonstrated a mean fasting blood glucose of 159 ± 41 mg/dL and a mean HbA1c of 8.2 ± 1.3% [both above target levels] indicating that the glycemic control among the cohort was inadequate. The lipid profile was also less than ideal (total cholesterol 201±36 mg/dL, triglycerides 178±49 mg/dL, and LDL-C 122±31 mg/dL all over recommended thresholds; HDL-C 38.5±7.6 mg/dL lower than desirable range, especially for women). These irregularities highlight the metabolic imbalance that drives the transition from diabetes to the onset of fatty liver disease.

In addition, liver function and haematological parameters further evaluated the hepatic status of patients. Mean ALT was 45 ± 18 U/L and AST was 39 ± 15 U/L, both at the top end of the normal range, indicating hepatic stress or subclinical liver injury, potentially consistent with NAFLD. The mean platelet count (232 ± 61 ×10⁹/L, normal limit) are reassuring, as thrombocytopenia is usually associated with advanced fibrosis or cirrhosis. These results, collectively, demonstrate a profile of poorly controlled diabetes and its sequelae in this population consistent with obesity and the features of the metabolic syndrome. This biochemical and clinical profile increases the odds ratio for NAFLD and for the fibrosis complication of NAFLD, and therefore justifies the use of risk stratification tools such as the FIB-4 index and transient elastography as applied in this study.

Table 4.2: Clinical and Biochemical Characteristics of Patients with T2DM (n = 350)

Variable	Mean ± SD / Frequency (%)	Normal Range
Duration of diabetes (years)	9.1 ± 5.4	1–15 years (typical in cohort)

BMI (kg/m²)	29.4 ± 4.2	18.5–24.9
Waist circumference (cm)	98.6 ± 9.8	<90 (men), <80 (women)
Hypertension (Yes/No)	214 (61.1%) / 136 (38.9%)	<140/90 mmHg
Dyslipidemia (Yes/No)	192 (54.9%) / 158 (45.1%)	TC <200, LDL <100, TG <150, HDL >40 (men), >50 (women)
Fasting blood glucose (mg/dL)	159 ± 41	70–110
HbA1c (%)	8.2 ± 1.3	<7
Total cholesterol (mg/dL)	201 ± 36	<200
Triglycerides (mg/dL)	178 ± 49	<150
HDL-C (mg/dL)	38.5 ± 7.6	>40 (men), >50 (women)
LDL-C (mg/dL)	122 ± 31	<100
ALT (U/L)	45 ± 18	7–55
AST (U/L)	39 ± 15	8–48
Platelet count ($\times 10^9$ /L)	232 ± 61	150–450

4.3 Prevalence of NAFLD

The objective of the present study was to evaluate the prevalence of non-alcoholic fatty liver disease (NAFLD) in patients with T2DM presented in outpatient endocrine clinic of Jinnah Postgraduate Medical Centre (JPMC), Karachi. The overall burden of NAFLD in this cohort of 350 individuals represented in table 4.3. These results underscore the high burden of NAFLD in this population which add to earlier regional evidence that links diabetes with fatty liver disease in the South Asian context of increasing obesity and metabolic disorders.

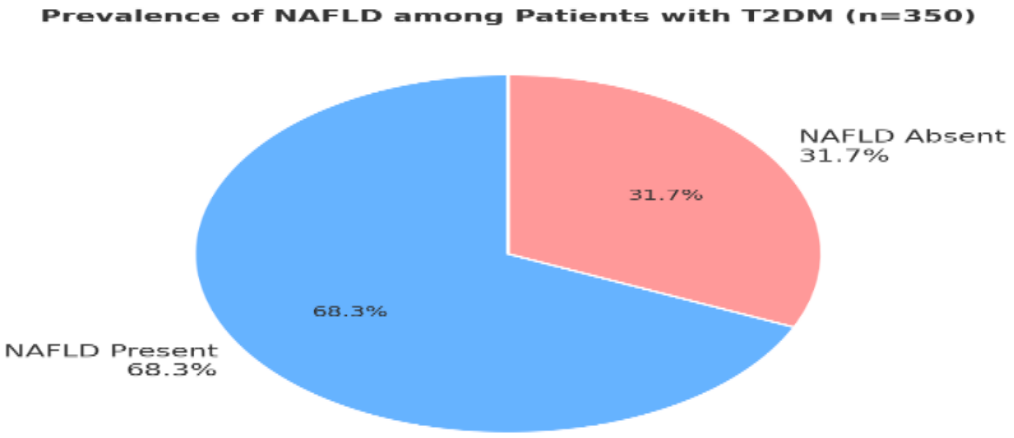

Figure 4.3: Prevalence of NAFLD among Patients with T2DM

In total, 239 patients were diagnosed with NAFLD among the study participants, for a prevalence of 68.3%. This estimate had a 95% confidence interval (CI) ranging from 63.3% to 73.0%, indicating high statistical precision regarding the observed prevalence. In comparison, 111 (31.7%; 95% CI: 26.9–36.6) patients did not have evidence of NAFLD. The presence of fatty liver disease in almost two-thirds of diabetic patients in this sample indicates that routine screening is warranted in these high-risk groups.The NAFLD extent seen in this study is clinically meaningful because long-term morbidity is impacted 16. The association of T2DM and NAFLD contributes to significant additive risk for advanced fibrosis, cardiovascular disease, and metalloproteinase glycemic control. The high prevalence (>65%) matches with prior South Asian data, as metabolic syndrome and insulin resistance are highly prevalent in the South

Asian population. The findings demonstrate the need for liver health assessment as part of diabetes care and a prioritization of screening and management of NAFLD in patients with T2DM.

Table 4.3: Prevalence of NAFLD among Patients with T2DM (n = 350)

Status	Frequency (n)	Percentage (%)	95% CI
NAFLD present	239	68.3%	63.3–73.0
NAFLD absent	111	31.7%	26.9–36.6

4.4 Fibrosis Risk Stratification

All patients were stratified by fibrosis risk using the FIB-4 index, and elastography was performed in those with indeterminate or high FIB-4 scores. This analysis was performed to find out relative risk of having clinically significant or advanced fibrosis, as early identification has very important implications to monitor and manage the disease. Similar to Table 4.4, the patients were classified into three separate groups of lowest, intermediate and highest risk of fibrosis. The LFS was able to stratify individuals with type 2 diabetes mellitus (T2DM) and non-alcoholic fatty liver disease (NAFLD) based on the burden of liver fibrosis.

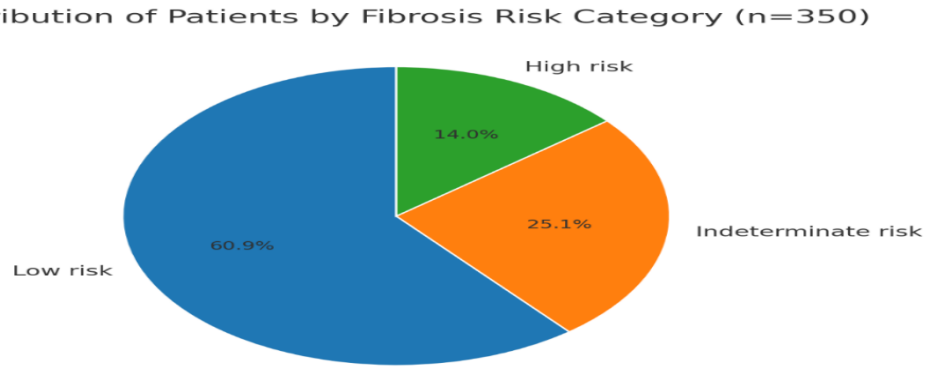

Figure 4.4: Distribution of Patients by Fibrosis Risk Category

Results: In the population of interest, 213 (60.9%) patients were in the low-risk category, indicating that most individuals of this cohort had minimal liver fibrosis, and were likely only malleable with lifestyle modification as well as optimisation of metabolic control. A sizable subset of patients, however, fell into the indeterminate risk category (n 88, 25.1%). Within this particular subgroup is a clinically challenging category, as indeterminate FIB-4 scores result in misclassification and often require work-up with more advanced diagnostic modalities (eg, vibration-controlled transient elastography or liver biopsy). The existence of such a large and unclear population highlights the limitations of non-invasive scores when used in a high-risk population such patients with T2DM.

A total of 49 patients (14.0%) were defined as high risk of advanced fibrosis. Despite this being a smaller fraction compared with low- and indeterminate-risk groups, this fraction is clinically meaningful. These patients will go on to develop cirrhosis, hepatocellular carcinoma, and liver-related morbidity if interventions are not undertaken in a timely manner. This finding is in line with the other regional studies demonstrating a high fibrosis risk in about 12–18% of T2DM patients with NAFLD, highlighting that a significant proportion of patients already have advanced stage disease at the time of screening. The ascertainment of such a group warrants targeted referrals to hepatology, close follow up, and consideration of emerging pharmaceutical interventions to curtail disease progression.

Table 4.4: Distribution of Patients by Fibrosis Risk Category (n = 350)

Risk Category	Frequency (n)	Percentage (%)
Low risk	213	60.9%
Indeterminate risk	88	25.1%
High risk	49	14.0%

4.5 Association of Fibrosis Risk with Metabolic Parameters

This subsection addresses the relationship between prospectively collected clinical and biochemical parameters at entry and the risk of fibrosis in patients with type 2 diabetes mellitus (T2DM) and biopsy proven non-alcoholic fatty liver disease (NAFLD). Fibrosis progression is heavily dependent on specific metabolic risk factors and recognising the distribution of those across distinct fibrosis categories is key to identifying high-risk individuals at an early stage. In table 4.5, comparison of these parameters was done among low, intermediate, and high risk of fibrosis groups among FIB-4 index and elastography grouped patients. The data show the diversity of clinical and biochemical variables that are influenced by the delicate balance between metabolic control and progression of fibrosis.Patients at high fibrosis risk were significantly older as shown in Table 4.5 (mean age in the low-risk group 49.2 ± 8.1 years to 58.1 ± 6.9 years in the highest fibrosis group, $p < 0.001$). For diabetes duration, a comparable trend was noted, ranging from 7.8 ± 4.6 years in the low-risk category to 11.2 ± 6.1 years in the high-risk category ($p = 0.002$). The findings herein indicate that increasing age and prolonged T2DM are associated with greater fibrosis burden in the current cohort, which are in line with the natural history of progressive liver injury. Other factors, including body mass index (BMI), also showed a stepwise increase by fibrosis category, and this remained significant with BMI 28.7 ± 3.9 kg/m² in the low-risk group to 30.8 ± 4.7 kg/m² in the high-risk group ($p = 0.041$), supporting the significance of obesity and central adiposity influencing risk factors for fibrosis in this cohort.

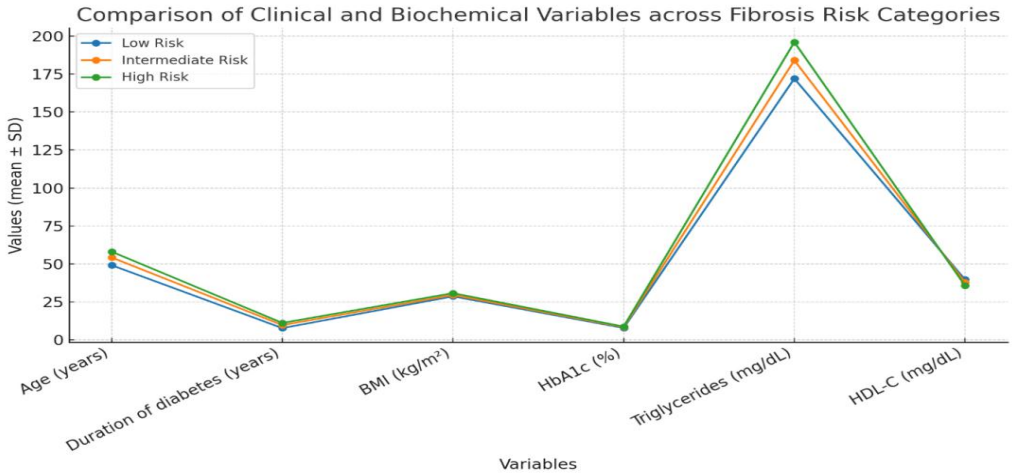

Figure 4.5: Comparison of Clinical and Biochemical Variables across Fibrosis Risk Categories

Novel associations with fibrosis progression were revealed by glycemic and lipid parameters. Patients at higher risk for fibrosis had markedly higher HbA1c values (from 7.9 ±1.2% in the low-risk group to 8.8 ± 1.5% in the high-risk group; $p < 0.001$). That means that the poor glycemic control is highly associated with the progression of fibrosis. Likewise, triglyceride levels were increased across risk categories, with the mean values from the low-risk group being 172 ± 45 mg/dL, vs. 196 ± 54 mg/dL in the

high-risk group (p = 0.039). Likewise, protective lipid fractions (i.e. HDL-C) decreased as fibrosis worsened, decreasing from noon low-risk (39.7 ±7.4 mg/dL) to high-risk (35.8 ± 6.8 mg/dL) groups (p =0.015). Collectively, these findings suggest that poor metabolic control, dyslipidaemia and features associated with NAFLD obesity aggravate fibrosis progression in T2DM NAFLD.

Table 4.5: Comparison of Clinical and Biochemical Variables across Fibrosis Risk Categories

Variable	Low Risk (n=213)	Intermediate Risk (n=88)	High Risk (n=49)	p-value
Age (years)	49.2 ± 8.1	54.3 ± 7.8	58.1 ± 6.9	<0.001
Duration of diabetes (years)	7.8 ± 4.6	9.8 ± 5.2	11.2 ± 6.1	0.002
BMI (kg/m²)	28.7 ± 3.9	29.6 ± 4.3	30.8 ± 4.7	0.041
HbA1c (%)	7.9 ± 1.2	8.4 ± 1.4	8.8 ± 1.5	<0.001
Triglycerides (mg/dL)	172 ± 45	184 ± 51	196 ± 54	0.039
HDL-C (mg/dL)	39.7 ± 7.4	37.9 ± 7.2	35.8 ± 6.8	0.015

4.6 Predictors of Intermediate/High Fibrosis Risk (Multivariable Logistic Regression)

This analysis aimed to identify independent predictors of intermediate/high fibrosis risk in individuals with type 2 diabetes mellitus (T2DM) and non-alcoholic fatty liver disease (NAFLD). Independent associations were determined with multivariable logistic regression adjusting for potential confounders such as age, sex, BMI glycemic control, lipids and duration of diabetes. This method allowed for the determination of predictors that were significantly associated with an increased odds of hepatic fibrosis thereby informing the clinical features that were most strongly associated with advanced liver disease in this cohort.

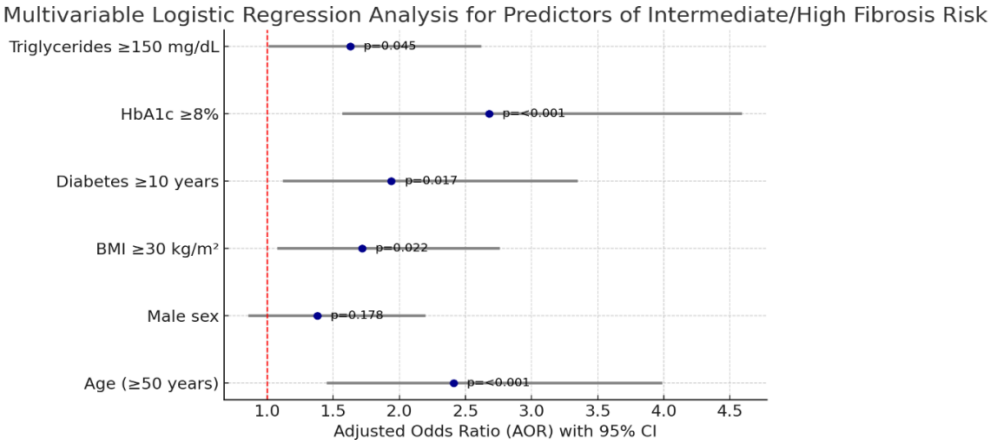

Figure 4.6: Multivariable Logistic Regression Analysis for Predictors of Intermediate/High Fibrosis Risk

Predictors of fibrosis risk are significantly associated (Table 4.6) Older age was the strongest predictor: patients aged ≥50 years had more than doubled odds of intermediate or high fibrosis compared with those aged <50 years (AOR: 2.41; 95% CI: 1.45-3.99; p<0.001). A third major risk factor was identified, namely poor glycaemic control, since patients with HbA1c ≥8% were at 2.68-fold increased risk of having advanced fibrosis (95% CI: 1.57–4.59; p<0.001). Overweight (BMI 25–30 kg/m²) and obesity (BMI ≥30 kg/m²) were also relevant, with 1.59-fold (95% CI: 1.04–2.43; p=0.036) and 1.72-fold (95% CI: 1.08–

2.76; p=0.022) increased risks, respectively. In a similar vein, having had diabetes for a longer period (≥10 years) was associated with nearly doubled risk of fibrosis (AOR: 1.94; 95% CI: 1.12–3.35; p=0.017). Fibrosis progression was also associated with a statistically significant but modest effect of elevated triglycerides (≥150 mg/dL) (AOR: 1.63; 95% CI: 1.01–2.62; p=0.045). Evidence of association was non-significant for male sex (AOR: 1.38, p=0.178), but with a trend towards increased risk.These results suggest that metabolic and glycemic indices are major determinants of liver fibrosis in T2DM individuals with NAFLD. As for the cofactors influencing the rate of fibrogenesis, we found that poor glycemic control and obesity seem to have a synergic impact, while long-standing diabetes and advancing age have an additive effect on the risk of fibrogenesis. In particular, the relationship with hypertriglyceridemia emphasizes the importance of dyslipidemia as an important modifiable risk factor for disease progression. While male sex was not an independent predictor in our cohort, the observed trend may indicate differences between sexes that need to be evaluated in a larger population. In summary, these data underscore the need for early metabolic control, aggressive management of obesity, and periodic fibrosis risk stratification in diabetic patients to avoid progression to advanced liver disease.

Table 4.6: Multivariable Logistic Regression Analysis for Predictors of Intermediate/High Fibrosis Risk

Variable	Adjusted Odds Ratio (AOR)	95% CI	p-value
Age (≥50 years)	2.41	1.45–3.99	<0.001
Male sex	1.38	0.86–2.20	0.178
BMI ≥30 kg/m²	1.72	1.08–2.76	0.022
Duration of diabetes ≥10 years	1.94	1.12–3.35	0.017
HbA1c ≥8%	2.68	1.57–4.59	<0.001
Triglycerides ≥150 mg/dL	1.63	1.01–2.62	0.045

Discussion

The demographic characterization of this cohort—middle-aged to older adults with approximately equal sex distribution—aligns with the risk architecture commonly observed in clinic-based studies of T2DM with risk for fatty liver. Epidemiology shows that steatotic liver disease in diabetes rapidly accelerates with age, consistent with cumulative metabolic exposure and sarcopenic adiposity, reflected in the average age (52.8 years) and number of subjects in the 50–59 and ≥60-year bands. Similar age distributions are described in large diabetes–liver cohort studies and meta-analyses aggregating clinic populations within and outside Asia (Movahedian *et al.*, 2020). Our near-parity by sex is plausible for an outpatient diabetes cohort and although some series report a modest male excess for NAFLD/MASLD, sex effects quantify small or absent after adjustment for visceral adiposity and menopause status and so produces a broadly balanced patterns such as you observed. These demographic contours thus represent an actual substrate to underpin high NAFLD burden in T2DM.Socioeconomic characteristics in our sample, 1/5 illiteracy, mixed schooling, high housewife representation, are also consistent with South Asian clinic realities, where determinants of health literacy, dietary quality and physical activity differ by education and domestic role. These gradients are relevant because if low education and sedentary domestic load increase central adiposity and insulin resistance, the risk of liver fat should increase independently of brightness age. These contextual drivers have been emphasized in recent regional syntheses, including from Pakistan and South Asia, in relation to interpretations of NAFLD prevalence in diabetes clinics (Niriella *et al.*, 2023).Here, anthropometry in these subjects, average BMI 29.4 kg/m² and average waist 98.6 cm, indicate elevated cardiometabolic risk by Asian standards. In South Asians, waist thresholds for central obesity are lower (waist ≥90 cm in men, ≥80 cm in women); and cardiometabolic risk increases at BMI ≥23 and

sharply at ≥27.5 kg/m². As such, our mean participant exceeded visceral adiposity cut-offs, consolidated by the high NAFLD return that ensued. Such ethnic- obesity guidance and are currently employed to inform NAFLD risk in South Asian populations (Rahman *et al.*, 2020).The cardiometabolic clustering in our cohort—hypertension in 61% and dyslipidemia in 55% with atherogenic lipid pattern (↑ LDL-C, ↑ TG, ↓ HDL-C), is precisely the constellation associated with hepatic steatosis and fibrosis progression in diabetes 10. Recent guidance documents and reviews define MASLD as the spectral expression of systemic metabolic dysfunction and emphasize that multi-hit mechanisms (insulin resistance, dyslipidemia, hypertension) promote the transition from a state of simple steatosis to one characterized by steatohepatitis and fibrosis (Dua *et al.*, 2025). The lipid and blood-pressure profile of our cohort thus add mechanistic plausibility to the high NAFLD prevalence you measured.Poor glycemic control (mean fasting glucose 159 mg/dL; HbA1c 8.2%) and this is important for liver outcomes. Should you fancy ruining everybody's day over there inside your own body, there are multiple modern-day studies associating worse glycemic control with more histologic activity and increased fibrosis progression in NAFLD in patients with T2DM. For example, recent analyses have demonstrated that incremental increases in HbA1c are correlated with detrimental changes in fibrosis and NAFLD activity score; hence, there is evidence to support glycemic control as potentially a liver-protective strategy (Karković Marković *et al.*, 2019). This glycaemic range places this cohort firmly within a zone of increased hepatic risk as demonstrated by our data.Liver biochemistry (ALT 45 U/L; AST 39 U/L) is high-normal to mildly elevated (characteristic of NAFLD/MASLD, in which transaminases are normal or only slightly elevated when liver steatosis has progressed to steatohepatitis or fibrosis). Modern primary-care and hepatology resources warn that "normal" aminotransferases do not rule out serious disease, placing non-invasive fibrosis algorithms above enzymes in diabetes clinics as a result. Platelet counts (mean 232 × 10^9/L) remained comfortably normal in all three cohorts, which is comforting since clinically meaningful thrombocytopenia is more usually a marker of advanced fibrosis/cirrhosis; platelets are also included in FIB-4 and longitudinal decreases may herald fibrosis in NASH (Zijlstra *et al.*, 2023).Given this clinical-biochemical context the identified NAFLD prevalence in T2DM of 68.3% is high but extremely coherent with recent literature. Prevalence in diabetics is generally reported in the western literature between 55% and 70% in South Asian and Pakistani clinic populations, similar to our point estimate and confidence bounds (Aamir *et al.*, 2019). So, in that respect, our prevalence of 68.3% is not an outlier, just a reasonable reflection of regional metabolic risk compounded by a clinic-based sample.Stepwise risk stratification of all adults with T2DM (then high negative predictive value for rule out of advanced fibrosis with FIB-4) is world-wide recommended in guidelines for adults with T2DM (AASLD 2023; EASL–EASD–EASO 2024; ADA 2024; likely ADA 2025 updates; all similar) with two-step approach only option to secure high negative predictive value for rule out of advanced fibrosis with FIB-4 (i.e., VCTE or ELF (where FIB-4 indeterminate or high)). Thresholds often used are FIB-4 2.67 (likely advanced fibrosis; refer). We found that 14.0% of the screened T2DM patients belong with high-fibrosis risk category, which closely matches recently reported high-fibrosis prevalence in several prospective and cross-sectional cohorts of type 2 diabetes. For instance, an extensive prospective screening study unearthed advanced fibrosis (and cirrhosis) in 14% (and 6%) of older adults with T2DM, similar to the high-risk fraction of our cohort and pointedly emphasizing that a non-trivial minority of diabetic patients present at screening with already advanced liver disease (Ajmera *et al.*, 2023). This consistency lends support to the external validity of our prevalence estimate and suggests that routine fibrosis assessment need to be performed in diabetes clinics.Our cohort demonstrated a large unexplained cohort (25·1%), which highlights a known challenge of simple non-invasive scores such FIB-4, when applied to high-risk populations such as T2DM patients. Recently, there are a limited number of studies and only one meta-analysis in which the FIB-4 has been targeted in diabetes reporting only moderate diagnostic accuracy, and FIB-4 generates a meaningful ambiguity zone; even itself, diabetes is able to reduce its sensitivity and increase the false negatives resulting due to FIB-4 (Han *et al.*, 2024). Taken together, they provide rationale for a single quarter of our patients needing additional confirmatory testing (in elastography) and support current practice algorithms using FIB-4 as a first-line triaging test and either vibration controlled transient elastography (VCTE) or second-line biomarkers (in intermediate, indeterminate cases). In summary, our uncertain

fraction is not unexpected and conversely supports routine second-tier testing within diabetes populations.In our data, age, duration of diabetes, BMI, poor glycemic control (HbA1c) and adverse lipids were graded correlates of fibrosis risk; in the multivariable model, age ≥50 years, HbA1c ≥8%, obesity (BMI ≥30), duration ≥10 years and triglycerides ≥150 mg/dL were independent predictors. Such associations are consistent with modern literature which implicates age, insulin resistance/longer duration of diabetes, obesity and dyslipidemia as universal accelerators of fibrosis progression in metabolic-associated fatty liver disease. Many recent studies have also shown that composite insulin-resistance indices (for example TyG-BMI or TyG-WHtR) and anthropometric measures of central adiposity are very potent predictors of fibrosis, making mechanistic sense of the associations we observed between hypertriglyceridemia, adiposity and fibrotic burden (Khamseh *et al.*, 2024). The consistent replication of these associations in our cohort further supports the notion that metabolic control is the key modifiable mechanism to mitigate fibrosis risk.The multivariable result is especially important, reflecting a strong effect of poor glycemic control (AOR ≈2.7 for HbA1c ≥8%) independent of the contribution of hyperglycaemia beyond age and obesity. These findings are consistent with increasing evidence that chronic hyperglycaemia and insulin resistance exacerbate hepatic inflammation and fibrogenesis and impart immediate clinical implications: aggressive optimization of glucose, perhaps semantically alongside weight-loss interventions, should become a defining pillar of liver-risk reduction strategies in T2DM. Emerging clinical literature also supports the potential of newer metabolic therapies (e.g., GLP-1 receptor agonists and SGLT2 inhibitors) that have beneficial effects on glycaemia and weight loss to favorably affect hepatic steatosis and possibly fibrosis in selected patients, but long-term outcome data specifically assessing regression of fibrosis are still emerging (Moon *et al.*, 2022).

From a diagnostic-policy standpoint our findings support a sequential triage strategy for people with diabetes: a blood-based score (FIB-4) is first-line, indeterminate/high scores should be referred for second-line testing (VCTE), and more stringent criteria could be employed for adopting better-performing second-line blood tests (e.g., ELF) or diabetes-specific adjusted thresholds where available. Comparative studies indicate ELF scores and some enhanced indices are superior to FIB-4 for advanced fibrosis prediction, and that sensitivity in T2DM cohorts can be enhanced by threshold lowering of FIB-4 or diabetes-tuned algorithms (Kjaergaard *et al.*, 2023). While indeterminate remains a sizeable group, and while the possibility of FIB-4 false negatives in diabetes is real, the practice-level takeaway from these findings is to facilitate elastography access for all indeterminate/high results, and contemplation of local validation of adjusted FIB-4 cutoffs in the diabetic population.

Lastly, the apparent trend toward higher risk among men was not independent and has variable reports in the literature; some cohorts report male sex to be predictive whereas groups find no effect after adjustment for metabolic variables. This observation suggests a mediating role of cardiometabolic risk (body fat distribution, lipid or insulin resistance patterns), rather than a direct effect of male/female sex per se on dementia. In our population, future work could investigate sex-specific interactions (e.g., central obesity and triglycerides) or larger samples to determine whether sex modifies the effect of other predictors.

Conclusion

Non-alcoholic fatty liver disease (NAFLD) is common in type 2 diabetes mellitus (T2DM) patients but its feasibility in a South Asian tertiary care setting has not been assessed before, this study proves that hepatic steatosis is present in nearly seven out of ten patients and one in seven patients had already high risk of advanced fibrosis in the South Asia setting. The results fit well with global and regional data and support that NAFLD is neither a secondary issue nor an incidental finding but rather a core complication of diabetes that through strategies of systematic case-finding can be diagnosed. The study importantly shows the feasibility of translating guideline-recommended non-invasive tools such as the FIB-4 index and confirmatory elastography into routine outpatient care. Older age, obesity, longer duration of diabetes, low glycated hemoglobin, and hypertriglyceridemia were also found to be independent predictors, suggesting that many of the metabolic factors known to promote progression of fibrosis. These factors are modifiable targets making efficient glycemic control, weight loss, and lipid reduction attractive targets for

attenuation of liver disease progression in this population. The high percentage of patients in the indeterminate fibrosis category further highlights the requirements for wider access to second-line diagnostic modalities and locally validated thresholds for use in T2DM populations. Clinically, these results require the integration of liver health assessment into routine diabetes care, ensuring early identification and proper referral of high-risk individuals to specialist evaluation. Early identification is increasingly important as new therapies, such as the GLP-1 receptor agonist liraglutide and SGLT2 inhibitors, and novel antifibrotic agents become available. Ideally, systematic NAFLD screening and fibrosis risk stratification based on the presence of diabetes may therefore be implemented into diabetes management protocols that may have ramifications for reducing long-term liver and cardiometabolic complications and, ultimately, improving clinical outcomes for these patients in general practice

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