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ORIGINAL ARTICLE

Clinical profile, referral trends, and real-world application of vibration-controlled transient elastography in children with non-alcoholic fatty liver disease in Singapore

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Abstract

Background and Aim: Pediatric non-alcoholic fatty liver disease (NAFLD) is a progressive disorder that is increasing in incidence globally. The study aims to describe the clinical profile and longitudinal outcome, including the utility of vibration-controlled transient elastography (VCTE), in children with NAFLD at a single tertiary liver unit in Singapore.

Methods: Retrospective review of patients aged 0–18 years referred for NAFLD from 2003 to 2020 was conducted. Diagnosis was based on persistent elevation of alanine transaminase ≥2× the upper limit of normal in at-risk patients, and/or radiologic detection of hepatic steatosis, with the exclusion of other etiologies. VCTE-derived liver stiffness measurements (LSMs) ≤7.0 , 7.1–9.0, and ≥9.1 kPa were used to differentiate normal (F0–F1), significant fibrosis (F2), and advanced fibrosis (F3–F4), respectively.

Results: The study included 210 patients (72.4% male, mean age 11.6 years). New cases increased from 1.7/1000 referrals in 2003–2008 to 12.7 and 24.5/1000 referrals in 2009–2014 and 2015–2020, respectively. Significant proportion had dyslipidemia (41.4%), impaired glucose tolerance/diabetes (IGT/DM, 26.7%), and hypertension (17.1%). Only 6.2% had resolution of NAFLD after a mean follow-up of 3.7 years. Based on VCTE ($n = 65$), 41.5% had normal LSM, while 26.2% and 32.3% had increased likelihood of significant and advanced fibrosis, respectively. Age ≥16 years (odds ratio [OR] 8.9), IGT/DM (OR 6.5), and aspartate transaminase >70 U/L (OR 11.0) were independent risk factors associated with increased likelihood of advanced fibrosis.

Conclusion: Incidence of pediatric NAFLD has increased dramatically in Singapore. Based on LSM estimation, pediatric NAFLD may be associated with an increased risk of developing advanced fibrosis by late adolescence.

Introduction

Non-alcoholic fatty liver disease (NAFLD) has emerged as the most common chronic liver disease affecting a quarter of the global population, and has become one of the leading indications for liver transplantation (LT) in adults.[1] With the rising trend of obesity in children, a corresponding increase in incidence of pediatric NAFLD has been observed in the Western as well as Asian populations.[2,3] NAFLD is now reported to be the most prevalent chronic liver disease in children in Europe and North America, and studies on the natural history of pediatric NAFLD have shown that it is a progressive disorder potentially leading to fibrosis, cirrhosis and end-stage liver disease.[4,5] It is postulated that pediatric-onset NAFLD may represent a more aggressive phenotype compared to adult NAFLD and may be associated with a more severe course.[6]

Liver histology remains the gold standard in the diagnosis and staging of NAFLD, specifically in distinguishing between isolated hepatic steatosis and the more severe non-alcoholic steatohepatitis (NASH) which determines risk of progression to fibrosis and cirrhosis.[7] However, owing to the cost and invasiveness of liver biopsy, it may not be routinely performed in most clinical settings. Alanine transaminase (ALT) may be a relatively simple surrogate marker but it has limited sensitivity in predicting the phenotype and severity of NAFLD.[6,7] There is growing interest in adapting noninvasive methods, such as clinical/biochemical scores and vibration-controlled transient elastography (VCTE), which are widely applied in adult practice,

for clinical use in pediatric patients.[8] However, none of these tools has been fully validated or can be recommended for routine clinical use in pediatric patients at present.

The primary aim of this study was to describe the clinical profile and longitudinal outcome of pediatric patients with NAFLD referred over an 18-year period at our tertiary liver unit in Singapore. Secondary aim was to evaluate the utility of VCTE in the estimation of disease severity and fibrosis in children with NAFLD.

Methods

This was a retrospective observational study of all pediatric patients (aged 0–18 years) diagnosed with NAFLD who had been referred to the specialist liver unit from 2003 to 2020 at KK Women's and Children's Hospital, which is the largest pediatric hospital in Singapore. Diagnosis of NAFLD was based on detection of hepatic steatosis on imaging (such as ultrasonography or computer tomography [CT] scans), with or without persistent elevation of ALT more than 2 times the upper limit of normal for more than 3 months in at-risk patients, with the exclusion of all other primary etiologies based on relevant clinical history and investigations (Table 1).[6] At-risk patients were defined as patients who were obese with body mass index (BMI) *Z*-score ≥1.64 (BMI ≥95th percentile), or overweight (BMI Z-score ≥1.04, or BMI ≥85th percentile but <95th percentile)[9] with additional risk factors including diabetes mellitus (DM), dyslipidemia, hypertension, or a family history of NAFLD/NASH. ALT ≥80 U/L was considered to be clinically predictive of an underlying NASH.[6] All patients underwent investigations to screen for other comorbidities related to obesity and metabolic syndrome. Criteria for diagnosis of DM, impaired glucose tolerance (IGT) and dyslipidemia, were based on established international and local clinical practice guidelines.[10,11] Liver histology was obtained primarily for the purpose of excluding other diagnoses in cases where there was diagnostic uncertainty.

Table 1 Investigations for evaluation of non-alcoholic fatty liver disease (NAFLD)

Screening for NAFLD and related comorbidities	• Liver function test • Prothrombin time, activated partial thromboplastin time, and international normalized ratio • Full blood count • Fasting blood glucose, oral glucose tolerance test, and serum insulin • HbA1c • Fasting lipid profile • Thyroid function test
Tests to exclude other etiologies (where appropriate)	Ceruloplasmin, with or without 24-h urine copper and penicillamine challenge Serum immunoglobulin G Antinuclear antibody, anti-smooth muscle antibody, anti-liver/kidney microsomal-1 antibody, anti-liver cytosol-1 antibody, anti-soluble liver antigen antibody Hepatitis B and C serologies Metabolic screen: serum amino acids, acylcarnitines, ammonia, lactate, pyruvate, uric acid, urine organic acids Alpha-1-antitrypsin levels/phenotype

Management involved dietary and lifestyle modification as recommended in standard guidelines.[6,12] Patients were reviewed at the outpatient clinic at 6-monthly intervals and underwent anthropometric measurements, physical examination, and laboratory investigations including liver biochemistry.

Since 2019, VCTE (Fibroscan, Echosens) was performed at yearly intervals for every patient to record liver stiffness measurement (LSM) and controlled attenuation parameter (CAP) score (measured in kPa and dB/m, respectively). Patient preparation, choice of probe (M and XL), and examination procedure were in accordance to manufacturer's recommendations.[13] No patient required the S probe. For the purpose of this study, LSM cut-offs of ≤7.0, 7.1–9.0, and ≥9.1 kPa were used to differentiate normal liver stiffness (F0–F1), significant fibrosis (F2), and advanced fibrosis (F3–F4), respectively[8]; CAP scores of 248, 268, and 280 dB/m were used to signify ≥5–10% (S1), ≥33% (S2), and ≥66% (S3), respectively.[14]

The primary outcome measure was resolution of NAFLD at the end of the study period, as defined in this study by normalization of liver biochemistry, resolution of radiologic features of hepatic steatosis, and normalization of LSM and CAP measured on VCTE. Improvement in liver biochemistry was defined by reduction of ALT and aspartate transaminase (AST) by ≥50% from peak values for at least 6 months. Secondary outcome measure was the incidence of significant and advanced fibrosis based on LSM estimation using VCTE.

Data on patient demographics, clinical history, as well as laboratory, radiologic, histologic and VCTE parameters at the time of referral and at the most recent follow-up were collected from medical records. Data analysis was performed using IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, N.Y., USA). Continuous variables are expressed as mean (standard deviation, SD), mean (95% confidence interval, 95 CI) or median (range), while categorical variables are expressed as number (percentage). Comparisons were performed using the *t*-test or the Mann–Whitney *U* test for continuous variables, and the χ^2-test or Fisher's exact test for categorical variables. Statistical significance was set at a *P*-value <0.05. The study was approved by Singhealth Centralized Institutional Review Board.

Results

There were 210 pediatric patients (72.4% male, mean age 11.6 years) with NAFLD who were referred to the liver unit during the study period; 14.1% were overweight and 80.8% were obese. Five percent had BMI Z-score in the non-overweight/non-obese range at the time of referral, of whom the majority (80%) had increase in BMI Z-score at follow-up. New cases of NAFLD were seen at an increasing rate, from 1.7 per 1000 referrals in the period 2003–2008 to 12.7 per 1000 referrals in the period 2009–2014 and 24.5 per 1000 referrals in the period 2015–2020, out of a total of 14 193 new outpatient referrals seen at the unit over the 18-year period (Fig. 1). Significant comorbid disorders

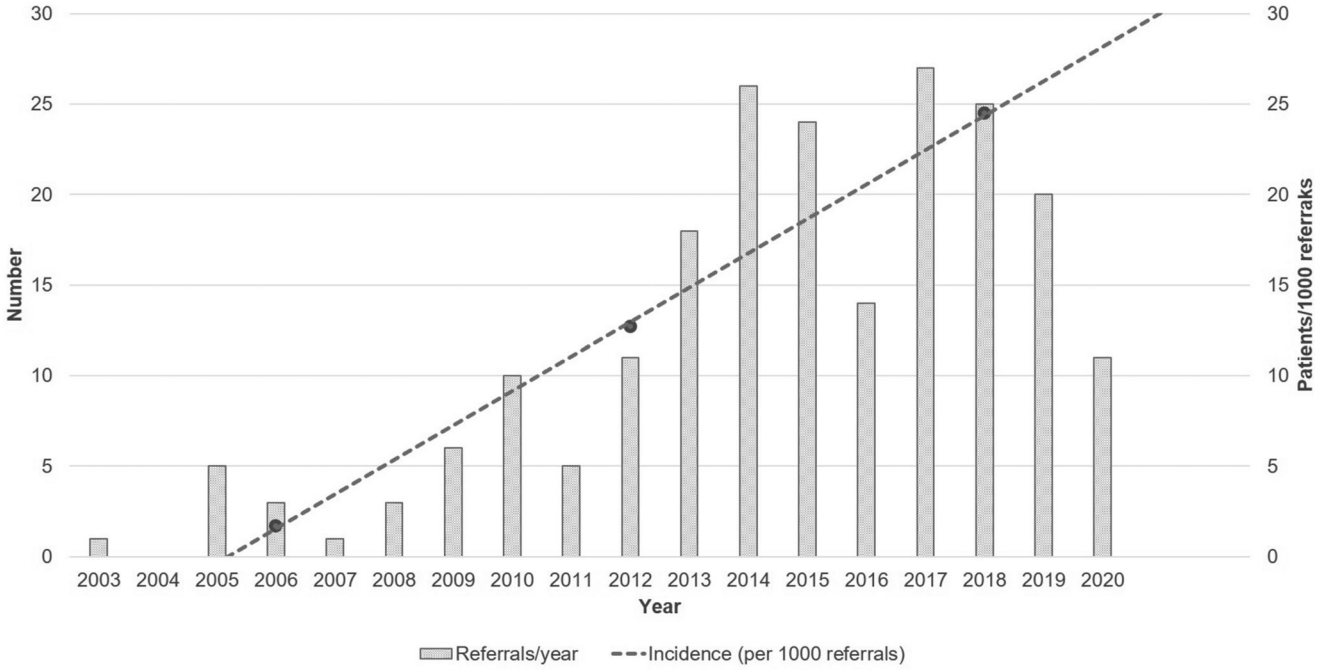

Figure 1 Number of new referrals per year and incidence trend of pediatric non-alcoholic fatty liver disease over the study period.

included dyslipidemia (41.4%), obstructive sleep apnoea (OSA, 21.0%), and hypertension (17.1%). Additionally, IGT and DM were diagnosed in 14.3% and 12.4% of patients, respectively. The number of patients who had at least one feature of dyslipidemia, hyperglycemia, or hypertension was 123 (58.6%). Patients who had hypopituitarism and epilepsy were on corticosteroid replacement and anti-epileptic drugs, respectively, which could be exacerbating factors for liver disease, but all of them were also overweight or obese based on BMI *Z*-scores. Patient demographics and clinical history are summarized in Table 2.

Data on the laboratory findings are detailed in Table 3. Most patients ($n = 132$, 62.9%) had progression in peak ALT level to ≥80 U/L through the course of follow-up. All 210 patients had ultrasonographic evidence of hepatic steatosis. Only six patients underwent liver biopsy, five of whom because of detection of autoantibodies and one for progressive liver disease and portal hypertension. NASH was confirmed in all patients; four had fibrosis grading of F0–F1, one was graded F2, and one had cirrhosis (F4). Patients with positive autoantibodies who did not undergo liver biopsy showed stable or improving liver biochemistry.

Adjunctive pharmacotherapy was started based on physician discretion and included vitamin E ($n = 31$, 14.8%), ursodeoxycholic acid ($n = 5$, 2.4%), and probiotics ($n = 5$, 2.4%). In addition, 25 patients (11.9%) were prescribed metformin for DM, 6 (2.9%) were on obesity treatment (orlistat), and 4 (1.9%) were on lipid-lowering drugs.

After a mean follow-up duration of 3.7 years (SD 2.2), reduction in BMI *Z*-score was observed in 103 patients (49%) with a significant mean difference of −0.18 (95% CI: –0.25 to –0.11, $P < 0.0001$) from the time of referral to the time at last follow-up. Resolution of NAFLD was achieved only in 13 patients (6.2%). Improvement in liver biochemistry was observed in 54 patients (25.7%), whereas persistent liver dysfunction affected most patients (68.1%). At the end of the study period, 81 patients (38.6%) remained on active follow-up, 77 (36.7%) defaulted and were lost to follow-up, 32 (15.2%) were transitioned to adult care, and 19 (9%) were discharged. One patient with panhypopituitarism who had NASH cirrhosis died at the age of 16 years from acute-on-chronic liver failure (ACLF) with spontaneous bacterial peritonitis, acute kidney injury, variceal hemorrhage, hepatic encephalopathy, and cardiorespiratory failure.

VCTE was performed in 65 patients, and median LSM was 7.6 kPa (range: 3.4–75). Twenty-seven (41.5%) patients had normal liver stiffness (≤7 kPa), 17 (26.2%) had LSM reading between 7.1 and 9.0 kPa suggestive of significant fibrosis, and 21 patients (32.3%) had LSM of ≥9.1 kPa suggestive of advanced fibrosis. Stratifying according to age group at the time of most recent follow-up, normal liver stiffness, significant fibrosis, and advanced fibrosis were estimated by VCTE in 59.4%, 28.1% and 19.0%, respectively, in patients younger than 16 years, as compared to 24.2%, 24.2%, and 51.5%, respectively in patients aged 16 years or older ($P = 0.0019$). Older age, obesity, IGT/DM, dyslipidemia, and higher ALT, AST, and gamma-glutamyltransferase (GGT) were significantly associated with the detection of advanced fibrosis based on VCTE (Table 4). Using multivariable logistic regression to correct for confounding factors, age ≥16 years (odds ratio [OR] 8.9; 95% CI: 1.89–42.11; $P = 0.0057$), IGT/DM (OR 6.5; 95% CI:1.48–28.30; $P = 0.0130$), and AST >70 U/L (OR 11.0; 95% CI: 2.46–49.36; $P = 0.0017$) were found to be independently associated with increased likelihood of advanced fibrosis. Based on the CAP scores derived from VCTE, the mean score was 309 dB/m (95%

Table 2 Patient baseline demographics and associated co-morbidities

Patient characteristics	$N = 210$
Mean age at presentation (years)	11.6 (2.95)
Male gender	152 (72.4%)
Ethnicity	
Chinese	156 (74.3%)
Malay	38 (18.1%)
Indian	10 (4.8%)
Eurasian	1 (0.5%)
Others	5 (2.4%)
Mean BMI	28.6 (6.07)
Mean BMI *Z*-score	2.065 (0.6814)
Comorbid conditions	
Dyslipidemia	87 (41.4%)
IGT/DM	56 (26.7%)
OSA	44 (21.0%)
Hypertension	36 (17.1%)
Hyperuricemia	26 (12.4%)
Dyspepsia/GERD	23 (11.0%)
Asthma	19 (9.0%)
Hypopituitarism, hypothyroidism	15 (7.1%)
Developmental disorders	14 (6.7%)
Epilepsy	8 (3.8%)
Family history	
DM	33 (15.7%)
Dyslipidaemia	27 (12.9%)
Hypertension	27 (12.9%)
Coronary artery disease	12 (5.7%)
NAFLD	8 (3.8%)
Cerebrovascular disease	5 (2.4%)
Hepatocellular carcinoma	1 (0.5%)

BMI, body mass index; DM, diabetes mellitus; IGT, impaired glucose tolerance; GERD, gastroesophageal reflux disease; NAFLD, non-alcoholic fatty liver disease; OSA, obstructive sleep apnea.

Table 3 Laboratory data

Liver biochemistry	Mean (95% CI)
Total protein (g/L)	77.5 (76.8–78.3)
Albumin (g/L)	42.0 (41.5–42.5)
Total bilirubin (μmol/L)	12.7 (11.5–13.9)
Direct bilirubin (μmol/L)	4.2 (3.8–4.6)
ALP (U/L)	226.5 (211.2–241.9)
ALT (U/L)	128.8 (114.9–142.8)
AST (U/L)	80.7 (70.3–91.2)
GGT (U/L)	66.4 (56.8–76.0)
Metabolic tests	**Mean (95% CI)**
Total cholesterol (mmol/L)	4.94
HDL (mmol/L)	1.16
TG (mmol/L)	1.58
LDL (mmol/L)	3.10
Fasting glucose (mmol/L)	4.9 (4.7–5.1)
Glucose at 120 min (oral glucose tolerance test) (mmol/L)	7.6 (7.2–8.0)
Fasting insulin (mIU/mL), $n = 69$	32.0 (27.1–37.0)
HbA1c (%)	5.70 (5.45–5.94)
Uric acid (μmol/L), $n = 32$	483.9 (430.4–537.3)
Autoimmune profile	***N* (%)**
Positive autoantibody	23 (11.0%)
Antinuclear antibody (ANA)	18 (8.6%)
Smooth muscle antibody (SMA)	4 (1.9%)
Anti-dsDNA	1 (0.5%)
Anti-liver cytosolic antigen 1 (Anti-LC1)	1 (0.5%)

Liver biochemistry values represent peak levels of total/direct bilirubin and liver enzymes and lowest levels of total protein and albumin during the course of follow-up. Data on metabolic tests were the most recent results at the end of the study period.
95% CI, 95% confidence interval; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma-glutamyltransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides.

CI: 297.5–322.0), with the majority of patients (79.7%) estimated to have S3 (>66%) steatosis.

Discussion

This is one of the first studies in Southeast Asia that has documented a sharp rise in the incidence of pediatric NAFLD with more than 10-fold increase in the rate of new referrals since 2003. Worryingly, a significant proportion of patients would have developed one or more comorbidities related to metabolic syndrome at a relatively young age. Our study has also highlighted that, based on LSM estimation, over half of pediatric patients with NAFLD may be at risk of developing advanced fibrosis by the time they reach late adolescence.

As our hospital is the largest tertiary pediatric facility in the country, the increase in new cases over the study period would be representative of the true rising disease burden in Singapore, which is a developed urban city-state in Southeast Asia with a population of around 5.5 million. It is possible that there was an era effect of increased awareness and screening for NAFLD in the recent years; however it was just as likely that there were many more undiagnosed cases in the community who had not been tested or referred, as NAFLD is largely a "silent" asymptomatic disease.

The rising incidence in NAFLD in Singapore follows similar trends around the world. NAFLD is already recognized as the most prevalent chronic liver disease in children, with a pooled mean prevalence of around 5–10% in the general pediatric population.[15,16] A recent population study reported a significant increase in pediatric NAFLD diagnosis over time, from 36.0/100000 children in 2009 to 58.2/100000 in 2018 in Southern California.[2] In East Asia, Park *et al*. have similarly found a rising prevalence of NAFLD in Korean adolescents from 7.8% in the period 2001–2005 to 11.2% in the period 2015–2017, with an increase in prevalence of obesity across these time periods.[3] Zhang *et al*. found that from 1990 to 2017, there was an estimated annual increase in the prevalence of NAFLD among children, adolescents, and young adults globally of 1.35% per year, and the largest percentage increase was in North America.[17]

Metabolic syndrome, including features of dyslipidemia, IGT, and elevated blood pressure, has been found to be significantly associated with the presence of biopsy-proven NAFLD

Table 4 Univariate comparison of clinical characteristics and biochemical features between patients who have increased likelihood of advanced fibrosis based on LSM ≥9.1 kPa *versus* those who had LSM ≤9 kPa

Characteristics	LSM ≤9.0 kPa ($n = 44$)	LSM ≥9.1 kPa ($n = 21$)	*P*-value
Mean age (years)	14.2 (2.86)	16.4 (1.89)	0.0018
Age ≥16 years	16 (36.3%)	17 (81.0%)	0.0008
Male gender	31 (70.5%)	16 (76.2%)	0.230
Mean BMI Z score	1.78 (0.68)	2.30 (0.76)	0.0082
Z score ≥1.64 (obese)	29 (65.9%)	19 (90.5%)	0.0370
DM/IGT	9 (20.5%)	12 (57.1%)	0.0033
Dyslipidemia	12 (27.3%)	11 (52.4%)	0.050
Hypertension	5 (11.4%)	6 (28.6%)	0.086
OSA	8 (18.2%)	6 (28.6%)	0.3444
Mean total bilirubin (μmol/L)	11.9 (7.45)	15.3 (12.41)	0.1766
Mean ALT (U/L)	115.6 (97.33)	190.0 (96.0)	0.0052
ALT >140 U/L	12 (27.3%)	14 (66.7%)	0.0026
Mean AST (U/L)	64.8 (52.88)	116.6 (68.78)	0.0015
AST >70 U/L	12 (27.3%)	16 (76.2%)	0.0002
Mean GGT (U/L)	56 (37.65)	84.0 (60.35)	0.0251
GGT >45 U/L	20 (45.5%)	16 (76.2%)	0.0207
Platelets ($\times 10^9$/L)	338 (101.5)	278 (77.9)	0.0194
Platelets <150 $\times$ 10^9/L	1 (2.3%)	1 (4.8%)	0.597
Positive autoantibody	7 (15.9%)	4 (19.0%)	0.7542

Data expressed in mean (standard deviation) or number (percentage).
ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; DM, diabetes mellitus; IGT, impaired glucose tolerance; GGT, gamma-glutamyltransferase; OSA, obstructive sleep apnoea.

(50%) in overweight and obese children, as compared to overweight/obese children with no NAFLD (15%).[18] In one retrospective study, 83% of children with NAFLD presented with at least one feature of the metabolic syndrome, namely obesity, hypertension, dyslipidemia, or hyperglycemia.[4] This was also evident in the high proportion (nearly 60%) of our cohort who developed one or more of these features of metabolic syndrome. Of note, a relatively high proportion of patients in our study developed DM (12.4%) in comparison to rates of 5–10% in other studies.[2,5,19] The reason could be the selection bias of patients who had more advanced disease in this study from a single tertiary center, although other genetic and extrinsic factors might also account for the difference in risk of DM between populations. Insulin resistance is believed to be the link between NAFLD and metabolic syndrome, but it remains unclear whether hepatic steatosis is the cause or effect of metabolic syndrome.[20] Nonetheless, the onset of these cardiovascular risk factors at such young age is of major concern, as metabolic syndrome in children has been shown to increase the odds of developing DM, atherosclerosis, and cardiovascular disease 14–30 years later.[21] Interestingly, we have also observed that one in five patients in our cohort had OSA. Recent studies have suggested that hypoxia related to OSA may promote progression of NAFLD and may be independently associated with fibrosis and NAFLD activity score in children.[22,23] However, we had not found any relationship between the presence of OSA and LSM estimation, probably due to the lower prevalence of OSA in our cohort.

VCTE is emerging to be an important noninvasive tool in the assessment of disease severity in NAFLD and has been incorporated into the latest clinical practice guidelines for adults.[24,25] Based on adult guidelines, LSM <8 kPa can be used to rule out advanced fibrosis, LSM of 8–12 kPa may be associated with fibrotic NASH, and LSM ≥12 kPa is associated with high likelihood of advanced fibrosis.[24] Recent pediatric studies have also demonstrated that VCTE can accurately predict histologic fibrosis in children with NAFLD. Nobili *et al.* obtained LSM using VCTE in 52 children with biopsy-proven NAFLD and reported area under the receiver operating characteristic (AUROC) curve for prediction of significant (≥F2) and advanced fibrosis (≥F3) of 0.992 and 1, respectively.[26] LSM cut-off of ≥5, >7, and >9 kPa have been proposed to rule-in "any" fibrosis (likelihood ratio, LR 5.923), significant fibrosis (LR 3.167), and advanced fibrosis (LR 22.50), respectively.[8,26] In another study comprising 206 pediatric participants, VCTE-derived LSM showed significant correlation with fibrosis stage, and was best able to differentiate between Ishak stage F0–F2 *versus* F3–F6, with AUROC of 0.7 specifically for the NAFLD group.[27] The study also found that CAP score positively correlated with steatosis grade, and a score of ≥259 dB/m was predictive of hepatic steatosis grades 1–3 with sensitivity of 94% and specificity of 91%.

Since 2019, VCTE has been performed as part of standard clinical practice for patients with NAFLD at our unit. At the end of the study period, over half of the patients who underwent VCTE had a high likelihood of significant fibrosis, or worse. Notably, the likelihood of advanced fibrosis was higher in patients aged 16 years and above, with around half of this group having LSM ≥9.1 kPa. The high proportion of patients with advanced VCTE readings may be explained by the selection bias resulting from the inclusion of patients from a tertiary hepatology referral clinic rather than the general population of patients with obesity managed by the general practitioner or pediatrician.

Patients in our cohort were more likely to have more severe biochemical liver dysfunction, with nearly two-thirds of patients having significantly raised ALT (≥80 U/L) associated with an increased probability of NASH.[6] Further research could be carried out on possible genetic, environmental, and cultural factors that may additionally impact on liver disease progression in children with NAFLD in our population.

Nonetheless, pediatric NAFLD may be a more aggressive disease as compared to adult NAFLD. Holterman *et al.* found that severely obese adolescents had higher incidence of fibrosis (83% *vs* 29%) and higher histologic NASH stage as compared to their adult counterparts.[28] Retrospective cohort studies have also reported the presence of fibrosis in 59–85% of children who had undergone liver biopsy, and progression of fibrosis stage was commonly detected in those who had repeat biopsies.[4,29] Repeat liver biopsies from the control arms of two clinical trials, which included 122 patients of whom 31% had definite NASH and 29% had at least stage 2 fibrosis, showed progression of histologic disease (NASH and fibrosis stage) in 36% of patients over a relatively short follow-up of 1.6 years.[5] The study also reported resolution of NAFLD only in three (2.4%) patients, which is not different from our modest resolution rate of 6% despite BMI *Z*-score reduction in nearly half of our patients.

Although uncommon, children may develop NASH cirrhosis leading to decompensated liver disease.[30] This was the case in a 16-year-old patient in our study with panhypopituitarism, an important association with NASH,[6] who eventually developed ACLF and died from multiorgan failure. NASH cirrhosis has been the most rapidly growing indication for LT in young adults in the United States since 2002 with an annual increment of 14% each year.[31] Liver disease progression is associated with adolescent age (≥13 years), higher waist circumference, high or rising ALT/AST/GGT, dyslipidemia, and DM based on the study by Xanthakos *et al.*[5] Although our study did not interrogate longitudinal progression of liver disease, our findings have comparably found age, high AST, and DM to be independent risk factors for elevated LSM (≥9.1 kPa) and increased likelihood of advanced fibrosis.

Although adjunctive pharmacotherapy such as with vitamin E had been used for some patients, at present there is no licensed treatment for NAFLD in children, and our study was not designed to evaluate the efficacy of these treatments.

The prevalence of overweight and obesity among children and adolescents has been on the rise in Singapore and globally.[32,33] As evident in our study, the increasing burden of NAFLD in the pediatric population, the chronicity of the disease, the propensity for liver disease progression, and the associated morbidity from metabolic syndrome are worrying trends that will have significant health implications and impact on healthcare utilization of the young adult population in the near future. NAFLD in children and young adults has been shown to be associated with increased mortality rates from cancer as well as liver and cardiometabolic causes.[19] Management and prevention of obesity and all its related complications must begin early in life and beyond the confines of healthcare. Our educational institutions must play a significant role in promoting healthy eating and physical activity to our young from an early age. Policies may be needed to limit the access of foods and beverages that are high in fructose and simple sugars to not just children but adults as well. Early screening for metabolic complications in children and adults at risk may lead to early intervention and positive change in dietary and lifestyle habits in the entire family unit.

We acknowledge several limitations of this study, including the inherent bias due to the retrospective nature of data collection, patient selection bias, and relatively high number of patients that were lost to follow-up. VCTE was available at our center only from 2019, hence only a segment of our cohort had this test performed. We were also unable to correlate VCTE results with histology, as liver biopsies were limited to only six patients owing to the reluctance to routinely perform this invasive procedure in our young patient cohort. Although our study is unable to provide data on the true prevalence, it still represents the largest cohort of pediatric NAFLD in the country and the findings can provide important insights into the clinical and epidemiological trends in pediatric NAFLD in Singapore and the Southeast Asian region.

Conclusion

Incidence of NAFLD in children has increased dramatically in Singapore over the past two decades, with many patients also developing metabolic and cardiovascular comorbidities associated with obesity. Pediatric NAFLD is a chronic and progressive liver disorder and may be associated with substantial risk of development of advanced hepatic fibrosis by late adolescence.

Ethics statement

Singhealth Centralized Institutional Review Board (CIRB 2018/2263) has approved waiver of patient consent for the study.

References

1 Younossi Z, Anstee QM, Marietti M *et al*. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. *Nat. Rev. Gastroenterol. Hepatol.* 2018; **15**: 11–20.

2 Sahota AK, Shapiro WL, Newton KP, Kim ST, Chung J, Schwimmer JB. Incidence of nonalcoholic fatty liver disease in children: 2009–2018. *Pediatrics*. 2020; **146**: e20200771.

3 Park SH, Park YE, Lee J *et al*. The change in prevalence of suspected non-alcoholic fatty liver disease in Korean adolescents from 2001 to 2017. *Paediatr. Int. Child Health*. 2020; **40**: 166–70.

4 Feldstein AE, Charatcharoenwitthaya P, Treeprasertsuk S, Benson JT, Enders FB, Angulo P. The natural history of non-alcoholic fatty liver disease in children: a follow-up study for up to 20 years. *Gut*. 2009; **58**: 1538–44.

5 Xanthakos SA, Lavine JE, Yates KP *et al*. Progression of fatty liver disease in children receiving standard of care lifestyle advice. *Gastroenterology*. 2020; **159**: 1731–51.

6 Vos MB, Abrams SH, Barlow SE *et al*. NASPGHAN clinical practice guidelines for the diagnosis and treatment of nonalcoholic fatty liver disease in children: recommendations from the Expert Committee on NAFLD (ECON) and the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN). *J. Pediatr. Gastroenterol. Nutr.* 2017; **64**: 319–34.

7 Kohli R, Sunduram S, Mouzaki M *et al*. Pediatric nonalcoholic fatty liver disease: a report from the Expert Committee on Nonalcoholic fatty liver disease (ECON). *J. Pediatr.* 2016; **172**: 9–13.

8 Alkhouri N. Putting it all together: Noninvasive diagnosis of fibrosis in nonalcoholic fatty liver disease in adults and children. *Clin. Liver Dis.* 2017; **9**: 134–7.

9 Hampl SE, Hassink SG, Skinner AC *et al*. Clinical practice guidelines for the evaluation and treatment of children and adolescents with obesity. *Pediatrics*. 2023; **151**: e2022060640.
10 American Diabetes Association Profressional Practice Committee. 2. Classification and diagnosis of diabetes: Standards of medical care in diabetes – 2022. *Diabetes Care*. 2022; **45**: S17–38.
11 Ministry of Health, Singapore.Ministry of health clinical practice guidelines on lipids. [Cited 2023, September 29]. Available from: https://www.moh.gov.sg/hpp/doctors/guidelines/GuidelineDetails/cpgmed_lipids
12 Rajwal S, McClean P. Non-alcoholic fatty liver disease. *Pediatr. Child Health*. 2017; **27**: 556–60.
13 Echosens. Fibroscan® procedure for users. [Cited 2023, September 29]. Available from: https://www.echosens.com/fibroscanprocedure
14 European Association for the Study of the Liver, Clinical Practice Guideline Panel. EASL clinical practice guidelines on non-invasive tests for evaluation of liver disease severity and prognosis – 2021 update. *J. Hepatol.* 2021; **75**: 659–89.
15 Anderson EL, Howe LD, Jones HE, Higgins JPT, Lawlor DA, Fraser A. The prevalence of non-alcoholic fatty liver disease in children and adolescents: a systematic review and meta-analysis. *PLoS One*. 2015; **10**: e0140908.
16 Nobili V, Socha P. Pediatric nonalcoholic fatty liver disease: current thinking. *J. Pediatr. Gastroenterol. Nutr.* 2018; **66**: 188–92.
17 Zhang X, Wu M, Liu Z *et al*. Increasing prevalence of NAFLD/NASH among children, adolescents and young adults from 1990 to 2017: a population-based observational study. *BMJ Open*. 2021; **11**: e042843.
18 Schwimmer JB, Pardee PE, Lavine JE, Blumkin AK, Cook S. Cardiovascular risk factors and the metabolic syndrome in pediatric nonalcoholic fatty liver disease. *Circulation*. 2008; **118**: 277–83.
19 Simon TG, Roelstraete B, Hartjes K *et al*. Non-alcoholic fatty liver disease in children and young adults is associated with increased long-term mortality. *J. Hepatol.* 2021; **75**: 1034–41.
20 D'Adamo E, Castorani V, Nobili V. The liver in children with metabolic syndrome. *Front. Endocrinol.* 2019; **10**: 514.
21 DeBoer MD. Assessing and managing the metabolic syndrome in children and adolescents. *Nutrients*. 2019; **11**: 1788.
22 Nobili V, Cutrera R, Liccardo D *et al*. Obstructive sleep apnoea syndrome affects liver histology and inflammatory cell activation in pediatric nonalcoholic fatty liver disease, regardless of obesity/insulin resistance. *Am. J. Respir. Crit. Care Med.* 2014; **189**: 66–76.
23 Sundaram SS, Halbower A, Pan Z *et al*. Nocturnal hypoxia induced oxidative stress promotes progression of pediatric non-alcoholic fatty liver disease. *J. Hepatol.* 2016; **65**: 560–9.
24 Rinella ME, Neuschwander-Tetri BA, Siddiqui MS *et al*. AASLD practice guidance on the clinical assessment and management of nonalcoholic fatty liver disease. *Hepatology*. 2023; **77**: 1797–835.
25 European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity. EASL-EASD-EASO clinical practice guidelines for the management of non-alcoholic fatty liver disease. *J. Hepatol.* 2016; **64**: 1388–402.
26 Nobili V, Vizzutti F, Arena U *et al*. Accuracy and reproducibility of transient elastography for the diagnosis of fibrosis in pediatric nonalcoholic steatohepatitis. *Hepatology*. 2008; **48**: 442–8.
27 Chaidez A, Pan Z, Sundaram SS *et al*. The discriminatory ability of Fibroscan liver stiffness measurement, controlled attenuation parameter, and Fibroscan-aspartate aminotransferase to predict severity of liver disease in children. *Hepatol. Commun.* 2022; **6**: 3015–23.
28 Holterman AL, Guzman G, Fantuzzi G *et al*. Nonalcoholic fatty liver disease in severely obese adolescent and adult patients. *Obesity*. 2013; **21**: 591–7.
29 Kader HH, Henderson J, Vanhoesen K *et al*. Nonalcoholic fatty liver disease in children: a single center experience. *Clin. Gastroenterol. Hepatol.* 2008; **6**: 799–802.
30 Alkhouri N, Hanouneh IA, Zein NN *et al*. Liver transplantation for nonalcoholic steatohepatitis in young patients. *Transpl. Int.* 2016; **29**: 418–24.
31 Doycheva I, Issa D, Watt KD, Lopez R, Rifai G, Alkhouri N. Nonalcoholic steatohepatitis is the most rapidly increasing indication for liver transplantation in young adults in the United States. *J. Clin. Gastroenterol.* 2018; **52**: 339–46.
32 World Health Organization. Obesity and overweight. [Cited 2023, September 29]. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
33 Ministry of Health, Singapore Obesity trend and programmes. [Cited 2023, September 29]. Available from: https://www.moh.gov.sg/news-highlights/details/obesity-trend-and-programmes