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Association of fatty liver with serum gamma-glutamyltransferase and uric acid in obese children in a tertiary care centre

Vidanapathirana Dinesha Maduri[1,2*], Jasinge Eresha[1], Samaranayake Dulani[3] and Wickramasinghe Pujitha[4]

Abstract

Background Obesity among the young is an emerging health problem with many metabolic changes including liver damage. Our objective was to investigate the association of fatty liver with serum uric acid (UA) and gamma-glutamyltransferase (GGT) in a cohort of obese children in Sri Lanka.

Methods A cross-sectional analytical study was conducted among 5-15-year-old obese children (based on WHO 2007 standards). After a 12-hour overnight fast, blood was drawn for glucose, lipid profile, alanine aminotransferase (ALT), aspartate aminotransferase (AST), insulin, UA and GGT. Height, weight, waist circumference, blood pressure and fat mass were measured. Ultrasound scan of abdomen was performed to determine fatty liver.

Results We studied 146 obese children with a mean age (SD) 9.86 (2.1) years. The fatty liver group showed significantly elevated levels ($p < 0.05$) of UA, oral glucose tolerance test (OGTT), triglycerides (TG), AST, ALT, GGT, insulin resistance (HOMA-IR) and a reduced AST/ALT ratio, compared to the non-fatty liver group. Chi square test showed statistically significant associations between fatty liver and AST, ALT, AST/ALT ratio, HOMA-IR, UA and GGT. With existing cut offs, GGT (> 30 U/L) and UA (> 330 µmol/L) the sensitivity and specificity of GGT in predicting fatty liver was 26.9% and 94.1% respectively while for UA it was 38.5% and 83.8% respectively. A cut-off value of 18.5 U/L (sensitivity 76.9% and specificity 52.9%) for GGT, 277µmol/L (sensitivity 70.5% and specificity 57.4%) for UA, 27.5 U/L (sensitivity 70.5%, specificity 51.5%) for AST, 21.5 U/L (sensitivity 80.8% and specificity 61.8%) for ALT, a ratio of 0.99 (sensitivity 77.9% and specificity 55.1%) for AST/ALT and 2.02 (sensitivity 73.2%, specificity 58.5%) for HOMA-IR predicted fatty liver.

Conclusion GGT and UA are associated with fatty liver and these biomarkers can be used to predict fatty liver disease.

Keywords Fatty liver, Uric acid, Gamma-glutamyltransferase, Obesity

*Correspondence:
Vidanapathirana Dinesha Maduri
maduri@sjp.ac.lk
[1]Department of Chemical Pathology, Lady Ridgeway Hospital, Colombo, Sri Lanka
[2]Department of Pathology, Faculty of Medical Sciences, University of Sri Jayewardenepura, Nugegoda, Sri Lanka
[3]Department of Community Medicine, Faculty of Medicine, University of Colombo, Colombo, Sri Lanka
[4]Department of Paediatrics, Faculty of Medicine, University of Colombo, Colombo, Sri Lanka

Background

Globally, childhood obesity is increasing, impacting both industrialized and developing nations.

In 2016, the prevalence of childhood obesity was 5.6% for girls and 7.8% for boys worldwide [1, 2]. A recent survey conducted in Sri Lanka in an urban setting showed the prevalence of obesity and overweight among 5–18-year-olds to be 10.3% and 11.3% respectively [3, 4]. There are many causes attributed to the high incidence of childhood obesity in the developing world which include sedentary behavior, urbanization, and unhealthy dietary habits.

In 2023, a multi-society Delphi consensus redefined NAFLD (non-alcoholic fatty liver disease) and nonalcoholic steatohepatitis (NASH) to metabolic dysfunction–associated steatotic liver disease (MASLD)/metabolic dysfunction–associated steatohepatitis (MASH) [5]. MASLD is one of the most prevalent health issues in obese children, along with the rising prevalence of juvenile obesity [6]. The frequency of MASLD in the pediatric population varies between 3 and 12%, according to studies, but it rises to 70–80% in obese children [7, 8]. There are significant regional variations in the prevalence of fatty liver disease. Asians are more likely than people with European, the Middle Eastern/North African, or North American ancestry to have MASLD [8].

Steatosis, metabolic dysfunction-associated steatohepatitis (MASH), with or without fibrosis, cirrhosis, and end-stage liver disease are all included in the range of hepatic disorders known as (MASLD) [9]. The extent of fat accumulation in the liver can serve as an indicator for assessing both the presence and severity of the disease [10, 11]. Imaging techniques such as ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) are commonly employed to evaluate MASLD [12]. Liver biopsy helps to determine presence and severity of inflammation and damage to the liver cells but due to its invasive nature, liver biopsy is rarely performed in children [13].

Several studies have shown an association between fatty liver and cardiovascular disease in obese children [14, 15]. Furthermore, many studies have revealed an association of serum gamma-glutamyltransferase (GGT) and uric acid (UA) with fatty liver [14, 16, 17].

Serum UA is the final product of purine metabolism in the liver, and its involvement in initiating inflammatory responses through various mechanisms, such as nitric oxide, interleukins, and increased oxidative stress in different tissues, has been proposed [18, 19]. Elevated UA levels, or hyperuricemia, are closely linked not only to cardiovascular diseases but also to insulin resistance in the liver [20]. A study showed that hyperuricaemia is independently associated with ultrasonically detected MASLD, regardless of insulin resistance [21].

GGT is crucial in the production and metabolism of extracellular glutathione, a key antioxidant in the body's defense system. Elevated GGT levels in individuals with MASLD have been linked to several factors, including oxidative stress, inflammatory response, and fat accumulation in the liver. These factors contribute to disrupted insulin signaling and the development of insulin resistance (IR) [22, 23].

Therefore, our aim was to determine the association of fatty liver with serum UA and GGT in obese children and to determine the validity of these markers in predicting fatty liver in a group of Sri Lankan children. To our knowledge to date there is no research conducted to explore the relationship of GGT and UA with fatty liver in Sri Lanka.

Method

One hundred and forty six, 5–15 year-old children with obesity, based on body mass index for age greater than two standard deviations from the median (WHO-2007 standards), attending the obesity clinic at Lady Ridgeway Hospital, a tertiary care centre hospital in Colombo, were recruited from October 2016 to February 2017. Children were referred by physicians after evaluating and excluding other possible pathologies for hepatomegaly. Children with long-standing illnesses, on long-term medication, children with an underlying illness that accounts for obesity and children recovering from an acute illness acquired within the last 2 weeks and any history of alcohol use were not included. Written informed consent from parent or guardian was obtained and ethical approval was obtained from the Ethics Review Committees of Lady Ridgeway Hospital and Faculty of Medicine, University of Colombo.

Using standard protocols, all anthropometric measurements (weight, height, waist circumference, and blood pressure) were obtained. Weighing was done barefoot and with little clothing, measured to the nearest 0.1 kg, using an electronic weighing scale (Soehnle, Soehnle-Waagen GmbH & Co, Germany). A stand-mounted stadiometer (Surgical and Medical Products, Brisbane, Australia) was used to measure the subject's height. Subjects were made to stand without shoes according to standard protocol, and measurements were made to the closest 0.1 centimeter. Using a plastic non-stretchable flexible tape, the waist circumference was measured to the nearest 0.1 centimeter at the end of a typical expiration, halfway between the iliac crest and lower rib border at the mid axillary line. After a 10-minute break, blood pressure was measured while seated using a mercury sphygmomanometer with proper size cuffs.

Using the InBody 230 BIA equipment (InBody®, South Korea), the bioelectrical impedance (BIA) approach was used to determine the body's fat composition. The

height-weight equation [24] and the BIA-specific equation [25] for Sri Lankan children verified the measurements taken by this device. The research participants were instructed to abstain from all forms of physical exertion and come to the laboratory in the morning after a 12 h overnight fast.

An expert radiologist used standard criteria to carry out liver ultrasonography [26, 27]. A slightly elevated liver echogenicity with normal vessels and no posterior attenuation was classified as mild steatosis; a moderately increased liver echogenicity with partial vessel dimming and early posterior attenuation was classified as moderate steatosis; and a diffusely increased liver echogenicity with no visible vessels and heavy posterior attenuation was classified as severe steatosis. Any level of fatty liver without alcohol consumption or hepatitis B and C virus infection was considered MASLD. The absence of fatty liver was the definition of normal liver.

Blood, after 12 h overnight fasting was taken for the measurement of glucose, lipid profile, alanine aminotransferase (ALT), aspartate aminotransferase (AST), insulin, UA, and GGT following a 12-hour overnight fast. Anhydrous glucose was administered in the oral glucose tolerance test (OGTT) at a dose of 1.75 g/kg body weight to a maximum of 75 g, and plasma glucose (PG) was measured two hours later.

Laboratory assays

Blood samples were assayed within 6 h after collection. Samples that could not be analysed on the same day serum/plasma were separated and stored at– 30 °C. Plasma glucose (both fasting plasma glucose and 2 h PG of the OGTT (hexokinase method), triglyceride (TG) (enzymatic colorimetric test without glycerol blanking), high density lipoprotein (HDL) (direct homogenous enzymatic method), ALT and AST (modified International Federation of Clinical Chemistry (IFCC) recommended enzymatic kinetic UV method), GGT (IFCC recommended gamma-glutamyl-3-carboxy-4-nitroanlide as substrate method), UA (enzymatic uricase method) were measured on an AU 480 fully automated Beckman Coulter biochemistry analyzer using standard reagent kits supplied by the manufacturer of the analyzer. Insulin was analysed by chemiluminescent enzyme immunometric assay on Immulite 1000 analyzer. The precision of all these assays was within the manufacturer's specifications.

Standard internal and external quality control procedures were carried out using serum-based quality control samples to ensure assay validity.

Statistical analysis

Data were analysed using SPSS® statistical package version 21.0 for windows. The cut off for homeostatic model assessment for insulin resistance (HOMA-IR) was taken as 2.5 [28]. The cut off values for abnormal GGT and UA were taken as > 30 U/L and > 330 µmol/L respectively [29, 30]. A serum ALT level of more than 40 IU/L and a serum AST level more than 30 U/L were considered abnormal [31, 32]. FBS > 100 mg/dL and 2 h OGTT > 140 mg/dL were considered abnormal [33].

Chi-square test was used to assess the association of UA and GGT with fatty liver. Receiver operator characteristic (ROC) curves were created and optimum cutoff values maximizing sensitivity and specificity were determined. All analysis were two tailed and level of significance was considered at $p < 0.05$.

Results

Between October 2016 and February 2017, we enrolled 146 obese children to our study. The cohort had an average age of 9.86 years (SD 2.1). Prevalence of fatty liver in the sample was 53.4% ($n = 78$).

Majority of the participants were boys ($n = 146$, 71.9%), with a significant representation from the Sinhalese ethnic group ($n = 146$, 73.3%).

Table 1 shows the descriptive statistics of biochemical parameters between obese children with fatty liver and non-fatty liver. Uric acid levels were higher in the fatty liver group (305.87) compared to the non-fatty liver group (280.06) with a significant difference ($p = 0.02$). Statistically significant differences ($p < 0.05$) were observed for UA, OGTT, TG, AST, ALT, AST/ALT, GGT, and HOMA-IR between the fatty liver and non-fatty liver groups (Table 1).

Table 2 reveals association of fatty liver with different metabolic parameters. Among the children who had fatty liver, 66.7% had elevated insulin resistance (HOMA-IR) while children with no fatty liver 33.3% had elevated HOMA-IR. This difference was significant ($p = 0.001$). Significant associations ($p < 0.05$) between HOMA-IR and AST, ALT, AST/ALT ratio, UA and GGT were seen (Table 2).

Analyzing the sensitivity and specificity of existing cutoffs for GGT (> 30 U/L) and UA (> 330 µmol/L) in predicting fatty liver, we found GGT to have a sensitivity of 26.9% and a specificity of 94.1%, while UA shows a sensitivity of 38.5% and specificity of 83.8%.

Figure 1a–e ROC curves for GGT, UA, ALT, AST, and AST/ALT, respectively, in predicting fatty liver. Notably, GGT's ROC curve yields an area under the curve of 0.704 (significant at $p = 0.000$) with a cutoff of 18.5 U/L with a sensitivity of (77.9%) and specificity (52.9%). For UA, AUC of 0.630($p = 0.007$), the cutoff value of 280.5 µmol/L yields a sensitivity (69%) and specificity (61%).

In the case of ALT, its ROC curve exhibits an AUC of 0.738 ($p = 0.000$), with a cutoff value of 21.5 U/L providing a sensitivity of 80% and specificity of 61%. For AST, the AUC is 0.673 ($p = 0.000$), with a cutoff of 28.5 U/L

Table 1 Descriptive statistics of biochemical parameters between obese children with fatty liver and non-fatty liver ($n=146$)

Metabolic parameter	Fatty liver present			Fatty liver absent			**Significance
	N	Mean	SD	*N*	Mean	SD	
Systolic blood pressure	78	-1.22	0.80	68	-1.41	0.74	$P=0.146$
Diastolic blood pressure (DBP)	78	0.97	0.76	68	0.86	0.73	$P=0.336$
FBS	78	86.95	9.74	68	86.42	8.60	$P=0.727$
OGTT	78	121.63	32.78	68	110.43	18.85	***P*=0.014**
Cholesterol	78	191.20	36.73	68	181.18	34.66	$P=0.094$
Triglyceride	78	123.07	61.40	68	101.19	44.04	***P*=0.016**
HDL	78	40.6	7.991	68	42.21	9.74	$P=0.277$
LDL	78	127.29	35.29	68	121.80	26.36	$P=0.295$
AST	78	43.19	47.43	68	30.59	19.00	***P*=0.042**
ALT	78	46.32	45.19	68	25.49	23.99	***P*=0.001**
AST/ALT ratio	78	1.16	0.72	68	1.45	0.58	***P*=0.010**
G GT	77	26.00	12.41	68	19.88	9.81	***P*=0.001**
Uric acid	78	305.87	63.60	68	280.06	68.53	***P*=0.020**
*HOMA-IR	71	3.65	2.61	65	2.16	1.53	***P*=0.000**

**Using independent samples T test

*There were 10 missing values in fasting insulin

Table 2 Association of fatty liver with metabolic abnormalities

Metabolic parameter		Fatty liver		Significance
		Present	Absent	
FBS	High	7 (50.0%)	7 (50.0%)	$X^2=0.073$
	Normal	71 (53.8%)	61 (46.2%)	df = 1
				$p=0.787$
OGTT	High	10 (71.4%)	4 (28.6%)	$X^2=2.017$
	Normal	68 (51.5%)	64 (48.5%)	df = 1
				$p=0.156$
Triglyceride	High	16 (61.5%)	10 (38.5%)	$X^2=0.837$
	Normal	62 (51.7%)	58(48.3%)	df = 1
				$p=0.360$
HDL	Low	43 (53.8%)	37 (46.2%)	$X^2=0.008$
	Normal	35 (53.0%)	31 (47.0%)	df = 1
				$p=0.931$
DBP	High	2 (66.7%)	1 (33.3%)	$X^2=0.000$
	Normal	76 (53.1%)	67 (46.9%)	df = 1
				$p=1.000$
*HOMA-IR	High	44 (66.7%)	22 (33.3%)	$X^2=10.747$
	Normal	27 (38.6%)	43 (61.4%)	df = 1
				$P=0.001$
AST	High	26 (81.2%)	6 (18.8%)	$X^2=12.752$
	Normal	52 (45.6%)	62 (54.4%)	df = 1
				$p<0.001$
ALT	High	31 (79.5%)	8 (20.5%)	$X^2=14.527$
	Normal	47 (43.9%)	60 (56.1%)	df = 1
				$p<0.001$
AST/ALT	Ratio > 1	35(39.8%)	53 (60.2%)	$X^2=16.592$
	Ratio < 1	43 (74.1%)	15 (25.9%)	df = 1
				$p<0.001$
Uric acid	High	30 (73.2%)	11 (26.8%)	$X^2=8.933$
	Normal	48 (45.7%)	57 (54.3%)	df = 1
				$p=0.003$
GGT	High	21(84%)	4(16%)	$X^2=11.333$
	Normal	57 (47.1%)	64 (52.9%)	df = 1
				$p=0.001$

*There were 10 missing values in fasting insulin

giving a sensitivity of 67% and specificity of 55%. Lastly, the ROC curve for AST/ALT in predicting fatty liver yields an AUC of 0.687 (significant at $p=0.000$), with a ratio of 0.99 providing a sensitivity at 55.1% and specificity both at 77.9%. Table 3 shows the validity of AST, ALT, AST/ALT, GGT and UA with existing cut-offs and new cut-offs in predicting fatty liver.

Discussion

MASLD is the most prevalent chronic liver condition in children and is a significant consequence of obesity [34]. Although percutaneous liver biopsy is the gold standard for diagnosing MASLD, its invasive nature highlights the need for noninvasive methods to detect the condition in children and adolescents. In our study, fatty liver was found more often in males than females, with a prevalence of 72% in boys compared to 28% in girls. This gender difference aligns with findings from studies conducted on obese children in Asia and America, where hepatic steatosis was also more commonly observed in boys than in girls [16, 35, 36].

Numerous studies in the literature have explored the connection between elevated UA, obesity, and metabolic syndrome. In our research, we found significantly higher UA levels in individuals with fatty liver ($p<0.015$) compared to those without detectable fatty liver. A study by Fu et al., involving 861 obese children, 587 of whom had MASLD, demonstrated a significant association between increased UA levels and the development of MASLD ($p<0.05$) [16]. Similarly, Sartorio et al. reported a notable difference in UA values between children with and without MASLD ($p<0.001$) [14].

Free fatty acids (FFAs) stimulate beta-oxidation and contribute to mitochondrial oxidative stress, leading to

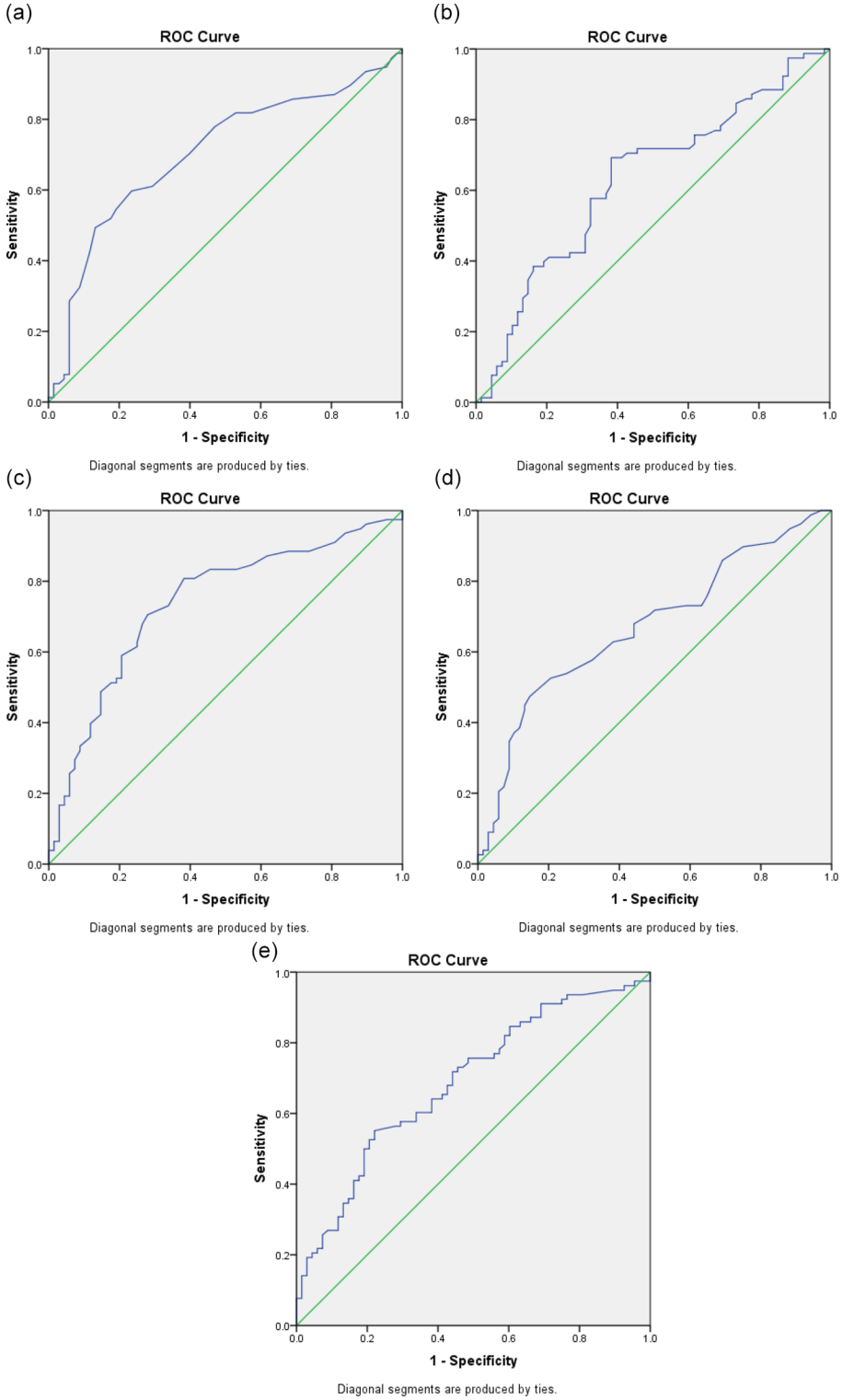

Fig. 1 **a** ROC for GGT in predicting fatty liver (AUC 0.704, $P < 0.000$, 95% CI 0.617 ~ 0.790). **b** ROC curve for serum uric acid in predicting fatty liver (AUC 0.630, $P < 0.007$, 95% CI 0.538 ~ 0.721). **c** ROC curve for ALT in predicting fatty liver (AUC 0.738, $P < 0.000$, 95% CI 0.656 ~ 0.821). **d** ROC for AST in predicting fatty liver (AUC 0.673, $P < 0.000$, 95% CI 0.585 ~ 0.760) **e** ROC for AST/ALT ratio in predicting fatty liver (AUC 0.687, $P < 0.000$, 95% CI 0.601 ~ 0.773)

Table 3 Validity of AST, ALT, AST/ALT, GGT and UA (existing cut-offs) and new cut-offs in predicting fatty liver

Parameter cut off	Existing cut-offs		Parameter	Cut-off	New cut-offs	
	Sensitivity	Specificity			Sensitivity (%)	Specificity (%)
AST (30 U/L)	62.8	61.8	AST (U/L)	28.5	67	55
ALT (40 U/L)	52.6	80.9	ALT (U/L)	21.5	80	61
AST/ALT (1)	56.4	72.1	AST/ALT	0.99	55.1	77.9
GGT (30 U/L)	26.9	94.1	GGT(U/L)	18.5	77.9	52.9
UA (330 µmol/L)	38.5	83.8	UA (µmol/L)	280.5	69	61

the production of free radicals [37]. This oxidative stress damages hepatocytes and may affect the hepatobiliary system in obese individuals, potentially increasing GGT levels in obese children with MASLD [38]. Our study found a statistically significant association between elevated GGT and fatty liver in obese children. Similarly, a study by Kim et al. showed that in obese children aged 10 years or younger, GGT levels were significantly different ($p < 0.001$) in those with MASLD compared to those without [17].

Our study showed an association between fatty liver and AST, ALT, AST/ALT ratio, HOMA-IR, UA and GGT. A study by Pirgon et al., which included 46 obese adolescents and 29 control subjects, found a significant difference in fasting insulin levels and HOMA-IR values between obese adolescents with and without hepatic steatosis ($p < 0.05$) [39]. However, no significant correlation was observed between fasting glucose levels and the presence of MASLD [39]. In our study we observed that HOMA-IR was significantly higher in the fatty liver children while there was no significant relationship between fasting glucose and fatty liver.

In obesity-related MASLD, increased ALT levels occur due to damage from the buildup of lipid droplets within the hepatocyte cytoplasm [40]. In this study, a significant increase in ALT levels was observed in children with fatty liver ($p = 0.004$). Similar findings were reported by Denzer et al., where a study involving 532 obese children revealed significantly higher ALT level in those with hepatic steatosis ($p < 0.001$) [41]. Additionally, a study by Radetti et al. demonstrated a significant correlation between MASLD and ALT levels ($p < 0.001$) [42].

In obesity-induced MASLD, ALT levels can either remain within the normal range or rise up to 10 times the normal value [11]. A study by Schwimmer et al. found that using ALT levels twice the gender-specific cutoff (ALT ≥ 50 for boys and ≥ 44 for girls) in overweight and obese children aged 10 and older had a sensitivity of 88% and a specificity of 26% for diagnosing MASLD [43]. In our study, the area under the curve for ALT in predicting fatty liver was 0.784, which was statistically significant. A cut-off value of 21.5 U/L was identified, providing good sensitivity (80%) and specificity (71%) for ALT in predicting fatty liver. It is noteworthy that the lower cut-off values for AST and ALT in our study, compared to the findings of Schwimmer et al., could be attributed to the smaller sample size in our study, which exclusively included obese children.

The cut-off values for GGT and UA can serve as practical guidelines for clinicians. For instance, a GGT level greater than 30 U/L and UA above 330 µmol/L can indicate a higher risk of fatty liver, helping healthcare providers to prioritize further evaluation and management for at-risk children. Therefore, this study provides valuable insights that can inform clinical practices, enhance early detection, and promote preventive measures against fatty liver disease in obese children.

Our study had several limitations. Firstly, ultrasonography is a generally available and non-invasive technology but it may underestimate the prevalence of fatty liver since it is unable to identify fatty infiltration in 30% of people. Secondly, while we did not conduct tests to rule out ALT elevations due to metabolic disorders including alpha-1-antitrypsin deficiency and Wilson's disease, we did exclude ALT elevations caused by alcohol consumption, viral infections, and medication use. Thirdly this study was a single center study design. Fourthly, disease-free controls were not used. Further, studies with larger sample sizes could provide more universally applicable cut-offs for GGT and UA to predict fatty liver in pediatric population. Furthermore gender specific cut offs were not used for ALT and its potential impact on the study findings is a limitation.

While our study identified a lower cut-off value for GGT in predicting fatty liver in obese children, we acknowledge its limitations in terms of sensitivity and potential clinical utility as a standalone screening tool. The relatively low sensitivity of GGT underscores the need for a multi-marker approach to improve diagnostic accuracy. Combining GGT with other biomarkers such as UA and ALT could enhance the predictive value for identifying children at risk of fatty liver disease.

The unique context of Sri Lanka, with its distinct combination of dietary patterns, genetic predispositions, and environmental factors, offers valuable insights into the association of fatty liver with serum GGT and UA. Our study addresses the paucity of local data on pediatric obesity and its metabolic complications, establishing locally relevant reference values and predictive cut-offs for biomarkers like GGT and UA. The findings, including

lower optimal cut-off values for these markers compared to international thresholds, underscore the need for population-specific research and interventions tailored to the Sri Lankan pediatric population.

Furthermore, our findings highlight the importance of validating these cut-offs in larger, more diverse cohorts to ensure their generalizability. Many biological parameters show lower cutoff levels in populations of South Asian ancestry. This is much clearer with anthropometric and body composition parameters, which has even led to use ethnic specific cutoff values in certain biological parameters in multi ethnic populations [44]. Therefore, although the cutoff values we described are quite low, they cannot be simply dismissed just because they appear low. Future studies should be conducted to explore their validity and integrate these biomarkers into predictive models tailored for clinical practice, particularly in resource-limited settings. These efforts would contribute to the development of effective, population-specific screening strategies for pediatric fatty liver disease.

In conclusion, fatty liver is associated with GGT and UA, and these biomarkers could be helpful in predicting fatty liver disease. The clinical use of noninvasive predictive markers for fatty liver, such as elevated serum GGT and UA levels, may be helpful in effectively examining children with obesity in the early stages of disease progression because it is more difficult, and sometimes may not be ethical, to perform an invasive diagnostic procedure on younger children than on adolescents and adults. Thus, these biomarkers could be useful biochemical predictors for early identification of fatty liver in obese children and aid in halting the progression of the disease with early lifestyle modification therapies, favoring long-term results.

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Author contributions
DMV has made substantial contribution to the conception, designing and drafting the manuscript. DS analyzed the data. EJ and PW revised the draft. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Written informed consent from parent or guardian was obtained and ethical approval was obtained from the Ethics Review Committees of Lady Ridgeway Hospital and Faculty of Medicine, University of Colombo (EC-16-170).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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