Comparison between non-alcoholic fatty liver disease screening guidelines in children and adolescents

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Graphical abstract

Prevalence of suspected NAFLD in overweight and obese children determined by two different NAFLD guidelines.Using the combination of elevated ALT and fatty infiltration on ultrasound (European guidelines) increases the detection rate of suspected NAFLD in at risk children.
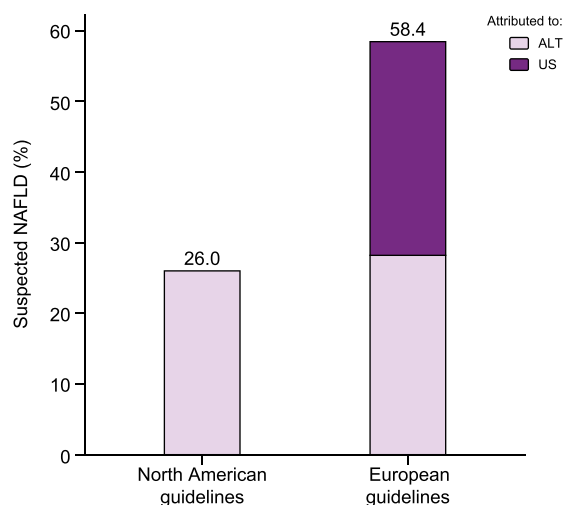
Highlights

- Non-alcoholic fatty liver disease might be missed in at-risk children by relying on ALT values alone.

- A significant percentage of obese children with fatty infiltration on ultrasound have low ALT values.

- Children with fatty infiltration on ultrasound and low ALT values were less likely to have metabolic syndrome.

Lay summary

Using the combination of elevated alanine aminotransferase and fatty infiltration on ultrasound increases the detection rate of suspected non-alcoholic fatty liver disease in at-risk children. Notably, a significant percentage of children with fatty infiltration on ultrasound have low alanine aminotransferase (<52/44). Children with fatty infiltration on ultrasound and low alanine aminotransferase may be less likely to have features of the metabolic syndrome.

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Background & Aim: There is currently no agreement on the screening strategy for non-alcoholic fatty liver disease (NAFLD) in children at risk. The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) recommends screening for NAFLD using alanine aminotransferase (ALT) in obese/overweight children, while the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommends using both ALT and abdominal ultrasound. The aim of this study was to assess the prevalence of suspected NAFLD in obese children based on the 2 screening strategies.
Method: Consecutive overweight/obese children seen at a weight-management program were included. Each child underwent a liver ultrasound and had ALT level measured at first visit. Two screening strategies were compared: the NASPGHAN strategy using ALT >2x the gender specific cut-off and the ESPGHAN strategy using elevated ALT >45 IU/L and/or fatty liver on ultrasound. Univariate and multivariate analyses were performed to assess predictors of low ALT in individuals with evidence of suspected NAFLD on ultrasound.
Results: Overweight/obese children were included. NAFLD was suspected as follows: 26% based on the NASPGHAN strategy, and 58% based on the ESPGHAN strategy. Fatty liver was present on ultrasound in 53% of our cohort. ALT was >2x the gender specific cut-off in only 26% of children with fatty liver on ultrasound. Univariate and multivariate analyses indicated that children with fatty infiltration on ultrasound and low ALT were less likely to have metabolic syndrome, insulin resistance, or hypertriglyceridemia.
Conclusion: By relying on ALT values alone to screen for NAFLD, suspected NAFLD might be missed in many children who are at risk. Children with fatty infiltration on ultrasound and low ALT may be less likely to have metabolic syndrome, insulin resistance or hypertriglyceridemia.

Introduction

Non-alcoholic fatty liver disease (NAFLD) has become the most common cause of chronic liver disorders in children and adolescents in the United States. NAFLD is defined by the presence of excessive hepatic fat accumulation in the absence of significant alcohol intake or other liver disorders. NAFLD encompasses a board spectrum, ranging from non-alcoholic fatty liver (NAFL) or simple steatosis to non-alcoholic steatohepatitis (NASH) which is characterized by inflammation and ballooning of hepatocytes with potential progression to fibrosis, cirrhosis, and hepatocellular carcinoma [1]. In children, the whole spectrum of NAFLD can be seen from NAFL to cirrhosis, even hepatocellular carcinoma has been reported as a complication of NAFLD [2,3]. It has been recognized that obese

children and adolescents with NAFLD are at increased risk of other medical health problems such as cardiovascular disease and metabolic syndrome, compared to obese children and adolescents without NAFLD [4–6].

Biopsy-proven NAFLD is estimated to be present in 9.6% of all children between 2 and 19 years of age and 38% of obese children in the United States [7]. It is a growing epidemic among children and some studies estimate that the prevalence more than doubled over the past 20 years, affecting 10.7% of adolescents in the United States between 2007-2010 [8]. This alarming increase highlights the need to develop effective screening guidelines. Unfortunately, to date there has been no agreement on screening strategies for NAFLD in children at risk. In 2007, The American Academy of Pediatrics recommended screening for NAFLD starting at age of 10 years or older by measuring alanine aminotransferase (ALT) and aspartate aminotransferase (AST) biannually in overweight children whose body mass index (BMI) was between the 85th to 94th percentile if there are risk factors, and in obese children whose BMI was >95% even if there are no risk factors [9]. In 2012, European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommended screening all overweight and obese children (>3 years age) for NAFLD by performing

abdominal ultrasound and liver tests [10]. No recommendations were made by The American Association for the Study of Liver Diseases for screening of overweight and obese children for NAFLD due to "insufficient evidence" [11]. The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) recommended screening for NAFLD, in obese children with or without risk factors and overweight children with additional risk factors, by measuring ALT, but did not recommend abdominal ultrasound [12]. In this study, we aimed to assess the prevalence of suspected NAFLD in overweight and obese children based on screening strategies that are recommended by different practice guidelines; The North American Guidelines (NASPGHAN) compared to the European Guidelines (ESPGHAN).

Patients and methods

We retrospectively reviewed charts of overweight and obese children seen in our multidisciplinary weight-management program at Cleveland Clinic Children's hospital between 11/2011 and 7/2016. Patients were referred to our clinic for NAFLD evaluation if they were obese or overweight with risk factors for NAFLD such as insulin resistance. This study was approved by the Institutional Review Board at Cleveland Clinic and due to the retrospective nature of the study, informed consent was not needed. Each child underwent a liver ultrasound and had ALT level measured at the time of their first visit. Overweight, obese and severely obese were defined as follows: BMI percentile between 85–94.9%, 95–98.9% and ≥99%, respectively. We excluded individuals missing BMI percentile, ALT or fatty liver on ultrasound, as well as those in the BMI percentile <85%. Two screening strategies were compared: the NASPGHAN strategy using ALT >2x the gender specific cut-off (>52 IU/L for boys and >44 IU/L for girls) was compared to the ESPGHAN strategy using elevated ALT >45 IU/L and/or fatty liver infiltrate on ultrasound. ALT was considered low if it was <2x the gender specific cut-off. Other etiologies of chronic liver disease were ruled out. Metabolic syndrome was defined as central obesity (waist ≥90th percentile) with any 2 of the following: impaired fasting glucose/type 2 diabetes, hypertension (defined as systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥ 85 mmHg), high-density lipoprotein (HDL) <40 mg/dl or triglycerides >150 mg/dl).

Statistical analysis

Data are presented as median [interquartile range] or frequency (%). Prevalence of suspected NAFLD was defined as the percentage of individuals meeting each definition. A univariate analysis was performed to assess differences between individuals with low and high ALT in those with evidence of fatty infiltration on ultrasound. Multivariate logistic regression analysis was performed to assess independent predictors of low ALT in those with evidence of fatty infiltration on ultrasound. Kruskal-Wallis tests were used to assess differences in continuous variables and Pearson's chi-square tests, or Fisher's exact tests were used for categorical factors. All variables except non-traditional CV risk factors, AST, medical history and medications were considered for inclusion in the model and an automated stepwise variable selection on 1,000 was used to choose the final model; variables with inclusion rates of at least 50% were included in the final model. SAS (version 9.4, The SAS Institute, Cary, NC) was used for all analyses and a p <0.05 was considered statistically significant.

Results

A total of 344 patients were included in the analysis. Median age was 13 years, 55% were male and 60% of them were severely obese. Table 1 shows a summary of patient characteristics. Fig. 1 shows the prevalence of suspected NAFLD based on the 2 guidelines. NAFLD is suspected in 26% of at-risk patients based on ALT >52/44 (NASPGHAN guidelines), this number goes up to 54% if the cut-off is lowered to 26 for boys and 22 for girls. NAFLD is suspected in 58.4% based on the ESPGHAN guidelines compared to 26% based on NASPGHAN guidelines (McNemar's p value <0.001).

Interestingly, out of the 201 individuals that have suspected NAFLD based on the ESPGHAN guidelines, 8.5% (n = 17) are classified based on their ALT value only, 39.8% (n = 80) are classified based on both ALT and ultrasound and 51.7% (n = 104) are classified based on ultrasound alone (low ALT + fatty infiltration).

If ultrasound was also added to the NASPGHAN guidelines, the prevalence of suspected NAFLD would go up from 26% to 58.4%.

Subjects with fatty infiltration on ultrasound and low ALT (≤52/44)

A total of 184 individuals had evidence of fatty infiltration on ultrasound, 61% of those had ALT levels less than the 52/44 cut-off values (Fig. 2) and 25% had normal ALT based on the 26/22 cut-off values. On univariate analysis, low ALT levels (<52/44) in individuals who had evidence of fatty infiltrate on ultrasound were significantly associated with the absence of metabolic syndrome, absence of hypertrigliceridemia and lower levels of albumin, and bilirubin, and higher platelet count (Table 2). On multivariate analysis, absence of hypertrigliceridemia, lower albumin and higher platelet count were found to be significantly associated with low ALT levels in individuals with fatty infiltration on ultrasound. Those without hypertrigliceridemia were 2.5x more likely to have low ALT levels than those with hypertrigliceridemia (p = 0.017) (Table 3).

Discussion

The major findings of this study are the following: 1) a screening strategy using the combination of elevated ALT and fatty infiltration on ultrasound increases the sensitivity of detection of suspected NAFLD in at-risk children; 2) a significant percentage of overweight/obese children with fatty infiltration on ultrasound have low ALT values; 3) children with fatty infiltration on ultrasound and low ALT (<52/44) were less likely to have features of the metabolic syndrome.

With the increased prevalence of obesity and metabolic syndrome among children, screening for NAFLD is more important than ever before. Pediatricians and primary care providers are at the frontline of the obesity epidemic and they need a useful screening tool to help them identify children with NAFLD. Several strategies have used ALT level as a screening tool for NAFLD in at-risk populations since it is simple, inexpensive and readily available test. However, the upper limit of normal used by most laboratories is extrapolated from adult reference ranges and is not validated in children. Recent efforts have been made to redefine the upper limit of normal for ALT in children. The Screening ALT for Elevation in Today's Youth (SAFETY) study revealed that the upper ALT thresholds used in different laboratories of children's hospitals in United States, are set very high for detecting

Table 1. Patient characteristics.

Factor	n	Median [IQR] or n (%)
		Total (N = 344)
Age (years)	344	13.0 [11.0–16.0]
Gender	344	
Male		189 (54.9)
Female		155 (45.1)
Race	321	
White		209 (65.1)
Black		55 (17.1)
Hispanic		39 (12.1)
Other		18 (5.6)
Metabolic syndrome	316	227 (71.8)
Obesity	344	
Overweight		24 (7.0)
Obese		118 (34.3)
Severely obese		202 (58.7)
BMI (kg/m^2)	344	33.1 [28.2–38.4]
BMI percentile	344	99.2 [98.0–99.7]
Hypertriglyceridemia	320	164 (51.3)
Low HDL	327	247 (75.5)
IR/pre-diabetes	321	203 (63.2)
Hypertension	339	70 (20.6)
Non-traditional CV risk factors	274	151 (55.1)
OSA	317	87 (27.4)
Aspartate aminotransferase (IU/L)	344	26.0 [20.0–35.0]
Alanine aminotransferase (IU/L)	344	26.5 [18.0–50.5]
Albumin (g/dl)	339	4.5 [4.3–4.7]
Bilirubin (mg/dl)	340	0.30 [0.20–0.40]
Alkaline phosphatase (IU/L)	339	174.0 [100.0–259.0]
White blood cell count (x10^9/L)	297	7.5 [6.3–9.1]
Absolute neutrophil count (/μl)	292	3,960 [3,090–5,125]
Lymphocyte count (/μl)	291	2,600 [2,080–3,140]
Hemoglobin (g/dl)	299	13.3 [12.6–14.2]
Platelet count (x10^3/μl)	298	291 [248–335]
Insulin (mIU/L)	260	27.7 [17.3–43.6]
Glucose (mg/dl)	330	84.0 [77.0–90.0]
HOMA-IR	258	5.5 [3.4–9.3]
HbA1C (%)	279	5.5 [5.3–5.7]
HsCRP (mg/L)	263	2.2 [0.80–5.1]
Triglycerides (mg/dl)	315	126.0 [73.0–185.0]
Total cholesterol (mg/dl)	328	167.5 [143.0–192.0]
LDL (mg/dl)	312	96.0 [79.0–118.0]
HDL (mg/dl)	328	41.0 [35.0–49.0]
Fatty infiltration on US	344	184 (53.5)

ALT, alanine aminotransferase; BMI, body mass index; CV, cardiovascular; HbA1C, glycated hemoglobin; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; OSA, obstructive sleep apnea.

chronic liver diseases in children. The study used data from the National Health and Nutrition Examination Survey between 1999–2006. After excluding children with viral hepatitis, iron overload, hepatotoxic medications and obese/overweight children, the study demonstrated that by lowering the ALT threshold to 25.8 IU/L in boys and 22.1 IU/L in girls, the sensitivity of identifying NAFLD increased to 80% in males and 91% in females, with specificity of 79% and 85%, respectively. The same study also revealed
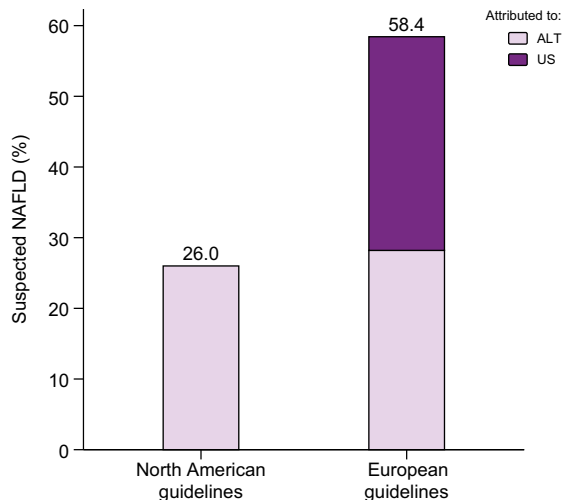
Fig. 1. Prevalence of suspected NAFLD in overweight and obese children determined by 2 different NAFLD guidelines. ALT, alanine aminotransferase; NAFLD, non-alcoholic fatty liver disease; US, ultrasound.

that by setting an upper ALT threshold of 53 IU/L, the sensitivity of detecting NAFLD decreased to 36% in females and 32% in males [13]. Using those limits and in a population based study, Schwimmer et al. found that 2x the upper limit (50 IU/L for boys and 44 IU/L for girls) was 88% sensitive to accurately detect NAFLD in children older than 10 years of age [14]. In its most recent NAFLD guidelines, NASPGHAN recommended screening for NAFLD in children with persistently elevated ALT (more than 3 month) above twice the upper limit of normal, as defined in the SAFETY study [12]. However, it is important to mention these criteria may miss some children with NASH and advanced fibrosis [14].

Combining ALT level with ultrasound as a screening tool was recommended by ESPGHAN in their latest pediatric NAFLD guidelines [10]. Ultrasound does not include radiation exposure and can detect signs of portal hypertension. It is also an
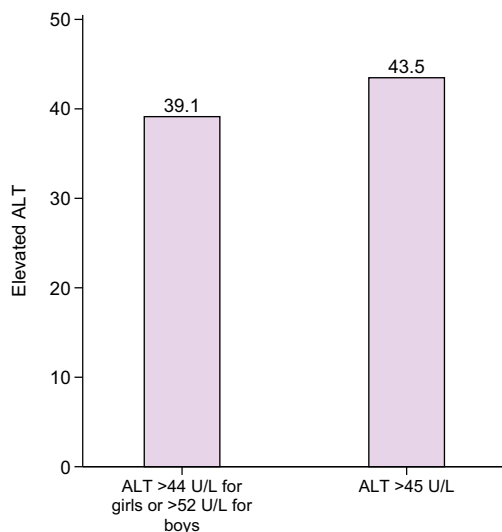

Fig. 2. Elevated ALT in overweight and obese children with evidence of suspected NAFLD on ultrasound (n = 184). ALT, alanine aminotransferase; NAFLD, non-alcoholic fatty liver disease; US, ultrasound.

inexpensive imaging modality compared to other emerging tools for liver imaging like magnetic resonance elastography. In adult studies, ultrasound sensitivity ranged between 60–96% compared to biopsy. Although ultrasound has poor sensitivity in children with mild steatosis, the sensitivity is acceptable in those with moderate to severe steatosis [15]. A prospective study by Shannon et al., which included 208 children with liver biopsy-proven NAFLD, showed that ultrasound had sensitivity and specificity of almost 80% and 86%, respectively, for the diagnosis of moderate to severe steatosis [16]. The same study showed that serum aminotransferases are poor predictors of the presence or severity of fatty liver disease. In the aforementioned study by Schwimmer et al., even though using an ALT cut-off of 2x the upper limit of normal led to good sensitivity for the detection of suspected NAFLD, it had a low specificity of 26%, highlighting the need for surrogate diagnostic methods like imaging. In our study, lowering the ALT cut-off to 26 for boys and 22 for girls would have identified 75% of children with fatty infiltrate on ultrasound but 25% would have been missed. Also, adding ultrasound to ALT as recommended by the ESPGHAN guidelines would increase the prevalence of suspected NAFLD from 26% to 58.4%. In other words, at least 32% of patients with suspected NAFLD would have been missed by relying on ALT alone as recommended by NASPGHAN. This argues for the importance of using ultrasound as a valuable screening tool.

Low ALT level in individuals with steatosis on ultrasound was associated with lower prevalence of metabolic syndrome. This is in agreement with what Elizondo-Montemayor et al. found in Mexican school children. Using normal ALT level of <40, the prevalence of metabolic syndrome was 24.1% among overweight or obese children with normal ALT, which was significantly lower than in the high ALT group (50%, *p* = 0.002) [17]. A similar association was found in adult studies [18]. Low ALT level in individuals with fatty infiltration on ultrasound was associated with lower albumin. In order to explain this finding, histologic assessment is needed as prevalence of NASH within our cohort cannot be assessed accurately, which may affect both albumin and ALT levels. Papacocea et al. found lower albumin levels among patients with biopsy-proven NASH compared to those with simple steatosis [19]. We hypothesize that having low ALT reflects less liver injury and subsequently lower bilirubin levels. Higher platelet counts were associated with lower ALT levels. The decrease in platelet count might occur because of portal hypertension or because some chronic liver diseases may impact on the thrombopoietin hormone which stimulates platelet production.

Our study has several limitations. First, it is a retrospective study based in a tertiary center. Future studies should recruit patients from primary care practices, in order to provide a real estimation of suspected NAFLD prevalence using the aforementioned criteria. Second, diagnosis of NAFLD was not confirmed by histology or magnetic resonance imaging. With the advancement of non-invasive imaging techniques like controlled attenuation parameter score obtained from Fibroscan®, we can detect steatosis with good reliability. Third, our study design did not include repeated ALT measurements to confirm that the observed ALT levels were consistent. This limitation will be addressed in follow-up studies. Forth, our study cohort included a high percentage of severely obese children which likely overestimated the prevalence of suspected NAFLD detected by either screen strategy.

Table 2. Analysis of factors associated with low ALT in individuals with evidence of suspected NAFLD on ultrasound (n = 184).

Factor	n	Low ALT (≤52/44) (n = 112) Statistics	n	Elevated ALT (>52/44) (n = 72) Statistics	p value
Age (years)	112	13.5 [12.0–16.0]	72	14.5 [12.0–16.0]	0.35[b]
Gender	112		72		0.061[c]
Male		64 (57.1)		51 (70.8)	
Female		48 (42.9)		21 (29.2)	
Caucasian	105	70 (66.7)	67	49 (73.1)	0.37[c]
Metabolic syndrome	107	81 (75.7)	71	63 (88.7)	***0.030[c]***
Obesity	112		72		0.64[c]
Overweight		4 (3.6)		3 (4.2)	
Obese		29 (25.9)		23 (31.9)	
Severely obese		79 (70.5)		46 (63.9)	
BMI (kg/m^2)	112	34.4 [31.8–41.3]	72	34.2 [30.9–38.2]	0.31[b]
BMI percentile	112	99.4 [98.7–99.8]	72	99.2 [98.5–99.6]	0.12[b]
Hypertriglyceridemia	108	54 (50.0)	67	50 (74.6)	0.001[c]
Low HDL	109	82 (75.2)	70	58 (82.9)	0.23[c]
IR/Pre-diabetes	109	80 (73.4)	70	49 (70.0)	0.43[c]
Hypertension	110	32 (29.1)	70	15 (21.4)	0.25[c]
OSA	99	36 (36.4)	69	17 (24.6)	0.11[c]
Albumin (g/dl)	111	4.5 [4.3–4.7]	71	4.6 [4.4–4.8]	0.010[b]
Bilirubin (mg/dl)	111	0.30 [0.20–0.40]	72	0.30 [0.30–0.60]	0.006[b]
Alkaline phosphatase (IU/L)	111	162.0 [97.0–266.0]	72	162.0 [94.0–244.0]	0.78[b]
White blood cell count (x10^9/L)	101	7.6 [6.6–9.3]	61	7.9 [7.2–9.8]	0.27[b]
Absolute neutrophil count (/μl)	100	3,960 [3,215–5,220]	60	4,085 [3,325–5,355]	0.58[b]
Lymphocyte count (/μl)	99	2,730 [2,170–3,070]	60	2,770 [2,320–3,380]	0.25[b]
Hemoglobin (g/dl)	102	13.5 [12.6–14.2]	61	13.5 [12.7–14.6]	0.34[b]
Platelet count (x10^3/μl)	102	295.0 [254.0–353.0]	61	277.0 [239.0–316.0]	0.018[b]
Insulin (mIU/L)	89	28.7 [18.3–49.4]	56	35.1 [24.2–53.2]	0.13[b]
Glucose (mg/dl)	110	83.5 [78.0–92.0]	68	84.5 [78.5–89.0]	0.82[b]
HOMA-IR	89	6.6 [3.6–10.2]	55	7.3 [5.1–12.3]	0.099[b]
HbA1C (%)	101	5.5 [5.3–5.7]	60	5.5 [5.3–5.7]	0.19[b]
HsCRP (mg/L)	90	2.5 [1.00–6.4]	57	2.3 [1.2–4.7]	0.65[b]
Lp(a) (mg/dl)	79	19.0 [8.0–39.0]	44	13.5 [3.5–35.5]	0.15[b]
Triglycerides (mg/dl)	107	128.0 [74.0–189.0]	65	160.0 [126.0–232.0]	<0.001[b]
Total Cholesterol (mg/dl)	109	168.0 [144.0–191.0]	70	171.5 [153.0–201.0]	0.18[b]
LDL (mg/dl)	106	96.0 [78.0–118.0]	63	95.0 [83.0–122.0]	0.62[b]
HDL (mg/dl)	109	42.0 [37.0–48.0]	70	37.0 [32.0–42.0]	<0.001[b]

Subset of population used: Subjects with fatty infiltration on ultrasound.
Statistics presented as Median [interquartile range] or n (column%).
p values: b = Kruskal-Wallis test, c = Pearson's chi-square test.
ALT, alanine aminotransferase; BMI, body mass index; CV, cardiovascular; HbA1C, glycated hemoglobin; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; Lp(a), lipoprotein A; NAFLD, non-alcoholic fatty liver disease; OSA, obstructive sleep apnea.

Table 3. Multivariate analysis of factors associated with low ALT (≤52/44) in individuals with evidence of suspected NAFLD on ultrasound (n = 154)

Factor	OR (95% CI)	p value
No hypertriglyceridemia	2.5 (1.2–5.4)	0.017
Albumin (1-unit increment)	0.20 (0.06–0.65)	0.007
Platelet count (25-unit increment)	1.2 (1.05–1.4)	0.008

ALT, alanine aminotransferase; NAFLD, non-alcoholic fatty liver disease; OR, odds ratio.

In conclusion, by relying on ALT values alone for screening for NAFLD, suspected NAFLD might be missed in many children who are at risk to develop this worldwide growing health problem. Children with fatty infiltration on ultrasound and low ALT (< 52/44) may be less likely to have metabolic syndrome, insulin resistance or hypertriglyceridemia.

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