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Factors Influencing Online Prediction Tools of Non-Alcoholic Fatty Liver Disease

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ABSTRACT:
Objective: This studyaimed to identify clinical parameters which are highly influencing with Fatty Liver Index (FLI), lipid accumulation product (LAP), hepatic steatosis index (HSI),NAFLD liver fat score (NAFLD-LFS),Triglyceride and Glucose index(TYG).

Materials and Methods: This was a prospective observational study conducted in 128 patients aged between >18-80 years who attended SRM medical hospital and research center during July -Dec 2020. Based on inclusion and exclusion criteria, inultrasound diagnosed NAFLD patients the lab values are collected. These collected lab values are correlated with FLI, LAP, HSI, NAFLD-LFS, TYG according to cut-off values.

Results: This analysis shown a strong negative correlation found between FLI <30, FPG (P=0.044). Moderate positive correlations were found between FLI 30-<60 and BMI (P=0.010), WC (P=0.003). In the case of FLI >60, there is a moderate positive correlation found between FLI and weight (P<0.0001), BMI (<0.0001), WC (<0.0001), and weak positive correlation with TG (P=0.007), GGT (P=0.033). LAP<80 shown a strong positive correlation with TG (P<0.0001), a weak positive correlation with HOMA-IR (P= 0.045), and a weak negative correlation with Ht (P=0.011). LAP >80 shown a strong positive correlation with TG (P<0.0001). HSI <36 shown a moderate positive correlation in BMI (P=0.028). HSI >36 shown a moderate positive correlation in Wt (P<0.0001), WC (P<0.0001), fasting insulin (P=0.002), and a strong positive correlation with BMI (P<0.0001). NAFLD-LFS <-0.640 shown a weak positive correlation in fasting insulin (P=0.0407). NAFLD-LFS >-0.640 shown a strong positive correlation in AST (P<0.0001), moderate positive correlation with ALT (P<0.0001), fasting insulin (P<0.0001), and weak positive correlation with HOMA-IR (P=0.001). TYG >4.49 shown strong positive correlations in FPG (<0.0001), TG (P<0.0001), weak positive correlation with HOMA-IR (P=0.049).TYG >4.49 shown a weak negative correlation with BMI (P=0.007).

Conclusion: Other than variables derived to calculateFatty Liver Index (FLI), lipid accumulation product (LAP), hepatic steatosis index (HSI),NAFLD liver fat score (NAFLD-LFS),Triglyceride and Glucose index(TYG);FPG, insulin resistance, fasting insulin found to have a significant correlation.

Keywords: Fatty Liver Index (FLI), lipid accumulation product (LAP), hepatic steatosis index (HSI),NAFLD liver fat score (NAFLD-LFS), Triglyceride and Glucose index(TYG).

INTRODUCTION:

NAFLD which recently coined as Metabolic dysfunction associated fatty liver disease is defined as presence of steatosis >5% in hepatocytes (imaging, histological) in the absence of significant alcohol consumption and presence of at least 2 metabolic abnormalities: WC ≥ 90/80 cm (Asian men and women),HDL cholesterol < 40 mg/dL (1.0 mmol/L) in men, < 50 mg/dL (1.3 mmol/L) in women,Plasma triglycerides > 150 mg/dL (1.7 mmol/L), Blood pressure > 130/85 mmHg, Prediabetes,HOMA-IR score ≥ 2.5, and hsCRP level > 2 mg/L [1].Triglyceride accumulation in hepatic cells promotes diminished insulin sensitivity of the liver and thus increasing hepatic gluconeogenesis which further worsens T2DM[2-6]. The Prevalence of NAFLD globally accounts for 25.24% moreover 9–32% in India [7].

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Screening NAFLD is mattering as it is related to symptoms of metabolic syndrome such as abdominal obesity, insulin resistance, diabetes, dyslipidemia, and hypertension followed by the risk of CVDs. Thus, establishing the diagnosis of NAFLD is crucial [8].The usual diagnosis of NAFLD is made from findings of abnormal LFTs and steatosis imaging (USG, MRI-PDF, CT SCAN, FIBROSCAN), but in most cases (approx 80%) in NAFLD liver function tests would be in the normal range [9]. Data suggest patients with central obesity (70–80%) and T2DM (50–80%) have NAFLD on imaging. Hence relying on metabolic risk factors may provide better identification of NAFLD[10,11,12,13, 14, 15]. There are certain tools available online for predicting the existence of NAFLD. This analysis focuses on studying the clinical lab parameters of online tools for foretelling the carriage of NAFLD.

Metabolic and anthropometric variables-based indexes were available online for screening patients for NAFLD like fatty liver index, hepatic steatosis index, NAFLD fat score, triglyceride-glucose index, liver accumulation product [16,17,18,19,20]. These tools were made use for the identification of NAFLD in many epidemiological studies, yet the validation of other risk factor causing NAFLD arelimited.This analysisintention is to check the correlation between lab parameters and online available NAFLD diagnosing tools (FLI, LAP, HSI, NAFLD-LFS, TYG) and what parameters influence each.

MATERIALS AND METHODS:

This was a prospective observational study conducted in 128 patients aged between >18-80 years who attended SRM medical hospital and research center during July -Dec 2019. From each patient, the informed concern form was collected before proceeding with the study. This study was approved by the Institutional human ethical committee (1685/IEC/25/04/2019) following the revised version of the Declaration of Helsinki.All the patients with BMI >25kg/m2, T2DM, dyslipidemia, hypothyroidism, metabolic syndrome was included. Patients with other chronic liver diseases (hepatitis B or C, autoimmune hepatitis, cholestatic liver disease, Wilson's disease, hemochromatosis, cirrhosis were excluded.

Ultrasound:
Patients were screened for NAFLD using a convex probe and Philip HD 11 machine. The radiologist was blinded about the patient's identity and the purpose of the study. During scanning, the patient examination was done in the supine position.NAFLD grading determined based on [21]

- Grade I: when increased echogenicity seen.
- Grade II: When the echogenic liver shadowed the echogenic walls of portal vein branches,
- Grade III: when the echogenic liver shadowed the diaphragmatic outline.

Clinical and anthropometric parameters:
Collection of blood samples from patients done after 8-12hrs overnight fasting. 10ml of blood sample was used for FPG (70-110mg/dl), HbA1c (4.5-6%), fasting insulin (3-8uIU/ml), liver enzymes- AST (5-40/L), ALT (5-35U/L), GGT (9-48U/L), and serum lipid profile- TG(<150mg/dl), TC (<200mg/dl), HDL (>40mg/dl), LDL (<130mg/dl) and VLDL (<40mg/dl). Values outside this range were considered abnormal. Hitachi 7600 auto-analyzer was used for serum analysis.During the investigation, an anthropometric examination was performed by a skilled and certified examinee.Standard protocols for determining weight and height were followed[22].Mid of the lower rib border and iliac crest were used to calculate WC[23]. BMI was calculated as weight (kg)/height (m)2.
Online available tools for detecting the presence of NAFLD:

- FLI = (e 0.953*loge (triglycerides) + 0.139*BMI + 0.718*loge (ggt) + 0.053*waist circumference - 15.745) / (1 + e 0.953*loge (triglycerides) + 0.139*BMI + 0.718*loge (ggt) + 0.053*waist circumference - 15.745) * 100 [16]

- LAP for men = (WC [cm] - 65) × (triglycerides [mmol/L]) [24]
- LAP for women = (WC [cm] - 58) × (triglycerides [mmol/L])
- Hepatic steatosis index (HSI) = 8 × ALT/AST ratio + BMI (+2,if DM; +2,if female) [25]
- NAFLD-LFS = - 2.89 + 1.18 x Metabolic Syndrome (Yes: 1, No: 0) + 0.45 x Type 2 Diabetes (Yes: 2, No: 0) + 0.15 x Insulin in mU/L + 0.04 x AST in U/L – 0.94 x AST/ALT [26]
- TyG = ln [Fasting triglyceride (mg / dl) x Fasting glucose (mg / dl)] / 2 [27]

Statistical Analysis:

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Descriptive statistics performed to present the mean and standard deviation for all the variables taken in the study. The relationship between FLI, LAP, HSI, NAFLD-LFS, TYG with age, gender, height, weight, BMI, waist circumference, FPG, TG, AST, ALT, GGT, Fasting insulin, HOMA-IR found using Spearman correlation analysis. This correlation displays the relationship between each variable. The variable with a significance value less than 0.5 is significant. The correlation coefficient value indicates whether the significant variable is positively correlated or negatively correlated. The association between each variable with FLI, LAP, HSI, NAFLD-LFS,TYG was obtained using One-way ANOVA. Graph pad prism software was used for the analysis of this study.

RESULTS:

Table 1: ANOVA

Variable	GRADE I	Grade II	Grade III	P-value
	n=69	n=53	n=6	
AGE (yrs.)	51.31±11.06	53±9.56	49.67±12.6	0.56
BMI(kg/m2)	30.59±4.46	29.20±4.11	32.16±5.45	0.14
WC(cm)	104.4±9.36	99.96±8.91	105.62±10.23	0.02
FPG(mg/dl)	158.72±60	161±58.87	141±30.22	0.73
TG(mg/dl)	173±116	153±103	130±34	0.45
AST (U/L)	27.17±33.08	25.53±15.73	22.51±9.75	0.89
ALT(U/L)	26.67±22.96	26.75±19.84	26.83±11.42	1.01
GGT(U/L)	40.73±92.97	28.99±18.64	27.33±9.66	0.63
FASTING INSULIN (mIU/ml)	13.76±7.14	12.90±7.41	24.96±3.47	0.02
HOMA- IR	5.23±3.08	4.61±2.84	6.63±1.41	0.41

Values are expressed in Mean ±SD, level of significance *P<0.05*, P<0.01**, P<0.001**** BMI (Body Mass Index); WC (Waist circumference); FPG (Fasting Plasma Glucose);TG (Triglyceride); AST (Aspartate aminotransferase); ALT (Alanine aminotransferase); GGT (Gamma-glutamyltransferase);HOMA-IR (Homeostatic Model Assessment of Insulin Resistance).

We have examined 128 NAFLD cases out of which 69 were found to be grade I, 53 were grades II, and 6 were grade III. The mean age of patients with NAFLD was 51.929±10.39.Patients with GIII NAFLD shownincreased mean WCand fasting insulin when compared to grade I and grade II. This difference is statistically significant with P<0.024 (Table 1).

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Table 2: Correlation Between FLI and Clinical Parameters

FLI		HEIGHT (m)	WEIGHT (kg)	BMI (kg/m2)	WC (cm)	FPG (mg/dl)	TG (mg/dl)	AST (U/L)	ALT (U/L)	GGT (U/L)	INSULIN (mIU/ml)	HOMA -IR
< 30	r	-0.518	0.017	0.588	0.368	-0.646	0.062	-0.025	0.327	-0.067	0.077	-0.143
	P (2-tailed)	0.125	0.963	0.074	0.296	0.044	0.866	0.944	0.356	0.854	0.832	0.693
30-<60	r	-0.354	0.095	0.469	0.539	-0.011	0.038	0.133	0.026	0.011	-0.129	-0.177
	P (2-tailed)	0.059	0.624	0.010	0.003	0.955	0.843	0.499	0.894	0.956	0.60	0.468
>60	r	0.171	0.532	0.513	0.587	0.196	0.284	0.061	0.136	0.23	0.044	0.068
	P (2-tailed)	0.111	<0.0001	<0.0001	<0.0001	0.071	0.007	0.580	0.211	0.033	0.745	0.615

BMI (Body Mass Index); WC (Waist circumference); FPG (Fasting Plasma Glucose);TG (Triglyceride); AST (Aspartate aminotransferase); ALT (Alanine aminotransferase); GGT (Gamma-glutamyl transferase); HOMA-IR (Homeostatic Model Assessment of Insulin Resistance).

Spearman's analysis was performed to find the correlations between FLI, clinical and anthropometric parameters. The correlation was done according to the FLI cut-off values (<30, 30-<60 and >60) and various lab parameters. In the case of cut-off<30, this analysis showeda strong negative correlation found between FLI <30, FPG (P=0.044).In the case of FLI 30-<60, there aremoderate positive correlations found between BMI (P=0.010), WC (P=0.003). In the case of FLI >60, there is a moderate positive correlation found between FLI and weight(P<0.0001), BMI (<0.0001), WC (<0.0001), and weak positive correlation with TG (P=0.007), GGT (P=0.033) (Table 2).

Table 3: Correlation between LAP and clinical parameters

LAP		HEIGHT (m)	WEIGHT (kg)	BMI (kg/m2)	WC (cm)	FPG (mg/dl)	TG (mg/dl)	AST (U/L)	ALT (U/L)	GGT (U/L)	INSULIN (mIU/ml)	HOMA -IR
< 80	r	-0.283	-0.014	0.199	0.146	0.144	0.761	0.078	0.034	0.097	0.151	0.266
	P (2-tailed)	0.011	0.889	0.075	0.194	0.207	<0.0001	0.492	0.764	0.394	0.267	0.045
>80	r	0.103	0.022	-0.068	0.007	0.092	0.912	0.013	0.127	-0.049	-0.125	0.045
	P (2-tailed)	0.499	0.888	0.657	0.964	0.546	<0.0001	0.933	0.416	0.752	0.516	0.817

BMI (Body Mass Index); WC (Waist circumference); FPG (Fasting Plasma Glucose); TG (Triglyceride); AST (Aspartate aminotransferase); ALT (Alanine aminotransferase); GGT (Gamma-glutamyl transferase); HOMA-IR (Homeostatic Model Assessment of Insulin Resistance).

Similarly,LAP correlation categorized into <80,> 80 with clinical and anthropometric parameters. LAP less than 80 shown a strong positive correlation with TG (P<0.0001), weak positive correlation with HOMA-IR (P= 0.045), and weak negative correlation with Ht (P=0.011). LAP >80 shown a strong positive correlation with TG (P<0.0001) (Table 3).

Table 4: Correlation between HSI and clinical parameters

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HSI		HEIGHT (m)	WEIGHT (kg)	BMI (kg/m2)	WC (cm)	FPG (mg/dl)	TG (mg/dl)	AST (U/L)	ALT (U/L)	GGT (U/L)	INSULIN (mIU/ml)	HOMA -IR
< 36	r	-0.251	0.066	0.585	0.276	0.063	0.361	-0.125	0.081	-0.138	0.285	0.101
	P (2-tailed)	0.386	0.823	0.028	0.339	0.838	0.205	0.671	0.782	0.639	0.395	0.755
>36	r	-0.151	0.431	0.764	0.491	-0.034	-0.067	-0.079	-0.008	-0.054	0.361	0.227
	P (2-tailed)	0.119	<0.0001	<0.0001	<0.0001	0.725	0.492	0.416	0.934	0.580	0.002	0.055

BMI (Body Mass Index); WC (Waist circumference); FPG (Fasting Plasma Glucose);TG (Triglyceride); AST (Aspartate aminotransferase); ALT (Alanine aminotransferase); GGT (Gamma-glutamyl transferase); HOMA-IR (Homeostatic Model Assessment of Insulin Resistance).

In the same order, HSI categorized to <36 and >36 and correlated with clinical and anthropometric parameters. HSI <36 shown a moderate positive correlation in BMI (P=0.028). HSI >36 shown a moderate positive correlation in Wt (P<0.0001), WC (P<0.0001), fasting insulin (P=0.002), and strong positive correlation with BMI (P<0.0001) (Table 4).

Table 5: Correlation between NAFLD-LFS and clinical parameters

NAFLD-LFS		HEIGHT (m)	WEIGHT (kg)	BMI (kg/m2)	WC (cm)	FPG (mg/dl)	TG (mg/dl)	AST (U/L)	ALT (U/L)	GGT (U/L)	INSULIN (mIU/ml)	HOMA -IR
< -0.640	r	-0.219	-0.162	-0.060	-0.003	0.049	0.235	0.159	0.282	0.194	0.325	0.233
	P (2-tailed)	0.167	0.310	0.708	0.987	0.763	0.140	0.321	0.074	0.224	0.041	0.142
>-0.640	R	0.0009	0.006	0.077	0.123	-0.045	-0.201	0.667	0.585	0.118	0.597	0.479
	P (2-tailed)	0.995	0.968	0.622	0.429	0.774	0.195	<0.0001	<0.0001	0.449	<0.0001	0.001

BMI (Body Mass Index); WC (Waist circumference); FPG (Fasting Plasma Glucose);TG (Triglyceride); AST (Aspartate aminotransferase); ALT (Alanine aminotransferase); GGT (Gamma-glutamyl transferase); HOMA-IR (Homeostatic Model Assessment of Insulin Resistance).

In the same fashion, NAFLD-LFS categorized into <,>-0.640 and correlated with clinical and anthropometric parameters. NAFLD-LFS <-0.640 shown a weak positive correlation in fasting insulin (P=0.041). NAFLD-LFS >-0.640 shown a strong positive correlation in AST (P<0.0001), moderate positive correlation with ALT (P<0.0001), fasting insulin (P<0.0001), and weak positive correlation with HOMA-IR (P=0.001) (Table 5).

Table 6: Correlation between TYG and clinical parameters

TYG		HEIGHT (m)	WEIGHT (kg)	BMI (kg/m2)	WC (cm)	FPG (mg/dl)	TG (mg/dl)	AST (U/L)	ALT (U/L)	GGT (U/L)	INSULIN (mIU/ml)	HOMA -IR
<4.49	r	0.219	0.163	0.0179	-0.10	0.409	0.085	0.422	0.0366	0.638	-0.534	-0.003

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	P (2-tailed)	0.637	0.726	0.969	0.831	0.361	0.856	0.346	0.938	0.123	0.466	0.996
>4.49	r	0.173	-0.051	-0.248	-0.111	0.681	0.743	0.047	0.153	0.117	-0.182	0.217
	P (2-tailed)	0.064	0.585	0.007	0.234	<0.0001	<0.0001	0.622	0.104	0.213	0.104	0.049

BMI (Body Mass Index); WC (Waist circumference); FPG (Fasting Plasma Glucose);TG (Triglyceride); AST (Aspartate aminotransferase); ALT (Alanine aminotransferase); GGT (Gamma-glutamyl transferase); HOMA-IR (Homeostatic Model Assessment of Insulin Resistance).

TYG was also categorized to <4.49 and >4.49 and correlated with clinical and anthropometric parameters. TYG >4.49 shown strong positive correlations in FPG (<0.0001), TG (P<0.0001), weak positive correlation with HOMA-IR (P=0.049).
TYG >4.49 shown a weak negative correlation with BMI (P=0.007) (Table 6).

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DISCUSSION:

NAFLD is now becoming a silent pandemic all over the world. This risk is more prone in diabetes, dyslipidemia, hypothyroid, obesity patients. A sedentary lifestyle has majorly lessened the time for developing NAFLD. The irregular diet reduced physical exercise has made people fall into metabolic syndrome and then slowly progress to NAFLD. FLI, LAP, HSI, NAFLD-LFS, TYG are online available tools, easily accessible for diagnosing NAFLD. This study aimed to identify clinical parameters which are highly influencing with FLI, LAP, HSI, NAFLD-LFS, TYG.

we have categorized the FLI, LAP, HSI, NAFLD-LFS, TYG according to their cut-off values and correlated with the clinical and anthropometric parameters. To our observation, we noticed the following. When FLI cut off less than 30, FPG has shown eminent values. when FLI is cut off between 30-60, BMI and WC will have the potential to add value to the FLI score. Few studies have shown the FLI has a strong positive correlation with hepatocellular lipid content [28,29]. Our study has also shown similar results. If FLI was greater than 60, TG, GGT including BMI, WC showed significant potential to influence FLI score.

Lap had proven effective in predicting cardiovascular risk [24], supporting we observed the factor responsible for CVDs correlation with LAP. The height of the patients showed a negative correlation whereas TG, insulin resistance shown a positive correlation to the LAP score <80. only changes in TG have shown impact when LAP score >80. Derivation of HSI done based on BMI, AST, ALT, and presence of DM, similar results found in this study (25). Variations in BMI (when HSI <,>36) weight, WC, and fasting insulin would likely add on changes in values of HSI in case HSI >36. The NAFLD-LFS predicts the risk for metabolic diseases (26). In our study we observed, only fasting insulin was found to be a predictor for changes if NAFLD-LFS score <-0.640. Furthermore, if NAFLD-LFS score >-0.640; AST, ALT, fasting insulin, and insulin resistance showed a significant influence in varying the score. It is reported that TYG is a predictive risk indicator for DM, cardiovascular diseases [27,30,31,32,33), similar results obtained in our study. Only in TYG >4.49 BMI, FPG, TG, insulin resistance can predict in changing the values of TYG.

In conclusion, irrespective of the variables known to calculate the score in FLI, LAP, HSI, NAFLD-LFS, TYG other lab parameters can also have an influence. FPG, insulin resistance, fasting insulin shown to have supremacy in altering the scores in FLI, LAP, HSI, NAFLD-LFS, TYG.

Conflict of Interests

Authors declare no conflict of interests.

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