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Assessment of Hepatobiliary Status and Cardiometabolic Risk Markers among Type 2 Diabetes Mellitus Patients. A Cross-Sectional Study

ABSTRACT

Objective: Previous studies have shown a higher prevalence of non-alcoholic fatty liver disease (NAFLD) among patients with type 2 diabetes mellitus (T2DM), and NAFLD itself is a risk factor for cardiovascular diseases (CVD). With both NAFLD and T2DM, there is a vicious circle of disease worsening, with one disease aggravating the development and progression of the other, thereby predisposing to early CVD events. Hence, we aimed to study the association between hepatobiliary status and cardiometabolic risk among T2DM patients.

Material and methods: Eighty two patients with T2DM without any established liver and cardiac disease were recruited for the study. Routine biochemical parameters were measured by an autoanalyzer. Parameters such as triglyceride glucose index (TyG index), lipid pentad index, fatty liver disease index (FLDI) etc. were calculated using the established formulas. HbA1c was estimated using Biorad D10 autoanalyzer. Apolipoprotein B (Apo-B), Apo-A, lipoprotein (a) [Lp(a)], insulin, C-peptide were analyzed using ELISA.

Results: Significant positive correlation was seen between cardiometabolic risk biomarkers and hepatobiliary biomarkers and significant negative correlation with total bilirubin and De-Ritis ratio. Through stepwise regression, FLDI was found to be a significant factor in the prediction of lipid pentad index (LPI). LPI, TyG index, FLDI were able to differentiate patients with T2DM based on the gold standard HbA1c values for T2DM diagnosis.

Conclusions: Increase in hepatobiliary dysfunction contributes to increased CVD risk in T2DM patients. This study highlights the need for collaborative actions of diabetologists and hepatologists in identifying the people with NAFLD among T2DM patients, who should be targeted with intensive therapy to decrease their risk of future CVD events. (Clin Diabetol 2022, 11; 6: 393–400)

Keywords: type 2 diabetes mellitus, non-alcoholic fatty liver disease, cardiometabolic risk, lipid pentad index, lipid tetrad index, fatty liver disease index

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Introduction

Diabetes is a chronic disease manifested as hyperglycemia due to defects in insulin production, insulin function, or both [1]. India is the diabetes metropolis of the world with more than 73 million patients with diabetes mellitus (DM). The figure is likely to be 134 million by 2045 [2] and now it is heading to lead in

cardiovascular diseases (CVD) also because both share several common risk factors. Nonetheless, worldwide escalation in the prevalence of metabolic diseases like non-alcoholic fatty liver disease (NAFLD), type 2 diabetes mellitus (T2DM), and obesity, which are known risk factors for CVD, has been observed.

Insulin resistance (IR) is the underlying pathophysiological cause in the blossoming of DM [3]. IR causes peripheral lipolysis and thus enhances *de novo* lipogenesis (DNL). Increased lipolysis leads to elevated levels of circulating free fatty acids (FFA) which leads to hepatic non-esterified fatty acids (NEFA) uptake and DNL, altogether causing hepatic fat accumulation which presents as NAFLD [4, 5].

The prevalence of NAFLD among T2DM patients is around 69% (with USG) or 87% (with MRI or biopsy) [6]. NAFLD develops when the pace of hepatic triglyceride (TG) anabolism, owing to enhanced NEFA uptake and DNL, trumps the pace of hepatic TG catabolism because of NEFA oxidation and TG export as very low-density lipoprotein (VLDL) particles [7]. Patients with T2DM and NAFLD are at higher risk of the development of CVD as the risk factors like metabolic syndrome, DM, hypercholesterolemia, and obesity are shared. With both NAFLD and T2DM, there is a vicious cycle of worsening disease, with the existence of either disease aggravating the development and progression of the other, thereby predisposing to the early CVD events [8]. In such patients, elevated TG levels and decreased HDL-C levels have been witnessed, which bespeaks atherogenic dyslipidemia, thereby accelerating the process of atherosclerosis. IR, which leads to hyperglycemia, hepatobiliary dysfunction, and dyslipidemia can alter the lipid profile. These changes along with impaired insulin signaling lead to atherosclerotic plaque in the endothelium.

To the best of our knowledge, only traditional lipid and liver markers were assessed in diabetes patients to find an association between liver dysfunction and CVD risk in the Indian scenario. Though there are some reports of increased levels of comprehensive lipid tetrad index (CLTI) and lipid pentad index (LPI) in patients with diabetes and CVD, the reports on the status of these markers in assessing the association of hepatobiliary dysfunction and cardiometabolic risk among patients with diabetes are scanty. Since previous studies have studied NAFLD, CVD risk, and diabetes individually, our study was planned to study them together as they share complex metabolic links. Therefore, the objective of this study was to assess IR by using surrogate markers of IR such as homeostatic model assessment for insulin resistance (HOMA-IR), quantitative insulin sensitivity check index (QUICKI), TyG index, and hepatobiliary status [De-Ritis ratio, ALP, gamma-glutamyl transferase (GGT), fatty liver disease index (FLDI), hepatic steatosis index (HSI), fatty liver index (FLI)] and find their association with cardiometabolic risk biomarkers (LPI, CLTI, modified lipid tetrad index (MLTI), atherogenic index of plasma (AIP), triglyceride glucose index (TyG index)] in T2DM patients.

Materials and methods

Study participants

The study was conducted in the Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Pondicherry from January 2020 to February 2021. Approvals of the Institute Research Council and Institute Human Ethics Committee were obtained (JIP/IEC/2019/388 dated 11/12/2019). All procedures followed were by ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Patients with confirmed T2DM on oral hypoglycemic drugs and free from liver and heart diseases were recruited based on current criteria of the American Diabetes Association, 2012. T2DM patients with viral hepatitis, any form of jaundice, established fatty liver (grade I or II) upon ultrasound or fibroscan and age group below 30 years and above 60 years were excluded from the study. In addition, patients on lipid-lowering therapy, on insulin therapy, with neuropathic, retinopathic, and nephropathic complications, and chronic alcoholics were excluded.

Sample size calculation

The sample size was estimated using the formula for testing one correlation coefficient. The anticipated correlation coefficient between hepatobiliary status, IR, and cardiometabolic risk factors among T2DM patients was 0.35. The sample size was estimated to be 82 at 5% level of significance and 90% power.

Clinical and biochemical parameters

The study protocol was explained to the diabetes patients in their vernacular and written informed consent was obtained from all the participants before the recording of the study parameters. Personal, family and medical histories were recorded from all the participants. Anthropometric parameters such as height, weight, waist circumference were measured by the same observer. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (meter). Blood samples (5 mL) were collected from all the study participant's antecubital veins under strict aseptic conditions. Serum was separated by centrifugation at 3500 rpm for 10 minutes at room temperature. The collected serum was made into aliquots and one of the aliquots was sent for estimating the fasting blood glucose, li-

pid profile (HDL, LDL, VLDL, total cholesterol, TG,) and liver function tests (AST, ALT, ALP, GGT, bilirubin) using the clinical chemistry autoanalyzer (Beckman Coulter Au5800, Orlando, FL, USA). The rest of the aliquots were stored at –40°C for further analysis.

Serum Apolipoprotein B, apolipoprotein A1, and lipoprotein (a) were analyzed by ELISA kit (Elabscience Biotechnology, Houston TX, USA) following manufacturer's instructions. Serum insulin and C-peptide were analyzed by ELISA kit (Calbiotech Inc., El Cajon, CA, USA) following the manufacturer's instructions.

HbA1c was estimated using Biorad D10 autoanalyzer which works on the principle of ion-exchange high-performance liquid chromatography.

HOMA-IR, QUICKI, TyG index, AIP, FLDI, HSI, FLI, CLTI, MLTI, LPI were calculated using the established formulas [9–18].

Statistical analysis

Statistical analysis was performed using IBM SPSS statistics version 19. Both descriptive and inferential statistics were used to analyze the data. Baseline characteristics of the patients with DM were analyzed by descriptive statistics. The normality of continuous data (routine biochemical parameters, special parameters) was assessed by the Kolmogorov-Smirnov test. The normally distributed data were described by mean ± standard deviation, and median and inter-quartile range (IQR) were used for non-Gaussian data. Correlation between hepatobiliary status and cardiometabolic risk biomarkers was done by Pearson or Spearman rank correlation test, as appropriate. Analysis was carried out at 5% level of significance and $p < 0.05$ was considered as statistically significant.

Results

Baseline clinical characteristics and biochemical measurements

Eighty-two (82) T2DM patients conforming to the inclusion and exclusion criteria were recruited in the study. Out of 82 patients, 43 (52.4%) were males and 39 (47.5%) were females. The mean age of study participants was 51.15 ± 6.25 years. The BMI was 24.93 ± 2.23 and the waist circumference was 93.10 ± 7.42. Waist circumference showed higher correlation than BMI which is suggestive of that the abdominal obesity is a better predictor of diabetes than BMI which is a marker of general obesity. There was no statistically significant correlation of age with primary outcome parameters. Descriptive statistics of the parameters of glucose homeostasis, hepatobiliary biomarkers, and cardiometabolic biomarkers of the study participants are shown in Table 1.

Table 1. Parameters of Glucose Homeostasis, Hepatobiliary Biomarkers and Cardiometabolic Biomarkers of the Study Participants

Parameter	N	Mean ± SD/Median (IQR)
Glucose [mg/dL]	82	167.5 (143.5–211.3)
HbA1c [%]	82	9.22 ± 1.75
De-Ritis ratio (AST/ALT)	82	0.95 (0.835–1.115)
GGT [IU/L]	82	47.5 (27–79.25)
Total bilirubin [mg/dL]	82	0.68 ± 0.15
Fatty liver index (FLI)	79	55.24 ± 23.9
Fatty liver disease index (FLDI) [mg/dL]	82	220 (167.1–312.4)
Hepatic steatosis index (HSI)	81	36.4 ± 3.5
Total cholesterol [mg/dL]	82	183.5 (163.5–212)
HDL-C [mg/dL]	82	42 (38–49)
LDL-C [mg/dL]	82	131.87 ± 38.2
Triglycerides (TAG) [mg/dL]	82	188 (134–275.3)
Non-HDL [mg/dL]	82	144.56 ± 38.5
Atherogenic index of plasma (AIP)	82	0.647 ± 0.255
Triglyceride–Glucose (TyG) index [mg/dL]	82	9.73 ± 0.62
Lipoprotein (a) [mg/dL]	82	14.91 (10.79–22.22)
Apolipoprotein A [mg/dL]	80	150.79 ± 15.34
Apolipoprotein B [mg/dL]	82	119.71 ± 49.76
Comprehensive lipid tetrad index (CLTI)	82	10904 (5545–25959)
Modified lipid tetrad index (MLTI)	82	7913 (3583–21879)
Lipid pentad index (LPI)	80	427980 (174456–785665)

ALT — alanine transaminase; AST — aspartate transaminase; GGT — gamma glutamyl transferase; HDL — high-density lipoprotein; LDL — low-density lipoprotein; SD — standard deviation

Correlation between cardiometabolic risk biomarkers and hepatobiliary dysfunction markers

Cardiometabolic risk biomarkers (LPI, CLTI, MLTI, AIP, TyG index) showed a significant positive correlation with hepatobiliary dysfunction markers (FLDI, GGT, FLI, HSI) and a significant negative correlation with total bilirubin and De-Ritis ratio as shown in Table 2.

Comparison of cardiometabolic risk markers in groups

The median levels of LPI were significantly higher in the group having FLDI > 32 compared to the group having FLDI < 32 (653103.8 vs. 227724.3, $p < 0.0001$). The median levels of CLTI were significantly higher in

Table 2. Correlation between Cardiometabolic Risk Biomarkers and Hepatobiliary Status Biomarkers of the Study Participants

	AIP	TyG index	CLTI	MLTI	LPI
FLDI	0.960*	0.971*	0.852*	0.857*	0.760*
GGT [IU/L]	0.773*	0.816*	0.747*	0.757*	0.717*
FLI	0.763*	0.811*	0.685*	0.691*	0.631*
HSI	0.326*	0.362*	0.278*	0.280*	0.281*
De-Ritis ratio	–0.289*	–0.320*	–0.262*	–0.259*	–0.266*
Total bilirubin [mg/dL]	–0.761*	–0.820*	–0.756*	–0.770*	–0.711*

*P-value of < 0.05
AIP — atherogenic index of plasma; CLTI — comprehensive lipid tetrad index; FLDI — fatty liver disease index; FLI — fatty liver index; GGT — gamma glutamyl transferase; HSI — hepatic steatosis index; LPI — lipid pentad index; MLTI — modified lipid tetrad index; TyG — triglyceride–glucose

Table 3. Comparison of Cardiometabolic Risk Markers between People Having Normal and High FLDI Levels

Parameters	Group with FLDI < 32 (n = 35) Median (Q1–Q3)	Group with FLDI > 32 (n = 47) Median (Q1–Q3)	P-value
LPI	227724.3 (145153.1–466055.6)	653103.8 (300131.1–1249597.3)	< 0.0001*
CLTI	7371.7 (3836.1–12799.2)	20941.6 (7532.9–57587.6)	< 0.0001*
MLTI	5592.3 (2355.0–9098.2)	16679.5 (5733.8–43941.3)	< 0.0001*
TyG index	9.34 (9.04–9.73)	9.93 (9.465–10.6)	< 0.0001*

*The comparisons were carried out by Mann-Whitney "U" test; *P-value of < 0.05. TAG was converted to mmol/L for comparison
CLTI — comprehensive lipid tetrad index; FLDI — fatty liver disease index; LPI — lipid pentad index; MLTI — modified lipid tetrad index; TyG — triglyceride–glucose

the group having FLDI > 32 compared to the group having FLDI < 32 (20941.6 vs. 7371.7, p < 0.0001). The median levels of MLTI were significantly higher in the group having FLDI > 32 compared to the group having FLDI < 32 (16679.5 vs. 5592.3, p < 0.0001). The median levels of TyG index were significantly higher in the group having FLDI > 32 compared to the group having FLDI < 32 (9.93 vs. 9.34, p < 0.0001) (Tab. 3).

Diagnostic performance of various cardiometabolic risk markers and hepatobiliary status markers

The MLTI, CLTI, TyG index, AIP, LPI, FLDI were found useful in the differentiation of DM patients with HbA1c with > 9 and < 9. Among the cardiac parameters, MLTI was found to be most useful with an AUC of 0.90 (0.96–0.83). Utilizing the ROC curve for the value of MLTI, it was seen that the differentiation of T2DM patients with HbA1c > 9 and < 9 was seen at MLTI levels of more than 6317 (sensitivity of 85.7% and specificity of 81%, p < 0.001). Among hepatobiliary markers, FLDI was found to be most useful with an AUC of 0.81 (0.90–0.72). Utilizing the ROC curve for the value of FLDI, it was seen that the differentiation of T2DM patients with HbA1c > 9 and < 9 was seen at FLDI levels of more than 207 (sensitivity of 71.4% and specificity of 71%, p < 0.001) (Tab. 4, Fig. 1).

Discussion

The underlying pathophysiology seen in T2DM is insulin resistance. When insulin resistance sets in, the increased lipolysis of stored TG in adipose tissue leads to high levels of circulating fatty acids, which leads to hepatic non-esterified fatty acid uptake (NEFA), and *de novo* lipogenesis (DNL) causing non-alcoholic fatty liver disease [5]. The clinical troubles of NAFLD are not only due to liver abnormalities but also the development of DM, CVD, CKD. The risk of CVD in NAFLD patients deserves attention as the number of NAFLD patients is increasing which adds to the already considerable burden of CVD due to other causes prevailing in the society. NAFLD is associated with IR, atherogenic dyslipidemia, dysglycemia, and obesity, which are all established risk factors for CVD. In NAFLD patients,

Table 4. Diagnostic Performance of Various Cardiometabolic Risk Markers and Hepatobiliary Status Markers to Differentiate Diabetes Patients with HbA1c with > 9 and < 9

Parameter	AUC	95% confidence interval (UB-LB)	Cut off	P-value	Sensitivity (%)	Specificity (%)
MLTI	0.90	(0.96–0.83)	> 6317	< 0.001*	85.7	81
CLTI	0.89	(0.96–0.82)	> 8301	< 0.001*	85	78
TyG index	0.86	(0.94–0.79)	> 9.42	< 0.001*	81.6	71
AIP	0.85	(0.93–0.76)	> 0.54	< 0.001*	81.6	71
LPI	0.84	(0.92–0.75)	> 383743	< 0.001*	77.6	78
FLDI	0.81	(0.90–0.72)	> 207	< 0.001*	71.4	71
Apo-B/Apo-A	0.46	(0.60–0.33)	> 0.75	0.639	55	49
De-Ritis ratio	0.39	(0.50–0.25)	> 0.94	0.072	40.8	33

*P-value of < 0.05

AIP — atherogenic index of plasma; Apo-A/B — apolipoprotein A/B; AUC — area under the curve; CLTI — comprehensive lipid tetrad index; FLDI — fatty liver disease index; LB — lower bound; LPI — lipid pentad index; MLTI — modified lipid tetrad index; TyG — triglyceride–glucose; UB — upper bound

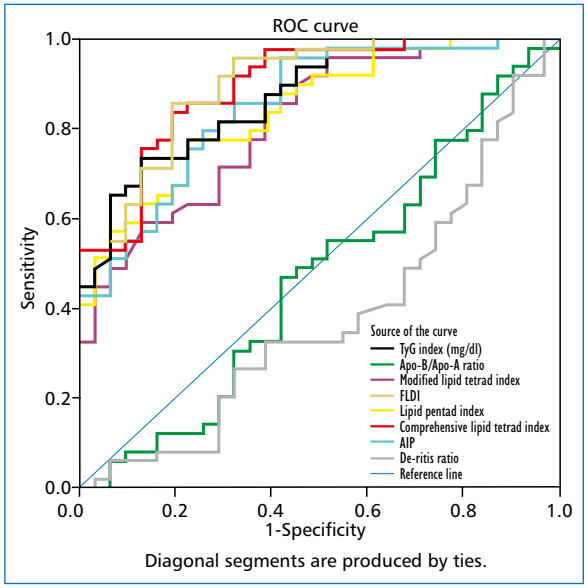

Figure 1. ROC Curve for MLTI, CLTI, TyG Index, AIP, LPI, FLDI, Apo-A/Apo-B, De-Ritis Ratio for Discriminatory Abilities towards Diabetes Patients with HbA1c > 9 and < 9
AIP — atherogenic index of plasma; CLTI — comprehensive lipid tetrad index; FLDI — fatty liver disease index; LPI — lipid pentad index; MLTI — modified lipid tetrad index; TyG — triglyceride–glucose

hepatic VLDL secretion goes unabated [19], which is the root cause of atherogenic dyslipidemia in IR, leading to hypertriglyceridemia, low HDL-cholesterol levels, and high small dense low-density lipoprotein (sdLDL)--cholesterol particles. sdLDL is an apolipoprotein B-rich molecule that promotes atherosclerosis. NAFLD is an independent factor for the establishment of CVD but when evaluating NAFLD patients we must not forget that NAFLD is a liver manifestation of IR, which means that these patients have additional cardiometabolic risk due toT2DM.

In our study, the BMI of the participants was 24.9 which is within the range of the overweight (23–24.9 kg/ /m^2) group, as per the Asia-Pacific body mass index classification [20]. Both BMI and waist circumference showed a significant positive correlation with HbA1c, TyG index, LPI, MLTI, CLTI, GGT, FLDI, FLI, HSI, HOMA1-IR, and significant negative correlation with total bilirubin and QUICKI. However, Waist circumference showed a higher correlation than BMI which is suggestive that abdominal obesity is a better predictor of diabetes than BMI which is a marker of general obesity. Consistent with our results, Bhuiyan et al., 2008; Lin et al., 2009; Takei et al., 2019, reported that bilirubin is inversely correlated with abdominal obesity [21–23]. Also, there was no statistically significant correlation of age with primary outcome parameters. Therefore, age can be considered to have minimal/no effect on the same.

In the comparison of the mean values of the parameters [LPI, CLTI, MLTI, TyG index, Lp(a)] between our study and the previous study comprising of a healthy group and a group of patients with diabetes and CVD, done in the Indian population, our results lie between the mean values of the above 2 groups [24, 25]. Since in our study, we excluded patients having clinically established cardiac problems, these findings suggest that there is an increasing trend in these parameters from healthy controls to patients with diabetes and CVD. The inclusion of apolipoproteins, Lp(a), and non-HDL--cholesterol in NCEP ATP-III guidelines [26] increased the need to update existing lipid indices. Thus, based on the conventional lipid profile and the emerging risk factors such as apo-A-I, apo-B, non-HDL, and Lp(a), the CLTI, MLTI, LPI appear as models in CVD risk assessment, considering the multi-factorial nature of CVD. A characteristic of these consolidated lipid indices is that they magnify the subtle changes in atherogenic

and non-atherogenic lipid particles and representing as a single value. Furthermore, the prevalence of CVD is higher in southern India than in Northern India, but there are paradoxically low levels of conventional risk factors in the south India population [27], which turns our focus to genetic susceptibility in such population. Hence, LPI, MLTI, CLTI estimation is significant as genetically determined parameters like LP(a) are used in their calculation.

We observed a significant positive correlation of AIP, TyG index, CLTI, MLTI, LPI with FLDI, GGT, FLI, HSI. It is suggestive of a positive association between hepatobiliary dysfunction and cardiometabolic risk in diabetes patients. The recent meta-analysis conducted by Ming-Hua et al. concluded that the prevalence of CVD in DM patients with NAFLD was increased two-fold compared with the non-NAFLD population (OR = 2.20, 95% CI: 1.67–2.90) [28]. Thus, diabetes and NAFLD have a synergistic effect on CVD development. However, it is still controversial whether NAFLD is a proatherogenic stimulus for CVD development or NAFLD is a clinical manifestation of CVD in diabetes patients.

GGT is not exclusively found in the liver but also in vascular endothelium where it metabolizes extracellular reduced glutathione (GSH), so that precursor amino acids are resynthesized for intracellular GSH synthesis [29]. Thus, serum GGT levels could serve as a biomarker of cellular oxidative stress. A positive correlation of GGT with glycemic parameters and cardiometabolic risk markers suggest increased oxidative stress in diabetes patients which further exacerbates liver dysfunction and CVD risk.

Also, we observed a negative correlation between AIP, TyG index, CLTI, MLTI, LPI with De-Ritis ratio, and total bilirubin which is suggestive of decreased hepatic function and increased oxidative stress in diabetes patients. Since previous studies have shown discrepant results regarding the De-Ritis ratio but in our study De-Ritis ratio was less than 1 and it may be explained by the fact that it represents aggressiveness of disease that can be predicted from the relatively short half-life of AST (18 h) compared to ALT (36 h). Thus, an elevated ratio is predictive of long-term complications like cirrhosis. Since our study participants include patients with diabetes without established clinical liver problems, a ratio less than 1 is suggestive of the initial stages of NASH [30–33]. These findings are important as the levels of liver enzymes remain in the normal range in NAFLD which may underestimate their clinical utility but correlating with other glycemic and cardiometabolic parameters can help the clinician to take decisive action. A negative correlation of bilirubin with glycemic markers, insulin resistance markers, beta-cell dysfunction (HOMA%B), and dyslipidemia markers suggests that decrease in bilirubin concentration in diabetes patients is due to oxidative stress, as bilirubin is a mighty antioxidant that protects pancreatic β cells from oxidative stress as well as prevents proatherogenic lipid particles from oxidation. Consistent with this data, several studies have demonstrated the same association of bilirubin with IR markers and CVD risk biomarkers [34, 35].

Results from our study reveal that FLDI has a significant strong correlation with cardiometabolic risk markers and significantly predicts their outcome in stepwise regression compared to HSI, and FLI. Fuyan et al. showed in their study that FLDI is a better index compared to NAFLD liver fat score and HSI in the Chinese population [12]. We then divided the study group based on FLDI value into two groups (FLDI < 32 and FLDI > 32) (Tab. 3). Using these cut-off values, our study participants mostly fall in the inconclusive range (28–37). Thus, we selected 32 as the cut-off value as there is no established cut-off for FLDI in diabetes patients. Also, by taking 32 as a cut-off value, the prevalence of NAFLD among diabetes mellitus patients is 57.3 (47 out of 82) which is comparable to the results reported by Vanjiappan et al. [36]. Based on this cut-off value, it was found that the median levels of LPI, CLTI, MLTI, TyG index were significantly higher in the group having FLDI > 32 compared to the group having FLDI < 32. These results suggest that there is a potential increment in CVD risk in patients with diabetes and hepatic dysfunction compared to patients with diabetes with normal liver function.

We also assessed the diagnostic performance of various liver and cardiac biomarkers in differentiating people with HbA1c values greater than 9 (n = 49) from people with HbA1c less than 9 (n = 31). The MLTI, CLTI, TyG index, AIP, LPI, FLDI were found useful in the differentiation (Tab. 4). Among the cardiac parameters, MLTI was found to be most useful with an AUC of 0.90, with a sensitivity of 85.7% and specificity of 81% at a cut-off value of 6317 (Fig. 1). Among hepatobiliary markers, FLDI was found to be most useful with an AUC of 0.81, with a sensitivity of 71.4% and specificity of 71% at a cut-off value of 207.

Firstly, the small number of patients recruited to the T2DM group and lack of control participants are insufficient to draw a firm conclusion. Secondly, our results could have been supplemented by incorporating few clinical parameters also in addition to biochemical parameters.

Conclusions

The present study demonstrates the significant positive correlation of cardiometabolic risk biomarkers

with hepatobiliary dysfunction markers and significant strong negative correlation with total bilirubin and significant weak negative correlation with De-Ritis ratio. MLTI, CLTI, TyG index, LPI, FLDI were able to differentiate DM patients based on the gold standard HbA1c values for DM diagnosis. FLDI upon linear regression was found to be significant predictor for various cardiometabolic risk biomarkers which suggest that it can be used as surrogate biomarkers for cardiometabolic risk among T2DM patients. Results from our study provide a strong foundation for future experimental studies on the elucidation of the molecular mechanism linking NAFLD and CVD in diabetes mellitus patients. This study highlights the need for collaborative actions of diabetologists and hepatologists in identifying the people with NAFLD among DM patients, who should be targeted with intensive therapy to decrease their risk of future CVD events.

Ethics approval and consent to participate

Approvals of the Institute Research Council and Institute Human Ethics Committee were obtained (JIP/ /IEC/2019/388 dated 11/12/2019). Informed consents were obtained from all participants included in the study.

Human and animal rights

No animals were used in this study. Procedures followed were by ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013.

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Conflict of interest

None declared.

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