ORIGINAL ARTICLE

STUDY OF HEPATIC STEATOSIS ALGORITHMS AS A POTENTIAL MARKER OF METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE

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ABSTRACT

Background: Metabolic dysfunction associated steatotic liver disease (MASLD) is the most common chronic liver disease worldwide, with increased liver-related morbidity and mortality. Various non-invasive algorithms have been developed for predicting the presence of MASLD using anthropometric and biochemical parameters. Hence, this study aims to determine hepatic steatosis algorithms as a potential marker of MASLD.

Methods: A total of 200 participants were included in the study, of which 100 were MASLD cases, and 100 were healthy control. Serum ALT, AST, TG, and Glucose were estimated, and Hepatic steatosis algorithms (LAP, FSI, TyG, and HSI) were calculated. The ROC curve was estimated to validate algorithms in patients with MASLD.

Results: Hepatic steatosis algorithms like FSI, LAP, TyG, and HSI were significantly higher ($p<0.05$) in patients with MASLD compared to healthy control. The AUROC of LAP, FSI, TyG, and HSI was 0.789 (95% CI,0.727-0.851), 0.776 (95% CI, 0.711-0.841), 0.765 (95% CI, 0.697-0.833) and 0.693 (95% CI, 0.620-0.766) respectively. The optimal cut-off value of LAP, FSI, TyG, and HSI for the prediction of MASLD were 31 (71% sensitivity and 70% specificity), 23 (74% sensitivity and 72% specificity), 8.9 (73% sensitivity and 70% specificity) and 34.5 (67% sensitivity and 62% specificity) respectively.

Conclusion: The non-invasive and cost-effective algorithms like LAP, FSI, TyG, and HSI can be potential screening tools for predicting MASLD.

Keywords: ***Metabolic dysfunction associated steatotic liver disease (MASLD), Chronic liver disease, Framingham steatosis index (FSI), Triglyceride and glucose index (TyG)***

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INTRODUCTION

Metabolic dysfunction associated steatotic liver disease (MASLD) is a significant cause of chronic liver disease marked by hepatic steatosis, with no other causes for secondary hepatic fat accumulation. There is substantial lipid accumulation (5-10%) in hepatic tissue in the absence of chronic alcoholic consumption [< 210 g/week in men and < 140 g/week in women](1, 2). It has become a common chronic disease in developed and developing countries with a high prevalence rate (3). The prevalence of MASLD is 24.7% worldwide, whereas 17% is in Nepal. According to the American Association for the Study of Liver Disease (AASLD), MASLD has evidence of hepatic steatosis in more than 5% of hepatocytes, either by imaging or histology in the absence of other causes of secondary hepatic fat accumulation, such as significant alcohol consumption, steatogenic medications, viral hepatitis or hereditary disorders (4).

Patients with MASLD frequently exhibit one or more symptoms of metabolic syndrome (MS), such as systemic hypertension, dyslipidemia, insulin resistance, or overt diabetes. The steatotic liver disease (SLD) is a milder form and has a liver-related low morbidity rate. Metabolic dysfunction associated steatohepatitis (MASH) is associated with lobular inflammation, ballooning, and progression to hepatic fibrosis, cirrhosis, carcinoma, and liver failure, which shows substantial liver-related mortality (5, 6). The aberrant hepatic metabolism that results from hepatic lipid accumulation in MASLD is caused by impaired insulin signaling. Fat accumulation in the liver is the initial stage of this process, which will make insulin resistance worse. The second stage of this process entails cellular and molecular alterations brought on by oxidative stress and the oxidation of fatty acids in the liver. This oxidation is due to numerous factors such as endoplasmic reticulum stress, pro-inflammatory cytokines, and gut-derived bacterial endotoxin that results in hepatic inflammation, cirrhosis, fibrosis and necrosis (7).

The liver biopsy is the gold standard for diagnosing MASLD, although it's still debatable whether or not every patient with suspected MASLD should undergo a liver biopsy. The patient's medical history, test results, and imaging studies are mainly used to create a presumptive diagnosis (8). Numerous publications have worked to validate basic and affordable indices for predicting MASLD, as liver biopsy and imaging procedures are expensive and intrusive for diagnosing MASLD. For the prediction of MASLD, several non-invasive and inexpensive algorithms based on metabolic and anthropometric characteristics have been established (9). Several indices, including those for hepatic steatosis, have been validated using anthropometric measurements, liver enzymes, and lipid profiles. These indices can be used to screen for hepatic steatosis in large epidemiological studies or to identify potential patients for further examination in clinical practice (9). Although, currently no specific pharmacological treatment for MASLD, it is thought that a combination of treatment objectives (lifestyle changes, increasing physical activity, and quitting smoking and drinking) may be helpful.

Thus, the study aimed to diagnose MASLD using the non-invasive, easily accessible, cost-effective, simple diagnostic tool as a potential marker of non-alcoholic fatty liver disease.

How to Cite

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MATERIALS AND METHODS

Study design and participants

This laboratory-based cross-sectional study was performed at Manmohan Memorial Medical College and Teaching Hospital, Kathmandu, Nepal, for three months (November 2020 to January 2021). Ethical approval was taken from the Institutional Review Committee (IRC), and written consent was obtained from each individual before they participated in the study. A total of 200 (100 MASLD cases and 100 healthy control) subjects were conveniently selected for the study from the patients visiting for regular medical check-ups. The diagnosis of MASLD was based on patients history, serological test (hepatitis B and C) an ultrasonographic examination.

Inclusion and exclusion criteria

A non-alcoholic individual with either total absence or with consumption of <20 g of alcohol per day, ultrasound suggestive of fatty liver, and a healthy control group were included in the study. Patients with a history of significant alcohol consumption; clinical, imaging, or liver biopsy features of liver cirrhosis; pregnant women; history of taking lipid-lowering drugs were excluded from the study.

Anthropometric parameters

Information regarding the patient's demography (age, sex), height, weight, Body mass index (BMI), waist circumference (WC), and blood pressure was collected and measured by standard protocol and recorded in a clinical profile form.

Measurement of laboratory parameters

Overnight fasting blood samples were collected in a gel vacutainer for determination of fasting plasma glucose (FPG), total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C), alanine aminotransferase (ALT), aminotransferase (AST). All blood samples were analyzed using a fully automated chemistry analyzer (VITROS® 350 Chemistry System, USA), maintaining internal quality control.

Statistical analysis

The data analysis was performed using SPSS Version 20 (IBM Corp., Armonk, NY, USA). Statistical tests like the Mann-Whitney U test, Chi-square test, Spearman's correlation test, and ROC curve were applied in SPSS. Data were expressed as mean ± standard deviation for normally distributed continuous variables and median ± interquartile range for non-normally distributed continuous variables. The Kolmogorov-Smirnov test was used to verify the normality distribution, and the Mann-Whitney U test was used to compare the parameters between the two groups. Categorical variables were expressed as frequency rates and percentages. Receiver operating characteristics (ROC) curves of various indexes were developed to predict the presence of MASLD. p-Value < 0.05 was considered statistically significant.

RESULTS

Out of 200 study subjects, 100 subjects diagnosed with MASLD based on ultrasonographic findings were considered cases, and 100 healthy subjects were considered as a control in the study. There were 49 males and 51 females in the control group and 44 males and 56 females in the MASLD cases. The mean ± standard deviation of all the demographic variables among the MASLD cases and control were listed in Table 1.

There was a significant increase in anthropometric variables like BMI, WC, and blood pressure in the MASLD case compared to the control (p <0.001). In comparison with the control, MASLD showed a significantly higher level of ALT (p=0.021), TG, and glucose (p<0.001). Similarly, hepatic steatosis algorithms like HSI, LAP, FSI, and TyG were significantly increased in MASLD than those with control (p<0.001) (Table 2).

Among MASLD subjects, LAP, FSI, and HSI revealed a strong connection with BMI and WC (p<0.001). Similarly, ALT demonstrated a significant correlation with FSI and HSI (p<0.001), whereas glucose also had a significant correlation with FSI and TyG (P<0.001) (Table 3).

Table 1: Distribution of variables among the study subjects (Mean±SD)

Variables	MASLD (N=100)	Control (N=100)
Age (years)	50.01±11.63	40.94±14.48
BMI (kg/m2)	26.92±3.70	24.84±3.37
WC (cm)	86.92±11.40	77.51±5.66
SBP (mmHg)	125.40±12.17	120.40±11
DBP (mmHg)	82.16±14.34	80.10±7.97
ALT (IU/ml)	40.68±30.07	30.23±16.42
AST (IU/ml)	39.63±36.29	31.38±18.21
TG (mg/dl)	203.66±100.96	142.63±96.29
Glucose (mg/dl)	110.42±37.88	101.59±32.64
LAP	59.86±43.17	27.57±23.36
FSI	0.32±0.23	0.16±0.18
TyG	9.19±0.50	8.66±0.65
HSI	37.14±5.38	33.95±4.28

Abbreviations: BMI: Body Mass Index, WC: Waist Circumference, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, TG: Triglyceride, LAP: Lipid Accumulation Product, FSI: Framingham Steatosis Index, TyG: Triglyceride and Glucose Index, HSI: Hepatic Steatosis Index

Table 2: Comparison of Anthropometric, Biochemical parameters and Hepatic Steatosis Algorithm between control and MASLD cases (using Mann-Whitney U test).

Variables	Control (Median (IQR)	MASLD(Median IQR)	p- value
Age (years)	39.50 (29-49.75)	50 (42-58)	<0.001
BMI (kg/m2)	24.89 (22.90-26.54)	26.50 (24.80-28.18)	<0.001
WC (cm)	76.20 (73.60-81.30)	84 (76-96.50)	<0.001
ALT (IU/ml)	25.50 (22-33)	30 (22-46)	0.021
AST (IU/ml)	28 (24-32)	27 (23-38.50)	0.485
SBP (mmHg)	120 (120-120)	120 (120-130)	0.002
DBP (mmHg)	80 (80-80)	80 (80-90)	0.034
TG (mg/dl)	105.50 (80-163.75)	185 (151-234.25)	<0.001
Glucose (mg/dl)	95.50 (87.25-105)	103 (92.25-115)	<0.001
TyG	8.57 (8.15-8.96)	9.15 (8.86-9.45)	<0.001
LAP	18.80 (11.68-36.25)	49.95 (28.53-76.93)	<0.001
FSI	0.09 (0.18-0.05)	0.26 (0.43-0.15)	<0.001
HSI	33.76 (30.93-36.28)	36.74 (33.73-39.37)	<0.001

Abbreviations: BMI: Body Mass Index, WC: Waist Circumference, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, TG: Triglyceride, LAP: Lipid Accumulation Product, FSI: Framingham Steatosis Index, TyG: Triglyceride and Glucose Index, HSI: Hepatic Steatosis Index

Table 3: Correlation between anthropometric variables, Biochemical parameters and hepatic steatosis algorithm in MASLD

Variables	LAP	FSI	TyG	HSI
BMI (kg/m2)	0.459**	0.496**	0.010	0.729**
WC (cm)	0.803**	0.438**	0.102	0.432**
ALT (IU/ml)	-0.018	0.268**	0.074	0.261**
AST (IU/ml)	-0.096	0.028	0.057	-0.094
TG (mg/dl)	0.649**	0.523**	0.882**	0.082
Glucose (mg/dl)	-0.082	0.283**	0.483**	0.113

***** Correlation is significant at the 0.01 level.***

Abbreviations: BMI: Body Mass Index, WC: Waist Circumference, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, TG: Triglyceride

The ROC of the hepatic steatosis algorithms was assessed to compare the area under receiver operating characteristics (AUROC) curves of hepatic steatosis algorithms to predict MASLD (Figure 1).

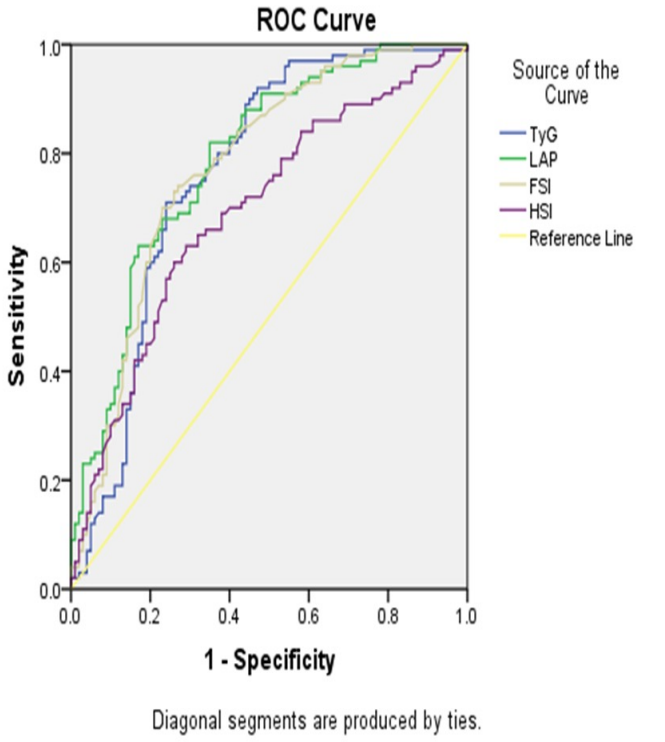

Figure 1: Receiver Operating Curve of the Hepatic Steatosis Algorithms

AUROC of LAP for predicting MASLD was (0.789; 95% CI, 0.727-0.851). It was significantly higher than AUROC of FSI (0.776; 95%CI, 0.711-0.841), TyG (0.765; 95% CI, 0.697-0.833), and HSI (0.693; 95% CI, 0.620-0.766) with p-value<0.01 (Table 4).

Table 4: Area under receiver operating characteristics of hepatic steatosis algorithms for predicting MASLD.

Algorithms	AUROC	S E	p-value	95% Confidence interval	
				LCL	UCL
LAP	0.789	0.032	<0.001	0.727	0.851
FSI	0.776	0.033	<0.001	0.711	0.841
TyG	0.765	0.035	<0.001	0.697	0.833
HSI	0.693	0.037	<0.001	0.620	0.766

Abbreviations: LAP: Lipid Accumulation Product, FSI: Framingham Steatosis Index, TyG: Triglyceride and Glucose Index, HSI: Hepatic Steatosis Index

The optimal cut-off value of hepatic steatosis algorithms with their sensitivity and specificity is shown in Table 5.The cut-off value of LAP was 31 (71% sensitivity and 70% specificity), FSI was 23 (74% sensitivity and 72% specificity), TyG was 8.9 (73% sensitivity and 70% specificity), and HSI was 34.5 (67% sensitivity and 62% specificity).

Table 5: Cut off values of hepatic steatosis algorithm with their sensitivity and specificity

Algorithms	Cut-off value	Sensitivity (%)	Specificity (%)
LAP	31	71	70
FSI	23	74	72
TyG	8.9	73	70
HSI	34.5	67	62

Abbreviations: LAP: Lipid Accumulation Product, FSI: Framingham Steatosis Index, TyG: Triglyceride and Glucose Index, HSI: Hepatic Steatosis Index

DISCUSSION

MASLD is a spectrum of liver disease encompassing the presence of >5% hepatic fat accumulation and the absence of other known causes of fatty liver are commonly used in clinical practice to make the first diagnosis (10). It has become an emergent public health concern with remarkable growth worldwide over the recent decades (11). Due to the sedentary lifestyles and diet patterns, the prevalence of MASLD is strongly associated with metabolic disorders, including abdominal obesity, hypertriglyceridemia, insulin resistance, and type 2 diabetes mellitus(T2DM) (12, 13, 14). At an early stage, MASLD patients do not present specific symptoms hindering prevention and early detection. The liver biopsy is considered the gold standard for hepatic steatosis, although it is not performed routinely due to its invasive procedure and frequent sampling error (4, 15). Thus, the diagnosis of MASLD is usually made by ultrasound (16). This study aimed to determine the hepatic steatosis algorithm as a potential marker of Non-alcoholic fatty liver disease, which is non-invasive, cost-effective, and easily accessible.

In this study, anthropometric variables (BMI and WC) were significantly higher in MASLD cases which were consistent with the study of Zheng et al. (17) and Lee et al. (18). Likewise, this study has depicted a significantly higher level of TG in MASLD cases

as compared to healthy control which is accordance with the study of Tomizawa and colleagues (19). Bajaj et al. (20) also reported that the subjects with MASLD had significantly higher values of total cholesterol and serum triglycerides. A poor diet and inadequate physical activity may be the probable causes of the increased occurrence of dyslipidemia (21). According to a study by Fabbrini E. et al., the likelihood of significantly higher TG, BMI, and WC levels in MASLD cases can be explained by an increased risk of non-alcoholic fatty liver disease. MASLD progresses when hepatic fatty acid intake from plasma and de novo fatty acid synthesis occurs at higher rates than fatty acid oxidation and export. An excessive level of intrahepatic triglycerides indicates an imbalance in the interplay of many metabolic activities (22).

Additionally, this study has demonstrated a significantly higher value of ALT in MASLD cases than that of healthy control, which is consistent with the study of Santhosakumari et al. and Pardhe et al. (22). Apart from AST and MASLD, a significant relationship between hepatic enzymes (ALT, GGT, and AST/ALT ratio) has been demonstrated by Novakovic et al. (23). According to Zakeri and Karmarat-Panah, dyslipidemia and ALT may play a role in the occurrence and progression of MASLD (24). The study by Esteghamati et al. explained the possibility of a significantly higher level of ALT in the MASLD population. The reason is associated with the influx of high fatty acids in the liver due to lipid peroxidation and mitochondrial dysfunction, which causes liver toxicity producing inflammatory cytokines such as IL-6 and TNF-6. TNF-6 plays a significant role in developing hepatocellular injury, causing fatty liver with a mild to moderate increase in liver enzymes and MASLD (25). We assessed five different hepatic steatosis algorithms that are currently available. In the present study, LAP levels in MASLD cases have been considerably more significant than in controls. This finding was comparable to that of Dai et al. (26) conducted on Chinese adults. Accordingly, it is plausible that the LAP, a combination of WC and TG, is significantly associated with MASLD. Moreover, a study by Zhang et al. revealed that TyG is considerably higher in MASLD than in the control group (27).

Similarly, other hepatic steatosis algorithms such as HSI, TyG, and FSI also increased significantly among MASLD compared with control. The accumulation of TG and other fats in the liver cells characterizes MASLD. Abdominal obesity and elevated TG in the hepatocytes produce adipocytokines (28) associated with chronic inflammatory response, characterized by abnormal cytokine production and activation of pro-inflammatory signaling pathways. These pathophysiological changes might promote the development of MASLD (26).

Our study outlined a significantly higher value of blood glucose in patients with MASLD as compared with control which is similar to the study of Pardhe et al. and Bajaj et al. (20). Among MASLD patients, FSI and TyG significantly correlated with hyperglycemia. There is evidence that MASLD is highly prevalent in diabetes mellitus patients, and increasing evidence suggests that diabetic patients are at high risk for developing MASLD (21). Insulin resistance leads to hepatocyte fat deposition by two pathways; lipolysis and hyperinsulinemia (29). In addition, insulin resistance is recognized as a major determinant of steatogenesis and possibly liver progression (28).

In our study, a marker of obesity, BMI, and WC could not find any significant correlation with TyG among MASLD subjects, but a significant correlation was observed between LAP, FSI, and HSI. According to Marceau et al. (30) and Fassio et al. (31), BMI and WC have been considered predictors of MASLD severity. Similarly, ALT showed a significant correlation with FSI and HSI but no significant correlation with LAP and TyG. However, none of the hepatic steatosis algorithms and AST showed a significant association. ALT is often the first sign to predict MASLD, with an increase of one to three times its reference value than AST (30). Liver enzymes such as ALT and AST are linked with hepatic steatosis due to the influx of high fatty acids in the liver due to lipid peroxidation and mitochondrial dysfunction. This dysfunction causes liver toxicity producing inflammatory cytokines such as IL-6 and TNF-6. TNF-6, which plays a major role in developing hepatocellular injury causing fatty liver (25). Triglyceride delineated a significant correlation with LAP, FSI, and HSI. Although the exact cause of MASLD dyslipidemia is unknown, it is most likely caused by excessive production of VLDL and improper clearance of lipoproteins from the blood by the liver (32).

Our present study has some limitations. The assessment of hepatic steatosis algorithms, along with other algorithms like the Fatty liver index (FLI), Korean index, ZJU index, and Visceral obesity index in large population sizes, would have given better outcomes. Better results would have been obtained if these algorithms had been evaluated in conjunction with others, all in a large population. In addition, the various grades of MASLD could not be separated out in our investigation.

CONCLUSION

MASLD is a severe and expanding clinical issue since obesity and overweight are becoming more common. The findings of our study showed that the hepatic steatosis algorithms could serve as a screening tool for non-alcoholic fatty liver disease. LAP, FSI, TyG, and HSI showed better results in predicting MASLD. The optimal cut-off values of LAP, FSI, TyG, and HSI to discriminate MASLD were 31, 23, 8.9, and 34.5, respectively, with acceptable sensitivity and specificity.

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ETHICAL CLEARANCE

This research work was approved by the Institutional Review Committee of Manmohan Memorial Institute of Health Sciences (MMIHS-IRC 491), Kathmandu, Nepal. Informed consent was taken from the patients before participating in the study. Data regarding personal information were coded and kept confidential.

DATA AVAILABILITY

All the data generated during this study are presented in this paper. The primary raw data will be made available to interested researchers by the corresponding author if requested.

COMPETING INTERESTS

All the authors declare no competing interest