Liver acoustic radiation force impulse (ARFI) in childhood obesity: comparison and correlation with biochemical markers

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Abstract

Purpose To compare and correlate the diagnostic efficiency of acoustic radiation force impulse (ARFI) elastography with biochemical markers for assessing hepatic changes in overweight and obese children.

Methods This prospective study was approved by the institutional ethics committee. It included 54 overweight and obese children and 50 normal children (as a control group) in the age range 5–18 years. For all children, we performed grayscale ultrasonography to diagnose fatty liver, ARFI elastography to measure liver stiffness, and biochemical evaluation for aspartate aminotransferase (AST), alanine aminotransferase (ALT), and serum triglyceride (TG) levels.

Results Of the 54 obese children, AST was elevated in 13 (24.1%) and ALT was elevated in 16 (29.6%); however, only 4 (25%) of these 16 obese children with abnormal aminotransferase levels had an AST/ALT ratio >0.8. Furthermore, all children with abnormal aminotransferase levels with AST/ALT ratio >0.8 also had abnormal readings of ARFI elastography. The TG was elevated (>150 mg/dL) in 2 out of 54 (3.7%) obese children. None of the normal children showed abnormal levels of aminotransferase and TG. Three out of 54 (5.6%) obese children

did not show fatty liver changes, while 29 (53.7%) showed grade-I fatty liver changes, and 22 (40.7%) showed grade-II fatty liver changes. The mean (SD) ARFI value was 1.13 m/s (SD 0.199) for obese children and 1.02 m/s (SD 0.11) for children in the control group. Of the 54 obese children, 49 (90.7%) showed ARFI values of <1.19 m/s (normal), 4 (7.4%) had ARFI values from >1.19 to <1.75 m/s, and 1 (1.9%) had an ARFI value >1.75 m/s. Four children with an increased ARFI value also had an AST/ALT ratio >0.8. However, one obese child with a raised ARFI value did not have an elevated AST/ALT ratio, and none of his aminotransferase levels were abnormal. All normal children had ARFI values <1.19 m/s. **Conclusion** ARFI elastography shows excellent correlation with AST/ALT ratios in obese children and may be used as a noninvasive tool to detect nonalcoholic fatty liver disease (NAFLD) and associated hepatic changes, especially in pediatric patients, for whom liver biopsy is not always feasible.

Keywords Children · Obesity · Liver · Elastography

Sommario

Scopo Confrontare e correlare l'efficienza diagnostica di Acoustic Radiation forza d'impulso (ARFI) elastografia con marcatori biochimici nella valutazione delle alterazioni epatiche nei bambini in sovrappeso e obesi.

Metodi Questo studio prospettico è stato approvato dal comitato etico istituzionale. 54 bambini in sovrappeso e obesi e 50 bambini normali (controlli) della fascia di età 5–18 years sono stati inclusi. In tutti i bambini, abbiamo eseguito l'ecografia in scala di grigi per la diagnosi di fegato grasso, ARFI elastografia per misurare la rigidità del fegato, e la valutazione biochimica per aspartato aminotransferasi (AST), alanina aminotransferasi (ALT) e livelli di trigliceridi nel siero (TG).

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Risultati Dei 54 bambini obesi, AST e ALT sono stati elevati in 13 (24,1%) e 16 (29,6%), rispettivamente. Tuttavia, solo 4(25%) questi 16 bambini obesi con valori anomali livelli di transaminasi hanno avuto rapporto AST/ALT >0,8. Inoltre tutti questi bambini con anomala del livello di aminotransferasi con il rapporto AST/ALT >0,8 ha avuto anche le letture anomale di ARFI elastography. La Tg è stata elevata (>150 mg/dL) in 2/54 (3,7%) bambini obesi. Nessuno dei bambini normali mostravano livelli anormali di aminotransferasi e TG. 3/54 (5,6%) bambini obesi non mostrano variazioni di fegato grasso, mentre 29(53,7%) hanno mostrato di grado I e 22 (40,7%) hanno mostrato il grade II fegato grasso modifiche. La media(SD) ARFI valore era di 1,13 m/s(SD: 0,199) per bambini obesi e 1,02 m/s(SD: 0,11) per bambini nel gruppo di controllo. Dei 54 bambini obesi, 49 (90,7%) mostrava ARFI valore di <1,19 m/s (normale), 4(7,4%) aveva valore ARFI di >1,19–<1,75 m/s e 1 (1,9%) aveva valore >1,75 m/s. Quattro figli con maggiore valore ARFI aveva anche il rapporto AST/ALT >0,8. Tuttavia, uno bambini obesi con aumentata ARFI valore non aveva elevato rapporto AST/ALT né i suoi livelli di transaminasi sono stati anormali. Tutti i bambini normali aveva valore ARFI <1,19 m/s.

Conclusione ARFI elastography mostra un'eccellente correlazione con il rapporto AST/ALT nei bambini obesi e può essere utilizzato come uno strumento non invasivo per rilevare steatosi epatica non alcolica (NAFLD) alterazioni epatiche associate, soprattutto in pazienti pediatriche nei quali la biopsia epatica non è sempre possibile.

Introduction

Nonalcoholic fatty liver disease (NAFLD) includes a spectrum of diseases ranging from hepatic steatosis to nonalcoholic steatohepatitis (NASH). An isolated hepatic steatosis is considered a benign condition; NASH, however, is an advanced liver disease that can lead to liver fibrosis and/or cirrhosis [1]. In children, obesity has emerged as a new chronic disease [2]. However, despite its significance and increasing prevalence, primary caregivers do not consistently diagnose childhood obesity and hence miss significant opportunities for early interventions [3, 4].

Ultrasound and magnetic resonance imaging (MRI) are the imaging modalities that do not involve any ionizing radiation and, hence, are safe to use in children [5–10]. NASH is conventionally diagnosed with the help of classical USG liver findings along with elevated serum levels of alanine aminotransferase (ALT) [1]. However, liver biopsy is still considered the gold standard for diagnosis.

The detection of isolated hypertransaminasemia is the usual mode of noninvasive screening and follow-up for

obesity-related liver diseases in the pediatric population [11]. However, the disease may go undetected because the rise in serum transaminase level occurs at a late stage of the disease and the levels are usually fluctuating and/or slightly elevated.

Ultrasonic elastography is one of the new functional ultrasonic imaging techniques that can be used in quantitative and semi-quantitative assessments of diffused liver lesions, such as cirrhosis after hepatitis, alcoholic cirrhosis, hepatic dysfunction after surgery, and other diseases [12–15]. Though many researchers have employed ultrasonic elastography in studies of chronic hepatic diseases, only a few studies have used it for the diagnosis of fatty liver [16, 17].

Recent studies have demonstrated the clinical feasibility of acoustic radiation force impulse (ARFI) elastography for the evaluation and diagnosis of liver fibrosis and cirrhosis. In a study by Horster et al., the mean shear-wave velocity (SWV) in healthy volunteers was found to be 1.19 m/s [18]. In a later study, Friedrich-Rust et al. reported that the area under a receiver operating characteristic (ROC) curve for the accuracy of ARFI elastography was 0.91 for the diagnosis of both moderate fibrosis ($F \geq 2$) and cirrhosis [19]. In their study, the cutoff value for liver cirrhosis was 1.75 m/s for all patients.

The advantages of ARFI over transient elastography (TE) are its visualization of grayscale or color Doppler images and ARFI images with the same equipment using software imaging control and detection algorithms. Furthermore, the SWV can be measured not only through the intercostal approach in the right lobe but also through the subcostal approach, or even in the left lobe. Furthermore, the TE readings are influenced by the thickness of subcutaneous fat/tissue; however, ARFI readings are not influenced by the same. The hepatic steatosis does not influence the ARFI readings either [20].

There is a paucity of information on the correlation between different radiological techniques, such as grayscale USG, ARFI elastography, and biochemical markers in the prediction of hepatic fibrosis in overweight and obese children with fatty liver. Studies of an adult population have shown that higher values of ARFI are associated with an increased degree of liver fibrosis [21].

The aim of our present study is to correlate results of ARFI elastography with biochemical markers in overweight and obese children.

Materials and methods

Patient enrollment

This prospective study was approved by the institutional ethics committee. Fifty-four children were enrolled who

were 5–18 years old, were overweight or obese with BMI >85th percentile, and were visiting the pediatric gastroenterology clinic. Informed written consent was obtained from the parents/guardians of all children included in the study. Consent was also obtained from the children aged 7 and above prior to their enrollment. The study excluded children on steroid therapy and children with known liver disease, endogenous obesity, diabetes mellitus, hormonal and gonadal disorders, portal venous thrombosis, active/chronic infections, or heart disease. All clinical details, examinations, and radiological findings were recorded.

Fifty children aged 5–18 with BMI <85th percentile and whose USG examination for indications other than liver diseases showed normal liver on USG and normal serum biochemistry were enrolled as age-matched controls.

Height was measured standing upright using calibrated scales, and body weight was recorded with a digital weighing machine (the children wore only light clothing); we recorded both parameters twice and then calculated the mean of the two readings. BMI was calculated with the help of height and weight, and thereafter the percentile BMI was obtained using the standard chart. The terms *overweight* and *obese* were defined according to the BMI percentile for the given age, separately for girls and boys, as given by the standard chart.

Grayscale USG and ultrasonic elastography

Ultrasound examination of liver and calculation of shear-wave velocity of ARFI elastography was performed with a SIEMENS ACUSON S2000 ultrasound system equipped with a 4C1 convex probe.

Hepatic steatosis was graded as mild, moderate, and severe. The scoring system was based on three sonographic features commonly used to detect fatty infiltration of the liver and to grade the severity of liver pathology similar to the one described by Tominaga et al. [22] on the basis of liver echotexture, liver–diaphragm differentiation in echo amplitude, hepatic echo penetration, and clarity of hepatic blood vessels. All ultrasounds were performed by a single observer. The saved images were subsequently reviewed by a senior radiologist who has around 10 years of experience in pediatric radiology.

Liver stiffness was measured through the intercostal space at the right anterior oblique position, keeping the right arm in maximum abduction. Liver elasticity was evaluated by placing a measuring box (10 mm long and 5 mm wide) at a depth of 3–3.5 cm below the liver capsule. Its speed, expressed in meters per second (m/s), was displayed on the screen. Five valid measurements were performed for each obese and normal subject, and the mean values were calculated. In our study, an ARFI elastography

value of <1.19 m/s was considered normal, as suggested by a previous study of healthy volunteers, while a value of >1.19 m/s was considered abnormal.

Biochemical investigations

The biochemical investigations included liver function tests (AST, ALT, and AST/ALT ratio) and serum triglyceride (TG) levels, and samples for the same were collected in the fasting state in the morning. Levels of AST, ALT, and TG were recorded, and the AST/ALT ratio was calculated if the aminotransferase levels were elevated. The cutoff value of 35 U/L for both AST and ALT was considered normal. An AST/ALT ratio of >0.8 for abnormal levels of AST and ALT was considered significant. An AST/ALT ratio >0.8 was considered significant only when children also had abnormally elevated AST and ALT levels. The normal cutoff value for the triglyceride level was 150 mg/dL.

Statistical analysis

Descriptive statistics such as mean, mode, range, and SD were applied. The ratio of AST and ALT was calculated for the cases with raised AST and ALT levels. Mean, range, and SD were calculated for ARFI elastography. Cases having abnormal ARFI elastography and AST/ALT ratio were expressed as percentages, and cases with normal liver and fatty liver were also expressed as percentages. The difference between the groups was calculated using the Mann–Whitney *U* test. Statistical analysis was done using SPSS (version 16.0) software.

Results

The age of obese children enrolled in this study was between 5 and 17 years (mean 10.22; SD 3.03). There were 39 (72.2%) male and 15 (27.8%) female obese children. The children in the control group were from 5 to 16 years of age (mean 9.07; SD 2.77) and included 34 (68%) males and 16 (32%) females.

The mean (SD) BMI of the obese children was 23.53 (SD 2.81; range 18.23–28.31), while that of the normal children was 17.95 (SD 1.75; range 15.89–22.91). In the obese group, 9 children had a BMI in the 90–95th percentile, 40 children had a BMI in the 95–97th percentile, and 5 children had a BMI in the >97th percentile. In the control group, 30 children had a BMI in the 50–75th percentile, while 20 children had a BMI in the 75–85th percentile. Three (5.6%) of the 54 obese children showed no changes to indicate the presence of fatty liver. Twenty-nine (53.7%) and 22 (40.7%) obese children showed grade-I and

grade-II fatty liver, respectively, on grayscale USG. Therefore, 51 out of 54 obese children had fatty changes. However, none of the obese children showed grade-III fatty liver.

ARFI elastography was performed in all the children. The mean (SD) ARFI elastography value for obese children was 1.13 m/s (SD 0.199; range 0.71–1.78), and that of the controls was 1.02 m/s (SD 0.11; range 0.73–1.17). Of the 54 obese children, 49 (90.7%) showed ARFI elastography values of <1.19 m/s, 4 (7.4%) showed values between 1.19 and <1.75 m/s (Fig. 1), and 1 (1.9%) showed a value of >1.75 m/s. All the control children showed ARFI elastography values of <1.19 m/s (Fig. 2). The mean difference of ARFI elastography between cases and controls was 0.09135 with a standard error of 0.03168. The median for cases was 1.11 and for controls was 1.045, and the difference was found to be highly significant using the Mann–

Whitney U test. This is summarized in the box plot (Fig. 3).

The mean (SD) level of AST in obese children was 29.5 U/L (SD 10.1; range 15.5–65), and in normal children it was 26.36 U/L (SD 5.89; range 14–34). The mean ALT level for the obese children was $36.67 \text{ U/L} \pm 13.12 \text{ SD}$ (range 19–74 U/L) and for the controls it was $29.12 \text{ U/L} \pm 3.9 \text{ SD}$ (range 18–34 U/L). Out of 54 obese children, AST was found to be raised in 13 children (24.1%) and ALT was raised in 16 children (29.6%). Therefore, only 16 (31.4%) out of 51 children with fatty liver showed abnormally elevated aminotransferase levels. Out of 16 obese children with abnormal aminotransferase (AST and ALT) levels, 12 (75%) showed an AST/ALT ratio <0.8 , whereas 4 (25%) had a ratio >0.8 , which is considered to be a biochemical indicator of steatohepatitis. Grayscale USG and ALT

Fig. 1 An 11-year-old obese female child with increased levels of AST, ALT, AST/ALT ratio, and TG. **a** Grayscale USG in right anterior oblique view showing diffuse moderate increase in liver echotexture with grade-II fatty liver. **b** ARFI elastography in right anterior oblique view at a depth of 4.3 cm showing shear-wave velocity of 1.71 m/s

Fig. 2 An 8-year-old male child with normal levels of AST, ALT, and TG. **a** Grayscale USG in right anterior oblique view showing normal liver echotexture. **b** ARFI elastography in right anterior oblique view at a depth of 3.9 cm with shear-wave velocity of 1.06 m/s

Fig. 3 Box plot comparing the ARFI elastography values between cases and controls

levels were not significantly correlated, the correlation coefficient being 0.112, which was weak and non-significant ($p = 0.420$) (Fig. 4). Similarly, the grayscale USG and AST levels were not significantly correlated, the correlation coefficient being 0.123, which was again weak and nonsignificant ($p = 0.374$) (Fig. 5). All 4 cases with AST/ALT ratio >0.8 also had abnormal ARFI elastographic value, of which 3 (75%) had ARFI elastographic values between 1.19 and <1.75 m/s, and one (25%) showed a value of >1.75 m/s. However, one of the cases with raised ARFI values did not show elevated levels of AST or ALT. ARFI elastography and AST/ALT ratio values were significantly correlated, the correlation coefficient being 0.005. Grayscale USG and AST/ALT ratio values were not significantly correlated, the correlation coefficient being 0.123, which was weak and non-significant ($p = 0.374$) (Fig. 6).

Fig. 4 Scatter diagram showing the grayscale USG correlation with AST levels

Fig. 5 Scatter diagram showing the grayscale USG correlation with ALT levels

Triglyceride levels were also recorded for all obese and normal children, with a mean level of 117.83 ± 42.11 mg/dL (range 50–361) and 83.05 ± 16.6 mg/dL (range 59–126), respectively. Of the 54 obese children, only 2

(3.7%) had TG levels of >150 mg/dL. None of the normal children had elevated levels of TG.

Tables 1, 2 and 3 summarize the findings of our study.

Fig. 6 Scatter diagram showing the grayscale USG correlation with AST/ALT ratio **Table 1** Table summarizing the findings in cases and controls

	Cases (<i>N</i> = 54)		Controls (<i>N</i> = 50)	
Gray scale USG	Normal	3	Normal	50
	Grade I	29	Grade I	–
	Grade II	22	Grade II	–
	Grade III	–	Grade III	–
AST level	Normal	41	Normal	50
	Elevated	13	Elevated	–
ALT level	Normal	38	Normal	50
	Elevated	16	Elevated	–
AST/ALT ratio	Normal	50	Normal	50
	Abnormal	4	Abnormal	–
TG level	Normal	52	Normal	50
	Elevated	2	Elevated	–
ARFI elastography	<1.19 m/s	49	<1.19 m/s	50
	>1.19 to <1.75 m/s	4	>1.19 to <1.75 m/s	–
	>1.75 m/s	1	>1.75 m/s	–

Table 2 Table comparing elevated AST and ALT with ARFI

		Elevated AST and ALT levels (<i>N</i> = 16)	
		AST/ALT ratio >0.8	AST/ALT ratio <0.8
ARFI elastography	Normal	–	12
	Elevated	4	–

Table 3 Table comparing ARFI and AST/ALT ratio

		ARFI value of cases	
		Normal	Abnormal
AST/ALT ratio (with abnormal AST and ALT level)	<0.8	49	1
	>0.8	–	4

Discussion

Childhood obesity has reached epidemic proportions worldwide, and its prevalence continues to rise. Children with NAFLD are usually obese and asymptomatic; however, their physical examination often shows hepatomegaly [23]. The histopathological features of NAFLD include microvesicular steatosis, mild inflammation, and different grades of fibrosis. Steatosis alone has an excellent prognosis, but the prognosis worsens for individuals with increased fibrosis, which may lead to liver cirrhosis in up to 15% of individuals [24].

There are two studies that have compared liver ultrasonography and liver histology for measuring the degree of hepatic steatosis. They concluded that USG is an insensitive technique to identify mild steatosis [25, 26]. In their study, the confounding factor, however, may be the presence of hepatic fibrosis, which is often indistinguishable from steatosis. Our study was an effort to diagnose liver fibrosis at its earliest stage in overweight and obese children with fatty liver disease using the new USG technique of ARFI elastography and to correlate the findings with a biochemical predictor of hepatic fibrosis (i.e., the AST/ALT ratio).

The serum ALT level is elevated in only 10% of obese children despite a higher frequency of hepatic steatosis reported in imaging studies [27]. This discrepancy is attributed to the insensitivity of serum aminotransferases to detect low levels of hepatic fat accumulation. Hence, the serum aminotransferases level is neither a reliable biomarker to determine the spectrum of fatty liver in overweight and obese children nor to stratify these children on the basis of aminotransferase levels. A liver biopsy needs to be conducted to confirm diagnosis of NAFLD and its sequelae, including NASH, liver fibrosis, and liver cirrhosis; however, this cannot be performed routinely in the pediatric population since it is an invasive procedure.

ARFI imaging is a radiation force-based imaging technique. This newer technique of elastography is provided by conventional B-mode USG. ARFI helps in observing the tissue's response to the radiation force using the conventional B-mode imaging pulses, and this technique can display the quantitative shear-wave velocity of ARFI displacement. The shear-wave velocity (in meters per second) is proportional to the square root of tissue elasticity. As the shear-wave velocity depends on tissue stiffness, it is highly influenced by the amount of fibrosis. Therefore, the ARFI elastography findings can serve as attractive biomarkers for hepatic fibrosis [28].

In our study, of 51 obese children with fatty liver disease, as revealed by grayscale USG, only 16 had abnormal levels of aminotransferases. As suggested previously, the

discrepancy may be due to the insensitivity of serum aminotransferases to detect low levels of hepatic fat accumulation. An incidental finding of abnormal serum aminotransferases leads to the diagnosis of fatty liver or NAFLD in adults and children in most instances. Franzese et al. [29] also demonstrated a lack of correlation between grayscale USG and level of serum aminotransferases in patients having fatty liver. In that study, only 31.6% out of 52.8% of obese children with fatty liver identified by ultrasound had elevated serum aminotransferases. The study findings also support the conclusion that heavy fat accumulation is required to induce abnormal levels of serum aminotransferases. In our study, all 50 normal children had AST and ALT levels within normal range.

Several investigators have a combined number of factors to predict hepatic fibrosis. The presence of either obesity or type 2 diabetes is the most robust predictor of fibrosis [30–35]. Age (older than 45 or 50) is a strong predictive factor for cirrhosis, which probably reflects the duration of time that steatosis is at risk for a subsequent second hit. The combination of an elevated ALT level, an AST/ALT ratio of greater than 0.8, hypertension, triglycerides, and a high insulin resistance index are also strong predictors [30, 34, 35]. These factors can be used to predict advanced disease. Patients with fatty liver on ultrasound, who are younger than 45 years, who have neither obesity or diabetes, and who have an AST/ALT ratio of less than 0.8, have only a minimal risk for developing significant fibrosis. In contrast, almost two-thirds of patients older than 45 who have diabetes or obesity and an AST/ALT ratio greater than 0.8 will have significant fibrosis. However, because our cohort subjects were of pediatric age (5–17 years), we selectively took three risk factors, including obesity, the AST/ALT ratio and TG levels, to predict NAFLD-related hepatic changes.

In our study, only 4 (25%) of the 16 cases with an abnormal aminotransferase level had an AST/ALT ratio >0.8 . An elevated AST/ALT ratio of >0.8 is a predictor of liver fibrosis, but this is based on a study of adults; no data are available for the pediatric population. All 4 cases with an elevated AST/ALT ratio also had abnormal ARFI elastography value of >1.19 m/s. Three (75%) of these obese children showed ARFI elastography values between >1.19 and <1.75 m/s, and 1 (25%) showed a value of >1.75 m/s. A total of 5 (9.3%) of the 54 cases had ARFI elastography values >1.19 m/s. Of these 5 obese children, 4 (80%) had a value between 1.19 and <1.75 m/s, and one (20%) case showed an ARFI elastography value of >1.75 m/s. Four (80%) out of 5 cases with increased ARFI elastographic values also showed an elevated AST/ALT ratio of >0.8 . However, one (20%) obese child with an increased ARFI elastographic value (1.48 m/s) did not

show elevated levels of AST/ALT ratio. This discrepancy can be attributed to the insensitivity of serum aminotransferase in detecting low levels of hepatic fat accumulation and its subsequent complications. None of the 50 normal children in our study showed ARFI elastographic values of >1.19 m/s.

Out of 54 obese children, TG levels were elevated (>150 mg/dL) in 2 (3.7%) patients. One of the obese children with a TG level of 206 mg/dL also showed an elevated AST/ALT ratio of 0.95 as well as an ARFI elastography value of 1.78 m/s. To the best of our knowledge, there are no published studies suggesting an association between liver changes and TG levels in children.

In this study, we have detected NAFLD-related liver changes by ARFI elastography and compared it with the AST/ALT ratio to find a correlation between two modalities in 54 overweight and obese children. Our study showed that ARFI elastography may be used as a noninvasive technique instead of the AST/ALT ratio to predict NASH-related hepatic changes, as there was one obese subject with a significant elevated ARFI elastographic value without an elevated AST/ALT ratio. Our study results need to be validated with further studies with a larger patient population.

Our study had several limitations. It lacked a standard test to confirm hepatic changes, especially NASH-related fibrosis, and it had a small sample population. AST/ALT ratio interpretation in our pilot study is based on a study that used only adults. To obtain a more reliable evaluation of liver changes, especially of the onset of early fibrosis in children with NAFLD by ARFI elastography, further studies are needed on a larger pediatric population and using specific histological categories, as different histological categories have different ARFI elastographic values.

In conclusion, ARFI elastography is a promising tool that can be used in the pediatric population to detect NAFLD-related hepatic changes, especially in a specific clinical setting where liver biopsy is not always feasible. ARFI can help identify children warranting increased follow-up or preselect for liver biopsy.

Compliance with Ethical Standards

Funding None.

Conflict of interest Author RK declares that he has no conflict of interest. Author KSS declares that he has no conflict of interest. Author BRT declares that he has no conflict of interest. Author AKS declares that he has no conflict of interest. Author AB declares that he has no conflict of interest. Author DD declares that he has no conflict of interest. Author NK declares that he has no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of

the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed written consent was obtained from the parents/guardians of all children included in the study. Assent was also obtained from the children aged 7 years and above prior to their enrollment.

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