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Non-Invasive Screening of Metabolic Dysfunction-Associated Fatty Liver Disease MAFLD among People with Type 1 Diabetes Mellitus

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ABSTRACT

Background: Metabolic dysfunction-associated fatty liver disease (MAFLD) encompasses hepatic steatosis with potential progression to steatohepatitis and fibrosis. It represents a principal contributor to end-stage liver disease. Indirect assessment of hepatic involvement can be achieved through non-invasive tools such as fatty liver index (FLI) and fibrosis-4 index (FIB-4).

Aim: This study aimed to screen for MAFLD in individuals with T1DM using non-invasive scores (FLI and FIB-4) and amino-terminal propeptide of P3NP.

Patients and methods: In this cross-sectional analysis, a total of 82 cases diagnosed with T1DM were categorized into low, intermediate, and high-risk groups according to the FLI. The evaluation of FIB-4 and P3NP levels was primarily conducted within the intermediate- and high-risk subgroups.

Results: Higher FLI scores were significantly associated with older age, female sex, longer T1DM duration, higher BMI, and elevated blood pressure. FLI also showed significant correlation with FIB-4. FIB-4 positively correlated with T1DM duration, BMI, systolic and diastolic blood pressure (SBP and DBP), and waist circumference. P3NP showed a significant correlation with FIB-4 but not with FLI.

Conclusion: FLI is a valid tool for non-invasive detection of hepatic steatosis in T1DM cases. FIB-4 can further stratify fibrosis risk without the need for invasive procedures. However, P3NP showed limited utility in this context.

Keyword: Fatty liver index, Fibrosis-4 index, Type 2 diabetes mellitus, Metabolic dysfunction-associated fatty liver disease.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) presently represents the most prevalent form of liver disease globally, impacting approximately one-third of adults and around 12% of the pediatric population [1]. The pathogenesis of this condition is closely associated with metabolic syndrome (MS), a cluster of metabolic disturbances that include overweight or obesity, T2DM, dyslipidemia, and arterial hypertension, of which the first two seem to be the strongest [2]. In 2020, an international panel of experts recommended renaming the disease as MAFLD [3, 4].

MAFLD represents the hepatic component of MS and includes a continuum of histopathological changes, beginning with the ectopic deposition of triglycerides within hepatocyte cytoplasm (steatosis), advancing to inflammatory responses and hepatocellular damage characteristic of nonalcoholic steatohepatitis (NASH), and potentially progressing to fibrosis. This fibrotic evolution significantly heightens the risk of cirrhosis, end-stage liver disease (ESLD), and HCC [5].

Emerging evidence highlights a rising incidence of NAFLD among individuals with T1DM. Although increasing occurrence of MS within this population may partially account for this pattern, certain genetic determinants exhibit a stronger association with fatty liver disease, yet their distribution in T1DM remains inadequately explored. Moreover, factors such as oxidative stress, sustained hyperglycemia, suboptimal glycemic control, and administration of exogenous insulin play a pivotal role in modulating intrahepatic lipid balance [6].

Egypt ranks among the top ten countries globally with the highest obesity rates. Of particular concern, the prevalence of overweight and obesity among school-aged children and adolescents has been reported at 31.5% and 12.7%, respectively [7].

According to European guidelines, non-invasive diagnostic tools are categorized into three main groups: Blood-based biomarkers, modalities assessing the physical properties of hepatic tissue, and imaging techniques that visualize liver morphology [8]. Serum biomarkers are presently utilized either independently for the diagnosis or grading of steatosis, or in conjunction with anthropometric measures to construct predictive models. These models incorporate serum-based indicators that have been assessed for their capacity to predict hepatic steatosis, with FLI being one of the most widely studied examples [9]. Histopathological assessment is widely recognized as the most reliable method for confirming the diagnosis and assessing disease stage [10].

Recent investigations have established an association between noninvasive biomarkers and liver-related morbidity and mortality. Although indirect fibrosis markers, such as FIB-4, offer an estimate of hepatic fibrosis, they do not directly capture the underlying fibrogenic processes. To address this limitation, direct fibrosis biomarkers that more accurately reflect active fibrogenesis have been developed. One such marker is PRO-C3, which is released during the deposition of excessive ECM, a key process in liver fibrosis progression. PRO-C3 serves as an indicator of dynamic turnover of ECM,

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encompassing both its formation and degradation. Given its role as a marker of fibrogenesis, PRO-C3 may prove valuable in assessing therapeutic response and monitoring longitudinal changes in liver fibrosis [11]. Accordingly, this study was conducted to screen for MAFLD in cases with T1DM utilizing non-invasive scoring systems alongside the measurement of amino-terminal propeptide of P3NP.

PATIENTS AND METHODS

Study design and setting: This cross-sectional study included 82 cases of individuals diagnosed with T1DM during their admission to Mansoura Specialized Medical Hospital or during their follow up at the Outpatient Clinic over six months fulfilling our inclusion and exclusion criteria.

Inclusion criteria: Age group: 18-50 yrs. Confirmed cases of T1DM diagnosed according to the 2023 American Diabetes Association standards of medical care [12].

Exclusion criteria: Age group: <18 or >50 years old. Other types of DM (DM type 2 & Gestational DM) and IGT. Inability or unwillingness to give informed content. Active malignancy. Active infection and/or active inflammatory processes. Other underling conditions that predispose to fatty liver or fibrosis.

The enrolled cases in this study were stratified into three groups based on FLI: High, intermediate, and low risk of steatosis. We subjected these three groups, especially the intermediate and high-risk groups to test using FIB-4 score, which is a validated non-invasive indicator of fibrosis, subsequently, FIB-4 results were contrasted with levels of Procollagen Type III, an inflammatory biomarker that has been shown to correlate positively with degree of fibrosis and is indicative of active fibrosis.

All cases included underwent a history taking process that encompassed sociodemographic details (Such as age, gender, education level, marital status, smoking habits, occupation, and whether they resided in an urban or rural area), duration of diabetes, level of control, type of treatment, and presence of chronic diabetic complications (Including neuropathy, nephropathy, and retinopathy).

The general examination included measuring body weight and height. Waist circumference was also measured. Additionally, both SBP and DBP were recorded. Chest, cardiac, and abdominal examinations were performed as well.

Laboratory investigations:

- Procollagen type III.
- FLI was calculated using the formula: FLI = [e(0.953 × ln(triglycerides) + 0.139 × BMI + 0.718 × ln(γGTP) + 0.053 × WC − 15.745)]/[1 + e(0.953 ×ln(triglycerides) +0.139 × BMI + 0.718 × ln(γGTP) + 0.053 × WC − 15.745)] × 100 [13].
- FIB-4 was calculated using the formula: FIB-4 = Age (years) × AST (U/L)/[PLT(109/L)×ALT1/2(U/L)] [14].

Ethical consideration: Ethical approval for the study protocol was obtained from IRB of the Faculty of Medicine, Mansoura University (Approval Code: MS.23.10.2566). Approval was obtained from the administrative authority of the hospital where the study was conducted. Participant confidentiality and personal privacy were upheld throughout all stages of research, and collected data were used exclusively for study purposes. The study adhered to the Helsinki Declaration throughout its execution.

Statistical analysis

Statistical analysis was conducted using SPSS software, version 22. Categorical variables were presented as frequencies and percentages. The Shapiro–Wilk test was employed to assess the normality of distribution for continuous variables. Data with normal distribution were expressed as mean ± SD, whereas non-normally distributed data were summarized as median and range. Statistical tests were selected based on the type and distribution of data, including Chi-square test for categorical variables, Student's t test, Mann-Whitney U test, paired t test, and Wilcoxon signed-rank test. Correlation analysis was also conducted. ROC curve analysis was employed to evaluate sensitivity, specificity, predictive values, and overall diagnostic accuracy. P ≤ was deemed as significant.

RESULTS

The study included 82 cases with a mean age of 30.2 ± 9.75 years, most were females (75.6%), non-working (72%), and urban residents (62.2%). Median diabetes duration was 13 years, and the majority were on basal-bolus insulin (81.3%). Diabetic complications included neuropathy (81.7%), nephropathy (15.9%), and retinopathy (28%). Mean BMI was 27.5 kg/m², and median FLI was 41, with 24.4% low, 47.6% intermediate, and 28% high risk. Median FIB-4 was 0.585, and Procollagen III was 496.95 (Table 1).

Table (1): Demographic characters, disease characters, laboratory findings and markers among studied cases

	N=82	%
Age / years	30.2±9.75 (18-50)	
Sex		
Male	20	24.4
Female	62	75.6
Occupation		
Not working	59	72.0
Working	23	28.0
Residence		
Rural	31	37.8
Urban	51	62.2
Special habits		
Non smokers	73	89.0
Smokers	9	11.0
Duration of DM (years)		
Median (range)	13(1-35)	
Mode of therapy		
Insulin ((Premixed)	15	18.3
Insulin (Basal bolus)	67	81.3
Neuropathy	67	81.7
Nephropathy	13	15.9
Retinopathy	23	28.0
BMI (Kg/m^2)	27.54±2.16	
Waist circumference (cm)	87.87±14.44	
DBP (mm/Hg)	74.14±9.68	
SBP(mm/Hg)	118.54±15.16	
Triglycerides (mg/dl)	141.5(50-452)	
GGT (U/L)	23.5(10-54)	
AST (U/ml)	21(8-216)	
ALT (U/ml)	19(9-196)	
Platelets	257.5(117-507)	
HBA1c	10.59±2.22	
Albumin/creatinine ratio	16.7(4-613)	
FLI		
Low (< 30)	20	24.4
Intermediate (30-60)	39	47.6
High (>60)	23	28.0
FIB-4	0.585 (0.16-3.69)	
Procollagen type III	496.95 (301.51-1482.3)	

A significant association was identified between higher FLI categories and older age, female sex, and longer duration of diabetes. Notably, all individuals classified within high-risk group were female. Additionally, the mode of therapy demonstrated a significant relationship with FLI risk stratification. Higher BMI, SBP and DBP were significantly associated with higher FLI risk. Neuropathy was more frequent in intermediate than low-risk FLI groups. Waist circumference, GGT, and triglycerides were excluded from comparative analysis since they are components of the FLI formula (Table 2).

Table (2): Relation between FLI and demographic and disease characters, clinical, laboratory findings and study markers of studied cases

	FLI			**Test of significance**	**Within group significance**
	Low N=20	Intermediate N=39	High N=23		
Age / years	23.55±6.18	29.23±7.84	37.61±10.56	F=15.63 P<0.001*	P1=0.016* P2=0.001* P3=0.001*
Sex Male Female	 5(25) 15(75)	 15(38.5) 24(61.5)	 0 23(100)	 MC=11.61 P=0.003*	P1= 0.30 P2= 0.01* P3=0.0006*
Occupation Not working Working	 15(75) 5(25)	 25(64.1) 14(35.9)	 19(82.6) 4(17.4)	 MC=2.58 P=0.276	P1= 0.396 P2= 0.541 P3=0.121
Residence Rural Urban	 7(35) 13(65)	 14(35.9) 25(64.1)	 10(43.5) 13(56.5)	 Mc=0.442 P=0.802	P1= 0.946 P2=0.571 P3=0.553
Special habits **Smokers**	1(5)	8(20.5)	0	Mc=7.19 P=0.027*	P1= 0.03* P2= 0.376 P3=0.019*
Duration of DM (years)	10(1-20)	13(1-30)	19(1-35)	KW=16.15 P=0.001*	P1=0.016* P2=0.001* P3=0.015*
<10 **≥10**	9(45) 11(55)	11(28.2) 28(71.8)	3(13) 20(87)	$\chi 2$=5.41 P=0.07	P1=0.197 P2=0.02* P3=0.168
Mode of therapy **Insulin** (Premixed) Insulin (Basal bolus)	 0 20(100)	 5(12.8) 34(87.2)	 10(43.5) 13(56.5)	 Mc=15.02 P=0.001*	P1=0.094 P2=0.001* P3=0.006*
Neuropathy	16(80)	34(87.2)	17(73.9)	MC=1.76 P=0.416	P1=0.468 P2=0.637 P3=0.187
Nephropathy	4(20)	7(17.9)	2(8.7)	MC=1.27 P=0.530	P1=0.848 P2=0.286 P3=0.318
Retinopathy	7(35)	11(28.2)	5(21.7)	MC=0.933 P=0.627	P1=0.592 P2=0.334 P3=0.574
Clinical findings					
BMI (Kg/m^2)	22.83±2.0	26.22±2.84	33.87±3.92	F=78.66 P<0.001*	P1=0.001* P2=0.001* P3=0.001*
DBP	67.50±6.38	74.10±9.38	80.0±9.05	F=11.16 P<0.001*	P1=0.007* P2=0.001* P3=0.01*
SBP	108.50±10.39	118.21±13.15	127.82±16.50	F=10.82 P<0.001*	P1=0.01* P2=0.001* P3=0.009*
Laboratory findings					
AST (U/ml)	18.5(10-84)	21(8-172)	27(11-216)	KW=3.32 P=0.190	P1=0.283 P2=0.05* P3=0.431
ALT (U/ml)	15(10-77)	20(9-173)	27(9-196)	KW=1.33 P=0.514	P1=0.340 P2=0.267 P3=0.867

	FLI			Test of significance	Within group significance
	Low N=20	Intermediate N=39	High N=23		
Platelets	268.5(117-482)	267(164-507)	247(161-446)	KW=0.599 P=0.741	P1=0.898 P2=0.706 P3=0.406
HBA1c	11.08±2.52	10.38±2.08	10.53±2.22	F=0.646 P=0.527	P1=0.264 P2=0.427 P3=0.804
Albumin Creatinine ratio	16.65(4-255)	15(4.9-613)	18(7.6-128)	Kw=1.01 P=0.602	P1=0.981 P2=0.465 P3=0.325
FIB-4	0.345(0.16-1.78)	0.560(0.25-2.07)	0.89(0.16-3.69)	KW=13.08 P=0.001*	P1=0.06 P2=0.002* P3=0.008*
Procollagen III	499.27 (337.78-1075.24)	503.48 (321.53-1097.63)	457.92 (301.51-1482.29)	KW=0.02 P=0.990	P1=0.860 P2=0.961 P3=0.988

Data expressed as mean ±SD, median (range), F: One Way ANOVA test, KW: Kruskal Wallis test, p1; difference between low versus intermediate, p2: difference between low versus high, p3: difference between intermediate versus high risk.

FIB-4 showed a substantial positive correlation with DM duration, BMI, blood pressure (both systolic and diastolic), and waist circumference (Table 3).

Table (3): Correlation between FIB-4 and demographic, clinical and laboratory findings (continuous variables).

	FIB-4	
	r	P
Duration of DM (years)	0.421	0.001*
BMI (Kg/m2)	0.356	0.001*
DBP	0.322	0.003*
SBP	0.356	0.001*
Waist circumference (cm)	0.341	0.002*
Triglycerides (mg/dl)	-0.035	0.753
GGT (U/L)	0.185	0.096
HBA1c	-0.044	0.694
Albumin Creatinine ratio	0.136	0.225

rs: Spearman correlation coefficient**,** *statistically significant

Higher median FIB-4 values were found among cases using premixed insulin and those with retinopathy, showing significant associations (Table 4).

Table (4): Correlation between FIB-4 and demographic, clinical and laboratory findings (categorical variables)

	FIB-4	**Test of significance**
	Median (min-max)	
Sex		
Male	0.615(0.2-2.07)	Z=0.103
Female	0.575(0.16-3.69)	P=0.918
Occupation		
Not working	0.58(0.16-3.69)	Z=0.093
Working	0.59(0.2-2.07)	P=0.926
Residence		
Rural	0.67(0.16-2.34)	Z=0.803
Urban	0.58(0.16-3.69)	P=0.422
Special habits		
Non smoker	0.57(0.16-3.69)	Z=0.994
Smokers	0.77(0.20-2.07)	P=0.320
Mode of therapy		
Insulin ((Premixed)	1.07(0.38-3.69)	Z=3.52
Insulin (Basal bolus)	0.52(0.16-2.2)	P=0.001*
Neuropathy		
-ve	0.58(0.2-1.78)	Z=0.516
+ve	0.59(0.16-3.69)	P=0.606
Nephropathy		
-ve	0.585(0.16-3.69)	Z=0.419
+ve	0.66(0.26-2.11)	P=0.675
Retinopathy		
-ve	0.565(0.16-3.69)	Z=2.08
+ve	0.755(0.32-2.2)	P=0.037*

Z: Mann Whitney U test, KW: Kruskal Wallis test, *statistically significant

Procollagen III levels positively correlated with age, AST, and ALT, but not with other clinical or demographic factors (Table 5).

Table (5): Correlation between Procollagen type III and demographic, clinical and laboratory findings (continuous variables).

	Procollagen III	
	r	P
Age / years	0.266	0.016*
Duration of DM (years)	0.201	0.071
BMI (Kg/m2)	0.061	0.584
DBP	0.151	0.175
SBP	0.163	0.144
Waist circumference(cm)	-0.124	0.266
Triglycerides (mg/dl)	0.048	0.667
GGT (U/L)	0.083	0.458
AST (U/ml)	0.382	0.001*
ALT (U/ml)	0.341	0.002*
Platelets	-0.209	0.059
HBA1c	0.153	0.170
albumin Creatinine ratio	-0.037	0.740

rs: Spearman correlation coefficient, *statistically significant

No significant correlation was observed between procollagen III levels and any of the categorical variables assessed, including gender, occupation, and presence of complications **(Table 6).**

Table (6): Correlation between Procollagen type III and demographic, clinical and laboratory findings (categorical variables).

	Procollagen III	**Test of significance**
	Median (min-max)	
Sex		
Male	513.92(321.53-1097.64)	Z=1.17
Female	481.42(301.51-1482.3)	P=0.241
Occupation		
Not working	494.77(301.51-1482.3)	Z=0.134
Working	499.12(321.53-1290.41)	P=0.893
Residence		
Rural	457.92(301.51-1310.91)	Z=1.62
Urban	508.42(321.53-1482.3)	P=0.105
Special habits		
Non smoker	482.01(301.51-1482.3)	Z=1.363
Smokers	516.83(432.97-1097.64)	P=0.172
Mode of therapy		
Insulin ((Premixed)	521.76(305.28-1482.3)	Z=1.4
Insulin (Basal bolus)	483.46(301.51-1290.41)	P=0.161
Neuropathy		
-ve	482.01(301.51-1075.24)	Z=0.888
+ve	503.48(305.28-1482.3)	P=0.375
Nephropathy		
-ve	506.67(301.51-1482.3)	Z=0.900
+ve	457.63(365.93-1110.97)	P=0.368
Retinopathy		
-ve	496.95(301.51-1482.3)	Z=0.474
+ve	497.68(321.53-1290.41)	P=0.636

z: Mann Whitney U test, KW: Kruskal Wallis test.

Finally, a significant positive correlation was observed between FIB-4 and both FLI and procollagen III, while no correlation was found between FLI and procollagen III **(Table 7).**

Table (7): Agreement between studied markers

	Procollagen III	**FBI**	**FLI**
Procollagen III	1.0		
FBI	r=0.497 p=0.001*	1.0	
FLI	r=0.022 p=0.842	r=0.390 p=0.001*	1.0

r: Spearman correlation coefficient, *statistically significant.

DISCUSSION

MAFLD encompasses hepatic steatosis and may progress to more severe manifestations such as steatohepatitis and fibrosis. Its development is driven by an adverse metabolic environment, primarily characterized by overweight or obesity, and is closely linked to disruptions in glucose regulation and lipid metabolism[15]. In 2023, a multisociety Delphi consensus recommended renaming NAFLD to MASLD. This change aims to better reflect the underlying metabolic dysfunction and to reduce stigma associated with the term "nonalcoholic." The new nomenclature encompasses individuals with hepatic steatosis who have at least one of five cardiometabolic risk factors, providing a more accurate and inclusive framework for diagnosis and research [16]. Numerous biomarkers have been investigated for their potential to predict presence of NASH in NAFLD cases, as well as to evaluate the extent of fibrosis in cases diagnosed with NASH. Although liver biopsy remains the definitive, yet invasive, method for diagnosing MAFLD, several non-invasive modalities demonstrating satisfactory concordance with histopathological findings have recently been validated [17].

This study aimed to screen MAFLD in people with T1DM using non-invasive scoring systems and the amino terminal pro peptide of procollagen type III. This cross-sectional study conducted at Mansoura Specialized Medical Hospital over six months, included 82 cases with T1DM.

The findings indicated that cases had a mean age of 30.2 ± 9.75 years, with ages ranging from 18 to 50 years. Females constituted 75.6% of the cohort, 72% were unemployed, 62.2% resided in urban areas, and 11% reported being smokers. Median disease duration was 13 years ranging from 1 to 35 years. Mode of therapy; 18.3% Insulin (Premixed) and 81.3% were Insulin (Basal bolus). Among studied cases; 81.7% neuropathy**,** 15.9% nephropathy and 28% retinopathy**.** Mean BMI was 27.54±2.16 Kg/m^2, mean waist circumference was 87.87±14.44 cm**,** mean DBP is 74.14±9.68**,** mean SBP is 118.54±15.16 mmHg, median triglycerides was 141.5 ranging from 50 to 452 mg/dl**,** median GGT was 23.5 ranging from 10 to 54 U/L**,**

median AST was 21 ranging from 8 to 216 U/L**,** median ALT was 19 ranging from 9 to 196 U/L**,** median platelets was 257.5 10^3/l ranging from 117 to 507 10^3/l and HBA1c was 10.59±2.22 gm/dl. Median albumin/ creatinine ratio is 16.7 ranging from 4 to 613.

Tang *et al*. [18] reported that individuals with T2DM and coexisting MAFLD exhibited more significant hepatic biochemical disturbances, including increased levels of ALT, AST, GGT, and total cholesterol, along with decreased HDL cholesterol. These liver function enzymes—particularly ALT, AST, and GGT—are well-recognized markers of hepatic integrity, as consistently demonstrated in earlier research. In a study by **Kang *et al*.** [19] participants were stratified based on absence or presence of advanced fibrosis. Those with advanced fibrosis were generally older and exhibited a higher prevalence of DM and hypertension compared to those without fibrosis. However, other metabolic parameters—including blood pressure, diabetes status, obesity, and dyslipidemia—did not differ markedly between two groups. Notably, among liver function markers, only AST levels were significantly elevated in advanced fibrosis group relative to non-advanced group. In contrast, **Abdelkhalik *et al*.** [20] reported that the majority of participants were single (91.1%) and predominantly smokers, with only 32% identified as non-smokers. Approximately one-third of the cohort was affected by metabolic disorders, including T2DM.

According to descriptive statistics of studied marker among studied cases, the current study revealed that median FLI was 41 ranging from 4 to 99 that was classified as; 24.4% low, 47.6% were intermediate and 28% were high. Median FIB4 was 0.585 ranging from 0.16 to 3.69. Median procollagen type III was 496.95 ranging from 301.51 to 1482.3. **Miele *et al*.** [21] identified that 4.83% of individuals with T1DM were clinically diagnosed with MAFLD. Statistical analysis revealed that T1DM-MAFLD group exhibited more advanced disease severity, as indicated by higher FIB-4 scores, compared to their non-T1DM MAFLD counterparts. **Srivastava *et al*.** [22] demonstrated that incorporating FIB-4 index in cases with indeterminate findings among NAFLD cases enhanced the detection of advanced fibrosis while concurrently decreasing rate of unnecessary specialist referrals.

The present study demonstrated relation between FLI and demographic characters of studied cases, there was a substantial positive correlation between risk of steatosis and the following risk factors; older age and female sex. Mean age of studied cases was 23.55±6.18 for cases with low FLI, 29.23±7.84 for intermediate and 37.61±10.56 for high-risk group. All cases in high-risk group were females, 61.5% of intermediate risk group and 75% of low-risk group were females. **Nivukoski *et al*.** [23] investigated the independent and combined effects of lifestyle-related risk factors on FLI, a biomarker indicative of hepatic steatosis, within the context of a population-based cross-sectional national health survey. It was noted that individuals with higher risk scores tended to have greater exposure to cigarette smoking and lower levels of physical activity. In males, a quadratic association emerged between age and lifestyle risk score categories, with mean age peaking in intermediate-risk group ($p < 0.01$). Conversely, in females, a significant linear relationship was identified, with age progressively increasing across ascending risk categories ($p < 0.0005$). Furthermore, smoking status demonstrated a significant linear association with rising risk scores in both genders ($p < 0.0005$). As well, **Chen *et al*.** [24] revealed the association between smoking and an increased FLI. A study based on data from NHANES identified a positive association between serum cotinine concentrations—a validated biomarker of tobacco exposure—and FLI scores. Individuals with higher cotinine levels, indicative of active smoking, exhibited higher FLI values compared to non-smokers and passive smokers. This suggests that both active and passive smoking may contribute to liver fat accumulation, as reflected by elevated FLI scores.

The current study demonstrated the relation between FLI and disease characters of studied cases. Statistically significant higher median disease duration was detected among cases with high risk followed by intermediate and the lowest for cases with low risk (19, 13, & 10, respectively). Mode of therapy demonstrated statistically significant association with FLI classifying risk for steatosis. Among cases with high-risk group; 56.5% were on insulin (basal bolus). Among intermediate risk group; 87.2% were on insulin (basal bolus) and 100% of cases with low risk had Insulin (Basal bolus) with statistically significant association. A statistically significant difference was detected between low and intermediate risk FLI as regard incidence of neuropathy. **Higashiura *et al*.** [25] investigated the association between FLI and incidence of newly diagnosed DM, demonstrating that elevated FLI levels are predictive of DM onset in the general population, irrespective of sex. Additionally, they reported a statistically significant relationship between FLI risk categories and the duration of diabetes.

There was substantial variation between FLI and duration of DM can be explained by the progressive nature of metabolic dysfunction in long-standing diabetes. Over time, chronic hyperglycemia and insulin resistance in people with diabetes lead to increased fat deposition in liver [26]. Prolonged exposure to high blood sugar levels disrupted normal lipid metabolism, causing excess fat to accumulate in liver cells. Additionally, as diabetes persists, there was often worsening insulin resistance and more pronounced MS features such as elevated triglycerides and increased BMI both key components of FLI formula. Therefore, the longer a person has diabetes, the greater the cumulative metabolic burden on the liver, which results in a higher risk of developing NAFLD and a correspondingly higher FLI score. Furthermore, **Movahedian *et al*.** [27] found a dose-response relationship between FLI levels and the incidence of diabetes, indicating that higher FLI

scores are associated with a greater risk of developing diabetes.

In the present study, the relations between FLI and clinical and laboratory findings among studied cases showed statistically significant relation between FLI and the following; BMI ($p<0.001$), DBP ($p<0.001$), SBP ($p<0.001$). FLI was calculated using waist circumference, BMI, and serum concentrations of TGs and GGT. It demonstrated robust diagnostic performance in identifying hepatic steatosis [9]. **Piazzolla** & **Mangia** [28] discussed the potential of emerging biomarkers as early diagnostic tools for the identification of NAFLD. They highlighted the availability of commercial panels incorporating specialized parameters—such as serum levels of total bilirubin, GGT, haptoglobin, ALT, alpha-2-macroglobulin, and apolipoprotein A1—alongside BMI and serum concentrations of TC, TGs, and glucose, adjusted for sex and age, to predict hepatic steatosis. Although these fatty liver indices offer moderate diagnostic accuracy and may function as surrogate markers for hepatic fat accumulation, imaging modalities have exhibited superior performance and reliability in the assessment of liver steatosis.

This study showed correlations between FIB-4 and demographic, clinical and laboratory findings (continuous variables). It demonstrated statistically notable positive correlation between FIB-4 and duration of DM, BMI, DBP, SBP and waist circumference with p value <0.05. **Boursier *et al***. [29] found that FIB-4 was a good marker in assessment of fibrosis, had its accuracy clearly reduced in cases with BMI above 28, which corresponds to a significant percentage of cases with NAFLD. There was a statistically notable positive correlation between FIB-4 and BMI. Also, According to **Tomah *et al***. [30] cases with overweight and obesity exhibited a markedly elevated risk of developing hepatic steatosis ($p < 0.0001$), with obesity emerging as the most influential determinant in condition progression.

According to correlations between FIB-4 and demographic, clinical and laboratory findings (categorical variables), this study demonstrated that higher median FIB-4 was detected among insulin (Premixed) than insulin (Basal bolus) with statistically significant association. Higher median FIB-4 was detected among retinopathy than without with statistically significant association ($p=0.037$). A strong association was observed between liver fibrosis and presence of retinopathy. Prior studies have indicated that individuals with NAFLD are at an increased risk of developing retinopathy [31].

Li *et al*. [32] identified retinopathy as a valuable predictor of advanced hepatic fibrosis, particularly among individuals with diabetes. This association may be mediated by hepatic X receptors, which play key roles in regulating inflammation, as well as glucose and lipid metabolism (Courtney & Landreth, 2016).

Our analysis demonstrated a substantial relation between FIB-4 and an increased risk of retinal abnormalities, particularly among individuals with advanced stages of fibrosis. These findings align with a meta-analysis by **Zhang *et al.*** [33] which reported a positive correlation between liver fibrosis and retinopathy, suggesting that presence of retinopathy may serve as an indicator of fibrosis severity in liver.

Concerning correlations between procollagen type III and demographic, clinical and laboratory findings (continuous variables), our study demonstrated that there was statistically significant positive correlation between procollagen III and age, AST and ALT with p value <0.05. Also, **Ahmed *et al***. [34] assessed the diagnostic performance of PIIINP in cases with NAFLD and NASH. The study reported that PIIINP levels were markedly higher in NASH cases relative to NAFLD cases, and positively correlated with AST and ALT levels, with p-values <0.05. These findings further support role of PIIINP as a biomarker for liver fibrosis and inflammation, and its association with liver enzyme levels.

Concerning correlation between procollagen type III and demographic, clinical and laboratory findings (categorical variables), our findings revealed that non-statistically significant correlation was detected between procollagen III and all studied demographic, clinical and laboratory findings among studied cases. Correlation between studied markers, showed statistically notable relation between FLI and FIB-4 ($p<0.001$) while there was no substantial relation between FLI and procollagen III with P value=0.990. This study showed that there was a relation between FLI and FIB-4 because both FLI and FIB-4 are liver-related indices. FLI estimates liver fat, while FIB-4 estimates liver fibrosis. As liver steatosis progresses, fibrosis can follow, hence the correlation. While there was no substantial relation between FLI and procollagen III because procollagen III may reflect active fibrogenesis (collagen production) rather than fat accumulation and study population may have early-stage NAFLD where procollagen III was not elevated. High variability or small sample size can obscure weak associations. **Iwasaki *et al***. [35] investigated the associations between the FLI and FIB-4 score with cardiovascular risk markers in Japanese men without any history of cardiovascular disease, compared how these two liver scoring systems relate to pathophysiological abnormalities associated with cardiovascular risk. They reported that there was statistically notable relation between FLI and FIB-4 with p value <0.001.

This study showed agreement between studied markers, there was statistically notable positive correlation between FIB-4 and procollagen III ($r=0.497$) and between FIB-4 and FLI ($r=0.390$). **Iwasaki *et al***. [35] assessed the correlation between FLI and FIB-4 score in a cohort of Japanese men without a history of cardiovascular disease. The results revealed a

significant positive correlation between FLI and FIB-4, suggesting a relationship between hepatic steatosis and fibrosis severity.

LIMITATIONS

This study had several limitations. Its cross-sectional design limited the ability to establish causality or track long-term progression of MAFLD in type 1 diabetes. The small sample size and single-center setting reduce results generalizability. The study lacked follow-up data to assess long-term outcomes. Finally, the severity of fatty liver was not evaluated, limiting clinical insights. These limitations suggest the need for larger, multi-center, and longitudinal studies to confirm the findings.

CONCLUSION

The FLI was a valid and reliable tool in detecting hepatic steatosis. The FIB-4 score also demonstrated capability of identifying advanced fibrosis without the need for invasive procedures, offering valuable clinical insight into fibrotic progression. However, procollagen type III in this context appeared limited.

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