

Triglyceride and Glucose Index (TyG) is a Reliable Biomarker to Predict Non-Alcoholic Fatty Liver Disease

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is a common liver disease worldwide. There is no specific biomarker for the diagnosis of NAFLD. Triglyceride and glucose index (TyG) may predict the subsequent occurrence of NAFLD in later life. This cross sectional study was aimed to evaluate the effectiveness of triglyceride and glucose index (TyG) as a possible biomarker of NAFLD. The study was conducted at the Department of Laboratory Medicine, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh from March 2019 to February 2020. A total of 124 subjects were taken as study population following selection criteria. Among them 62 were diagnosed patients of NAFLD and 62 were healthy subjects as control group. Fasting plasma glucose was measured by glucose oxidase method and serum triglyceride was measured by enzymatic-colorimetric method, while TyG index was calculated accordingly. The mean age was 39.5 ± 11.27 years in NAFLD patients and 37.10 ± 12.28 years in control subjects with male female ratio 1:1.7 and 1:1.8 respectively. Major portion of NAFLD patients (62.9%) were overweight (BMI \geq 25). The mean fasting plasma glucose level was 5.73 ± 1.47 mmol/L in NAFLD patients and 5.27 \pm 0.69 mmol/L in control group (p < 0.027). The mean serum triglyceride level was $237.19 \pm 96.47 \text{ mg/dl}$ in NAFLD patients and 117.32 ± 53.07 mg/dl in control group (p < 0.001). The triglyceride and glucose index (TyG) was 9.36 \pm 0.47 in NAFLD group and 8.53 \pm 0.42 in control group. TyG index was significantly higher in NAFLD patients

in comparison to control group (p < 0.001). In ROC analysis, cut off value of TyG index was 8.85 with sensitivity 93.5% and specificity 79%. As a fast and effective method, TyG index can be used as a diagnostic tool to predict NAFLD.

Keywords

Non-Alcoholic Fatty Liver Disease (NAFLD), Plasma Glucose, Serum Triglyceride, Triglyceride and Glucose Index (TyG)

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is considered to be a major health problem worldwide due to its increased prevalence [1]. It is a part of the metabolic syndrome characterized by diabetes or pre-diabetes (insulin resistance), being overweight or obese, elevated lipid such as cholesterol and triglyceride with high blood pressure [1]. NAFLD may be defined as steatosis affecting >5% of hepatocytes in absence of excessive significant alcohol consumption, other liver disease or the consumption of steatogenic drugs [2]. Histologically NAFLD is divided into nonalcoholic fatty liver (NAFL) or simple steatosis and nonalcoholic steato-hepatitis (NASH) [2].

NAFLD is affecting about one fourth of world population [1]. The prevalence of NAFLD is increasing in Asia pacific region, affecting 30% of the general population [3]. The prevalence of NAFLD in Bangladesh is 33.86% and there is no significant difference between the genders [4]. NAFLD is the hepatic manifestation of metabolic syndrome [5]. Hepatic steatosis or triglyceride accumulation is the hallmark histologic feature of NAFLD [6]. Triglyceride accumulation in the hepatocytes is due to an imbalance between lipid accumulation and removal [6]. Several causes may lead to this excess triglyceride accumulation such as increased fat supply due to high fat diet, decreased fat exports in the form of very low density lipoprotein (VLDL) and triglyceride, decreased free fatty acid beta oxidation and de novo lipogenesis [7]. This excess triglyceride leads to development of NAFLD through liver dysfunction [6] [7]. On the other hand, hepatic fat accumulation is related to insulin resistance [8]. Excess fatty acids derived from lipogenesis and fatty acid synthesis; accumulate in peripheral tissues, liver and adipose tissues, resulting in peripheral insulin resistance [9]. It is one of the characteristics features of NAFLD. In the pathogenesis of NAFLD insulin resistance not only increases circulating insulin but also increases hepatic gluconeogenesis, impaired glucose uptake, leading to hyperglycemia [7]. This condition promotes liver fat accumulation and progression of hepatic steatosis. Therefore, when fatty liver develops these two factors, triglyceride and glucose are over produced by the fatty liver [10].

NAFLD is a serious condition and measure should be taken for diagnosis of it as early as possible. There are many invasive and noninvasive markers for the diagnosis of NAFLD. To date histopathology of liver tissue is gold standard and reliable for diagnosis of NAFLD [11]. Liver biopsy, though useful, is an invasive procedure with its own complications. Many non-invasive markers are available as an alternative of liver biopsy like-red cell distribution width (RDW), mean platelate volume (MPV), liver function tests such as measurement of aminotransferase level, markers of extracellular matrix remodeling, radiological imaging studies etc [11] [12] [13]. But previous study showed that 79% of the NAFLD patients had normal ALT [10]. Imaging techniques include ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) are used to diagnose NAFLD. The sensitivity and specificity of ultrasound of hepatic steatosis are 60% to 94% and 66% to 97% respectively [14]. But these imaging techniques have some limitations. Computed tomography (CT) has ionizing radiation. Magnetic resonance imaging (MRI) needs expert opinion. Moreover, computed tomography (CT) and magnetic resonance imaging (MRI) are expensive technique. Therefore, it is necessary to find out an easy, reliable and cost effective marker for the diagnosis of NAFLD.

As triglyceride accumulation and insulin resistance is the hallmark of NAFLD, therefore triglyceride and glucose index (TyG) may predict the subsequent occurrence of NAFLD in later life. Studies showed that there is a strong and positive association between TyG and risk of NAFLD in different population [10] [15] [16] [17]. But there is scarce evidence to evaluate the triglyceride and glucose index (TyG) among NAFLD patients in Bangladesh. Therefore, this study aimed to evaluate the role of triglyceride and glucose index (TyG) to identify NAFLD among patients attending a tertiary care hospital (BSMMU) in Bangladesh.

2. Methodology

2.1. Study Design and Study Subjects

This was a cross sectional study conducted from March 2019 to February 2020 in the Department of Laboratory Medicine, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. The study was approved by the Ethical Review Committee, BSMMU, Dhaka, Bangladesh (IRB approval N0. BSMMU/ 2019/8124). According to the statistical calculation, a total of one hundred twenty-four (124) study subjects, age 18 years or above of either sex, who attended the outpatient department of Hepatology, BSMMU, Dhaka, Bangladesh during the study period were included in this study. Among them sixty-two (62) diagnosed patient of NAFLD who fulfilled the selection criteria were selected as cases. At the same time age and sex matched sixty-two (62) healthy subjects as control group were taken. Both NAFLD and control groups were selected according to the ultrasographic evidences.

The exclusion criteria were—pregnant women or lactating mother, subjects having significant alcohol consumption (more than 30 gm/day in case of male and more than 20 gm/day in case of female), subjects carrying hepatitis B & hepatitis C virus infections, patients with autoimmune hepatic disease, other chronic

hepatic diseases *i.e.* Wilson's disease, hereditary hemochromatosis, primary billiary cirrhosis, patients with diabetes mellitus, hypertension and dyslipidaemia or any other comorbidity and subjects on any medications including vitamin supplementation.

Full explanation regarding the aims, objectives of the study and necessity of the investigations were given to all participants. Informed written consent from the respondents was obtained prior to the enrollment in the study.

2.2. Sample Size Estimation

Sample size calculation based on sensitivity (Buderer's formula):

Sample size (n) based on sensitivity = $\frac{Z_{1-\alpha/2}^2 \times S_N \times (1-S_N)}{L^2 \times \text{Prevalence}}$

We hypothesized that TyG index should detect NAFLD with a sensitivity 80% or greater. The sample size was calculated for a power level greater than 80%, *a* error 0.05 and an expected sensitivity 72.2% based on previous report [10].

The ingredients for the sample size calculation were as follows:

n = required sample size.

 S_N = anticipated sensitivity.

 α = size of the critical region (1 – α is the confidence level).

 $Z_{1-\alpha/2}$ = standard normal deviate corresponding to the specified size of the critical region (*a*).

L = absolute precision desired on either side (half-width of the confidence interval) of sensitivity.

Prevalence = the estimated prevalence of the disease in the target population (Patients who have clinically suspected nonalcoholic fatty liver disease).

$$S_N = 80\%$$

 $\alpha = 5\%$
 $Z_{1-\alpha/2} = 1.96$
 $L = 10\%$

Prevalence = 50% (we consider this value as there was no relevant data in our hospital).

Using Above formula,

$$n = \frac{1.96^2 \times 80 \times (1-80)}{0.1^2 \times 50}$$

n = 123

Therefore, final sample size was 124, divided into two groups, NAFLD group (n = 62) and control group (n = 62).

2.3. Clinical Measurements and Biochemical Analysis

Each study participants' data—which includes demographic characteristics, medical history, family history, smoking and drinking status, clinical findings and laboratory reports were recorded accordingly in a data collection sheet. Their relevant physical examination was done and anthropometry obtained comprised of weight and height. Body mass index (BMI) was calculated as weight (in kilograms)/height square (in meters). BMI was classified according to the World Health Organization (WHO) Asia-Pacific guidelines [18]: normal weight (BMI < 25 kg/m^2) and overweight (BMI $\geq 25 \text{ kg/m}^2$).

Department of Laboratory Medicine, BSMMU was used for estimation of fasting serum triglyceride and fasting plasma glucose. Samples were obtained after an overnight (8 - 12 hours) fasting. About 4.0 ml venous blood was collected in a plain tube (6 cc) from each participant following standard procedure. Each tube was labeled with the subject's identification number. Then all blood samples were kept at room temperature ($22^{\circ}C - 24^{\circ}C$) in vertical position for 30 minutes. Serum was separated by centrifugation (around 5000 rpm) for 5 - 10 minutes in room temperature and preserved at $-20^{\circ}C$ until further analysis. Fasting serum triglyceride was measured by enzymatic-colorimetric method and fasting plasma glucose was analyzed by glucose oxidase method. All the measurements were done by an auto-analyzer (SIEMENS Dimension EXL with LM). The product of triglyceride and glucose [triglyceride and glucose index (TyG)] was calculated by recognized formula [19].

2.4. Estimation of Triglyceride and Glucose Index (TyG)

The triglyceride and glucose index (TyG) of each study subject's was calculated by the following formula [19]:

 $TyG = Ln [fasting triglyceride(mg/dl) \times fasting glucose(mg/dl)/2]$

2.5. Statistical Analysis

Data cleaning validation and analysis was performed using the SPSS (Statistical Package for Social Science version 26.0) software. Categorical data were presented as frequency/percentage and continuous variable was expressed as mean \pm SD (standard deviation). Chi-square test, Unpaired Student "t" test and Receiver–operator characteristic (ROC) curve were used to analysis data. p value < 0.05 was considered as a level of significance.

3. Results

This study was intended to evaluate the role of triglyceride and glucose index (TyG) to identify patients with non alcoholic fatty liver disease (NAFLD) in Bangladeshi adults. Total 124 study subjects were included in this study. Among them 62 were NAFLD patients and 62 were healthy subjects as control group. The mean age was 39.5 ± 11.27 years (range 20 - 70 years) in NAFLD group and 37.10 ± 12.28 years (range 20-60 years) in control group, difference of mean age between the groups was not statistically significant (p = 0.258). The majority (33.9%) of the NFALD patients were in 31 - 40 years age group, while the majority (40.3%) of the control subjects were between the 20 - 30 years age group (**Table 1**).

Among total study population female were more frequent in both group with male female ratio was 1:1.7 and 1:1.8 respectively, although the gender differences between two groups were not statistically significant (p = 0.852) (Table 2).

Majority of NAFLD patients (62.9%) were overweight (BMI $\ge 25 \text{ kg/m}^2$) and a large percentage of control subjects (74.2%) were within normal body weight (BMI < 25 kg/m²). There was significant difference in BMI between NAFLD group and control group (p < 0.001) (**Figure 1**).

It was observed that mean fasting plasma glucose level was 5.73 \pm 1.47 mmol/L

Age (in years)	NAFLD group (n = 62) No. (%)	Control group (n = 62) No. (%)	p value
20 - 30	16 (25.8)	25 (40.3)	
31 - 40	21 (33.9)	17 (27.4)	
41 - 50	15 (24.2)	12 (19.4)	
51 - 60	8 (12.9)	8 (12.9)	
61 - 70	2 (3.2)	0 (0.0%)	
Mean ± SD	39.50 ± 11.27	37.10 ± 12.28	0.258 ^{ns}
Range	20 - 70	20 - 60	0.258

Table 1. Distribution of age of the study subjects between NAFLD group and control group (N = 124).

Unpaired student t-test was performed to compare between two groups; Data were expressed as frequency with percentage and mean \pm SD; Values in the parentheses denote the corresponding percentage; ns = not significant.

Table 2. Gender distribution of the study subjects between NAFLD group and control group (N = 124).

Gender	NAFLD group n = 62 No. (%)	Control group n = 62 No. (%)	p value	
Male	23 (37.1)	22 (35.5)	0.852 ^{ns}	
Female	39 (62.9)	40 (64.5)		
Male: Female ratio	1:1.7	1:1.8		

Chi-squared Test (χ^2) was done to analyze the data; Values in the parentheses denote the corresponding percentage; ns = not significant.

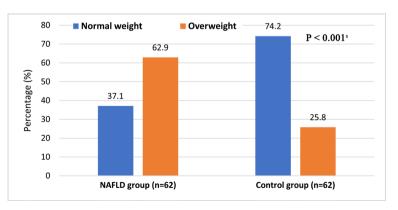


Figure 1. Bar diagram shows BMI distribution of the study subjects (N = 124).

in NAFLD patients and 5.27 \pm 0.69 mmol/L in control group. The difference was statistically significant between the groups (p < 0.027). The mean serum triglyceride level was 237.19 \pm 96.47 mg/dl in NAFLD group and 117.32 \pm 53.07 mg/dl in control group. Serum triglyceride level was significantly higher in NAFLD patients compared to the control subjects (p < 0.001) (**Table 3**).

The triglyceride and glucose index (TyG) were 8.6 - 10.7 (9.36 \pm 0.47) in NAFLD group and 7.7 - 9.3 (8.53 \pm 0.42) in control group. TyG index was significantly higher in NAFLD patients in comparison to control group (p < 0.001) (Table 4).

Figure 2 showed that the best cut off point of TyG index (blue color) was 8.85 for NAFLD. It showed the highest sensitivity (93.5%) and specificity (79%) with an area under curve (AUC) of 0.916 (95% CI; 0.0868 - 0.964), (p < 0.001).

Table 5 shows ROC curve analysis. It was found that, cut off point of TyG index was 8.85 for NAFLD. That was the highest sensitivity (93.5%) and specificity (79%) with an area under curve (AUC) of 0.916 (95% CI; 0.0868 - 0.964), (p < 0.001).

Table 6 shows effectiveness of TyG index to predict NAFLD. TyG index shows 93.55% sensitivity, 79.03% specificity, 81.69% positive predictive value and 92.45% negative predictive value.

Table 3. Comparison of fasting plasma glucose and serum triglyceride between NAFLE)
group and control group ($N = 124$).	

Variables	NAFLD group (n = 62) Mean ± SD	Control group (n = 62) Mean ± SD	p value
Fasting plasma glucose	5.73 ± 1.47 mmol/L	$5.27 \pm 0.69 \text{ mmol/L}$	0.027 ^s
Triglyceride	237.19 ± 96.47 mg/dl	117.32 ± 53.07 mg/dl	<0.001 ^s

Unpaired student t-test was performed to compare between the groups; Data were expressed as mean \pm SD; s = significant.

Table 4. Comparison of triglyceride and glucose index (TyG) between NAFLD group and control group (N = 124).

Variables	NAFLD group (n = 62) Range (Mean ± SD)	Control group (n = 62) Range (Mean ± SD)	p value	
TyG index	8.6 - 10.7 (9.36 ± 0.47)	7.7 - 9.3 (8.53 ± 0.42)	<0.001 ^s	

Unpaired student t-test was performed to compare between two groups; Data were expressed as range (mean \pm SD); s = significant.

Table 5. Receiver-operator characteristic (ROC) curve of TyG index to predict NAFLD (n = 124).

Test Result Variable(s): triglyceride and glucose index (TyG)						
AUC Cut	Crete ff a sint	nt p-value	Sensitivity	Specificity	95% CI	
	Cutoff point				Lower	Upper
0.916	8.85	< 0.001	93.5%	79.03%	0.868	0.964

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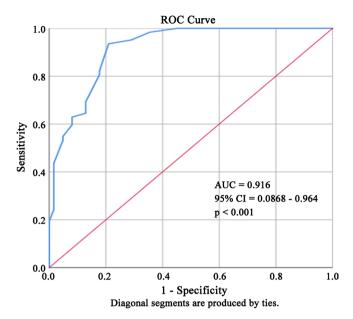


Figure 2. Receiver operating characteristic (ROC) curve of TyG index for the best prediction of NAFLD.

Parameters	Percentage (%)		
Sensitivity	93.55%		
Specificity	79.03%		
Positive Predictive Value	81.69%		
Negative Predictive Value	92.45%		

Table 6. Sensitivity and specificity of triglyceride and glucose index (TyG) to predict NAFLD.

4. Discussion

Non alcoholic fatty liver disease (NAFLD) has become one of the major causes of chronic liver disease and recently being an important public health concern worldwide. Several biomarkers associated with NAFLD have been the subject of research in last few decades. Biomarker related with metabolic syndrome provides valuable and timely diagnostic information for NAFLD. NAFLD is not only the hepatic manifestation of metabolic syndrome but also associated with type-2 diabetes mellitus, dyslipidemia, and hypertension [1]. Therefore, there is a possible relationship between triglyceride and glucose index (TyG) with NAFLD. In this study we compared the triglyceride and glucose index (TyG) between NAFLD patients and healthy control subjects. Total 124 subjects (62 diagnosed NAFLD patients and 62 healthy control subjects) were included.

In our study, it was observed that mean age of NAFLD patients was 39 (\pm 11.27) years and that of control group was 37 (\pm 12.28) years, the difference of mean age between the groups was not statistically significant (p = 0.258). These finding was consistent with previous studies [15] [20] [21]. While, in a study by Lee *et al.* the mean age of NAFLD patients was 53.11 (\pm 8.58) years and in control group

that was 52.29 (±9.70) years [5]. The mean age difference between two groups in their study was significant (p < 0.01). This result was not consistent with our study. It may be due to small sample size or demographic variable.

In our study it was observed that female were predominant in both groups. Alam *et al.* in a similar study showed female predominance, where female was 59.2% and male was 40.8% among NAFLD patients [22]. Another related study showed female predominating in NAFLD patients and that was 57% [23]. The results of the present study closely resembles with findings of these previous studies. On the other hand in another study by Zhang *et al.* observed significant difference (p < 0.0001) of the gender distribution in both groups; where male was 72.1%, female was 27.9% in NAFLD patients and in control group male was 56.5.% and female was 43.5% respectively [10]. These results were not consistent with this present study. It was reported that, fatty liver disease is a male predominant disease [10] [24], but we found female predominance in our study. This female predominance in this current study may be due to social conservative attitude which bounded most of females to stay at home for household activities, leading to sedentary life style and also due to demographic variable as reported in a previous study [4].

In this present study it was observed that majority of NAFLD patients (62.9%) were overweight (BMI $\geq 25 \text{ kg/m}^2$) and a large percentage of control subjects (74.2%) were within normal body weight (BMI < 25 kg/m²). In our study, the difference of bodyweight between the groups was statistically significant (p < 0.001). Similar results were observed in previous studies and reported that BMI is an important factor affected TyG efficacy for identifying the individuals with risk of NAFLD [4] [10] [24].

In this study, fasting plasma glucose and serum triglyceride were measured in NAFLD and control group. The mean fasting plasma glucose level was significantly higher in NAFLD patients than control group [5.73 (±1.47) mmol/L and 5.27 (± 0.69) mmol/L respectively, (p < 0.027)]. Zhang et al. in their study found the mean fasting plasma glucose level in NAFLD patient was 5.20 mmol/L and in control group that was 4.9 mmol/L, (p < 0.0001) [10]. Similarly, Lee et al. found significant higher fasting plasma glucose level in NAFLD patient [5.38 (±10.19) mg/dl] compared to control group [5.09 (± 10.50) mg/dl], (p < 0.01) [5]. Another study by Simental-Mendia et al. reported that the mean plasma glucose level in hepatic steatosis patients was significantly higher compared to control group $[5.7 (\pm 1.2)$ mmol/L versus 5.3 (± 2.5 mmol/L), (p < 0.001)] [25]. On the other hand in this study, there was significant increase in serum triglyceride level in NAFLD patients compared to control group [237.19 (±96.47) mg/dl versus 117.32 (±53.07) mg/dl (p < 0.001)]. In a similar study Zhang *et al.* showed that a significant increase in serum triglyceride level in NAFLD patients (61.87 mg/dl) when compared to control group (34.80 mg/dl) (p < 0.0001) [10]. Another related study Simental-Mendia et al. showed that the mean serum triglyceride level was significantly higher in patients with NAFLD (37.8 mg/dl) in comparison to control group (19.8 mg/dl) (p < 0.01)

[25]. These results were also consistent with this present study.

In the current study, it was observed that the mean triglyceride and glucose index (TyG) in NAFLD patients was 9.36 (±0.47) and in control group that was 8.53 (±0.42). The range of TyG index was 8.6 - 10.7 in NAFLD group and 7.7 - 9.3 in control group. There was significant increased in TyG index in NAFLD group as compared to control group (p < 0.001). Zhang *et al.* have shown that the mean TyG index was 8.8 (ranged 8.4 - 9.3) in NAFLD patients and 8.2 (ranged 7.8 - 8.6) in control group, which was statistically significant (p < 0.0001) [10]. Another study by Zheng *et al.* obtained the mean TyG index was 8.58 (ranged 8.25 - 8.91) in NAFLD patients and 8.21 (ranged 7.91 - 8.54) in control group, which was statistically significant (p < 0.0001) [15]. Simental-Mendia *et al.* showed that the mean TyG index was 4.95 (±0.22) in NAFLD patients and 4.50 (±0.28) in control group, which was statistically significant (p < 0.001) [25]. The results of the present study closely resemble findings from previous studies.

The receiver-operating characteristics (ROC) curve of TyG index for the diagnosis of NAFLD was depicted in our study. The area under the curve (AUC) for predicting the patients with NAFLD was 0.916 (95% CI, 0.868 - 0.964). Zhang *et al.* found the AUC was 0.782 (0.773 - 0.793) for diagnosis of NAFLD [10]. Another study by Zheng *et al.* found the AUC to predict the development of NAFLD was 0.76 (0.74 - 0.77) [15]. Yu *et al.* found the AUC of the ROC curve for TyG index for metabolic unhealthy male was 0.863 (95% CI, 0.857 - 0.869) and in female that was 0.867 (95% CI, 0.862 - 0.872) [26]. The finding of the present study was supported by the findings of those previous studies.

Using the receiver-operating characteristics (ROC) curve we calculate the potential cut-off value to diagnosis of NAFLD patients. An optimal cut-off value of TyG index for NAFLD patient was found 8.85. In this study, sensitivity and specificity of TyG index was found 93.5% and 79.03% respectively. Zhang *et al.* found cut-off point of TyG for diagnosing NAFLD was 8.5, with sensitivity of 72.2% and specificity of 70.5% [10]. Another study by Zheng *et al.* showed the cut-off point of TyG index for predicting NAFLD was 8.52, with sensitivity 67.3% and specificity 71.9% [15]. Simental-Mendia *et al.* observed the cut-off point of TyG index was 4.58 with sensitivity 94%, specificity 69% [25]. These findings were nearly consistent with the findings of this current study.

This study demonstrated a strong and positive association between TyG index and risk of NAFLD. Liver biopsy is an invasive procedure and the imaging techniques for NAFLD are not convenient in routine clinical practice, hence serum biomarkers are preferred. Therefore the TyG index may be widely used for identification of individuals with NAFLD. It is concluded that cut-off value for TyG index in our study population was 8.85, which might help the physicians as an additional tool for diagnosis of NAFLD.

5. Conclusion

The occurrence of NAFLD significantly increases with increasing level of TyG

index. It is a simple biomarker for routine clinical practice which can be done easily. Therefore, measurement of TyG index is effective to identify individuals at risk for NAFLD. A TyG cut-off value of 8.85 was highly sensitive for detecting NAFLD subjects and could be used as a diagnostic tool for NAFLD in Bangladeshi adults.

Limitations

It was a single centre study with a relatively small sample size. Moreover, the diagnosis of NAFLD was based on ultrasonography findings that may be less accurate compared to the diagnosis based on a liver biopsy.

Recommendation

A population based prospective study with large sample size should be done to establish the triglyceride and glucose index (TyG) as a reliable biomarker of NAFLD.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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