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Original Article

Transient liver elastography profiles in a hospital-based pediatric population with infectious mononucleosis in southern China

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Abstract: Objective: The goals of this study were to assess the feasibility of transient elastography (FibroTouch) and to examine liver elastography characteristics in children with infectious mononucleosis (IM) caused by Epstein-Bar virus (EBV) infection in Southern China. Methods: FibroTouch examinations were carried out in 357 pediatric patients (aged 1.0-18.0 years old). Hepatic fibrosis was assessed by liver stiffness measurement (LSM) and liver steatosis was determined by fat attenuation parameter (FAP). These results were then compared between the IM group (n=112) and control group (n=238). Risk factors for hepatic fibrosis (LSM > 6.5) were analyzed using univariate analysis and multivariate logistic regression. LSM, before and after therapy, for the IM group was also investigated. Results: Among 357 children examined, 350 children had successful FibroTouch examinations (98.0%; age range: 1.1-17.3 years old; 209 males). LSM values (expressed as mean ± SD) were significantly higher in the IM group (n=112, 5.1±1.8 kPa) than the control group (n=238, 3.5±1.3 kPa; P < 0.001). FAP values showed no significant differences between the IM group (198.9±23.1 dB/m) and control group (183.6±19.9 dB/m, P=0.060). In the IM group, body mass index (BMI) percentile (P=0.011), serum albumin (ALB) (P=0.007), EBV DNA load (P=0.045), and FAP (P=0.036) were associated with hepatic fibrosis, according to univariate analysis. Through multivariate analysis, BMI percentile ≥ 90% (P=0.013), ALB < 40 g/L (P=0.028), and FAP > 249 dB/m (P=0.039) were regarded as independent factors relevant with hepatic fibrosis. After treatment, the LSM of IM children decreased (P < 0.001). Conclusion: FibroTouch methodology is feasible for liver stiffness screening in Chinese children. Liver stiffness increases transiently in children with IM but decreases after treatment.

Keywords: Transient elastography, Epstein-Bar virus, infectious mononucleosis, liver profiles, children

Introduction

Epstein-Bar virus (EBV) is the major cause of infectious mononucleosis (IM) syndrome, characterized by fever, sore throat, lymph adenopathy, hepatosplenomegaly, and fatigue [1]. IM is one of the most common infections reported in children [2]. Complications of IM are variable, including hemolytic anemia, aplastic anemia, etc. [2, 3]. Additionally, EBV-induced liver fibrosis in children has been commonly reported in other countries [4, 5]. However, liver fibrosis in children caused by EBV has not been reported in China. Previous studies have found that about 70% of IM caused by EBV infections could lead to abnormal liver function and EBV-related hepatitis, possibly causing blood thirsty syndrome and increased mortality [3].

There are many methods to evaluate liver fibrosis caused by EBV infection. These include liver biopsy which has inherent disadvantages of invasive testing. In a previous study, it was found that transient elastography (TE) could well assess liver fibrosis caused by HBV infections [6]. TE, in theory, can assist in assessment of liver fibrosis in EBV-associated IM. However, certain hepatic features of EBV-

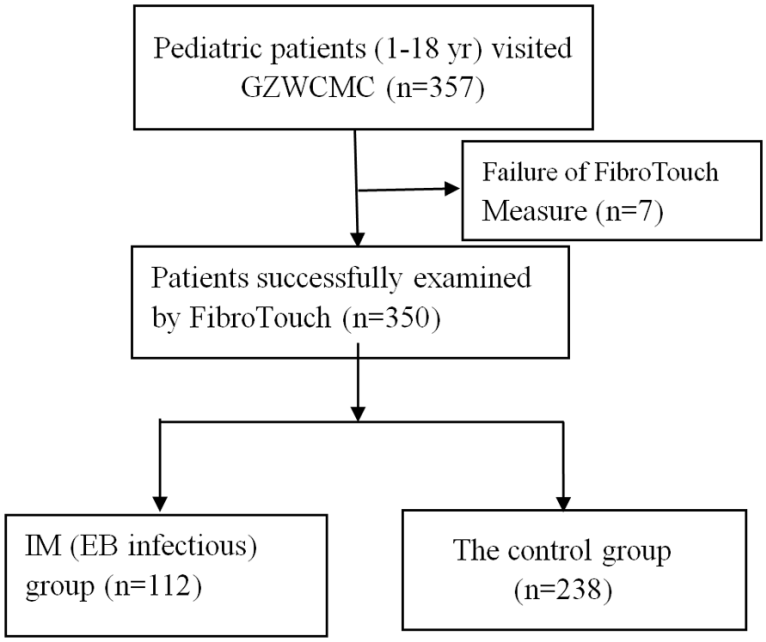


Figure 1. Selection of the study population. Patients examined by FibroTouch at a success rate greater than 60.0% with 10 valid measurements and an interquartile range (IQR) of 30.0% or less than 30.0% of the median LSM value were analyzed. Patients infected by Epstein-Bar virus (EBV) and without underlying liver diseases were included in the IM group. The control group was defined as having normal serum liver enzyme levels, an aspartate aminotransferase (AST)-to-platelet ratio index (APRI) score < 0.5, a normal-appearing liver on abdominal ultrasonography, and no episodes of liver disease.

associated IM have not been reported when using TE. Therefore, this study aimed to evaluate liver fibrosis in IM caused by EBV infection.

Newly-developed non-invasive diagnostic techniques, based on ultrasound imaging, have been used to assess liver stiffness and hepatic fat deposition [7]. Of these techniques, TE has been the most widely used evaluation method [8]. TE is an equipment-based measurement of the shear wave speed guided to the liver by a probe. Velocity indicates the stiffness of the liver, mainly depending on the quantity of fibrotic tissues. Therefore, LSM in kPa could reflect the degree of fibrosis. Additionally, TE is a non-invasive method of providing measures of liver elasticity that are highly accurate and reliable in identifying hepatic fat deposition and liver stiffness [9, 10]. However, there have been few studies investigating the feasibility and usefulness of TE, particularly in pediatric populations [11, 12].

FibroTouch (Hays Kyle, China), a newly-developed TE, has been available for clinical use in China since 2013 [13]. It integrates a two-dimensional (2D) image-guided system for precise positioning and uses a non-invasive method to detect and quantify liver fibrosis and hepatic steatosis with liver stiffness measurement (LSM) and fat attenuation parameter (FAP), respectively. In diagnosis and staging of liver cirrhosis, FibroTouch is highly consistent with liver biopsies [13]. FibroTouch can solve the above shortcomings, in theory, but there have been no large sample reports yet.

This study was conducted to identify the feasibility and usefulness of FibroTouch in Chinese children with a wide age range, paying attention to differences in liver profiles (i.e., liver stiffness and hepatic fat deposition) between IM and control pediatric populations. This study also evaluated changes in liver stiffness in pediatric patients with EBV-associated IM.

Materials and methods

Patients

The study population included pediatric patients (aged 1.0-18.0 years old) examined by FibroTouch in the Departments of Infectious Disease and Child Healthcare, in Guangzhou Women and Children Medical Center (Guangzhou, China), between April 2015 and August 2016.

This study was conducted in compliance with ethical guidelines of the Declaration of Helsinki. Informed consent (ICF) was provided by each patient's parent or legal guardian. A full explanation regarding objectives of the study, including any inconvenience or discomfort that may be caused, was imparted. This study was approved by the Human Ethics Committee of Guangzhou Women and Children Medical Center.

Patients with successful FibroTouch evaluations were assigned into two groups: IM group and control group. The IM group was comprised of patients without underlying liver disease.

Table 1. Variable conversion

Variables	Assignment explanation
Age	1="1 year ≤ age ≤ 3 years"; 2="3 years < age ≤ 7 years"
	3="7 years < age ≤ 18 years"
BMI percentile	1="BMI percentile ≥ 90%"; 2="BMI percentile < 90%"
ALT	1="ALT > 40 U/L"; 2="ALT ≤ 40 U/L"
GGT	1="GGT > 60 U/L"; 2="GGT ≤ 60 U/L"
ALB	1="ALB ≥ 40 g/L"; 2="ALB < 40 g/L"
DB	1="DB > 7 μmol/L"; 2="DB ≤ 7 μmol/L"
FAP	1="FAP > 249 dB/m"; 2="FAP ≤ 249 dB/m"
Size of liver	1="normal size of liver"; 2="abnormal size of liver"
EBV DNA load	1="EBV DNA load ≥ 500 cps/Ml"; 2="EBV DNA load < 500 cps/Ml"
LSM	1="LSM > 6.5 kPa"; 2="LSM ≤ 6.5 kPa"

Note: BMI, body mass index; ALT, aminotransferase; GGT, glutamyl transpeptidase; ALB, serum albumin; DB, direct bilirubin; FAP, fat attenuation parameter; EBV, Epstein-Bar virus; LSM, liver stiffness measurement.

Control subjects were defined as those with normal serum liver enzyme levels, aspartate aminotransferase (AST) -to-platelet ratio index (APRI) scores less than 0.5, livers appearing normal according to abdominal ultrasonography, and no occurrence of liver disease (**Figure 1**).

EBV-associated IM inclusion criteria were as follows: (A) Diagnostic criteria of EBV-associated IM (i.e., at least three EBV-related symptoms and signs: lymphadenopathy, fever, pharyngitis, palatal petechiae, rash, splenomegaly, or hepatomegaly); (B) Serological evidence met one of the following: anti-CA-IgM and anti-EBV-CA-IgG antibodies were positive and NA IgG was negative, anti-EBV-CA-IgM was negative but anti-EBV-CA-IgG antibody was positive, and low affinity antibody; and (C) Ratio of peripheral blood abnormal lymphocytes was ≥ 10.0%. The detection threshold of EBV DNA load was 500 genome copies/mL of whole blood, and viral loads of ≤ 500 copies/mL were classified as negative [14].

Clinical and biochemical data extraction

Clinical baseline data were collected from eligible patients, including age, gender, medication history, and BMI on the day of FibroTouch examination. Routine blood and liver biochemical tests (ALT, AST, GGT, ALP, ALB, DBIL, TBIL, etc.) were performed. EB antibody, EB antigen, and EBV DNA load were measured. Other routine tests were carried out, including platelet (PLT), blood sugar, blood ferritin levels, and percentage of abnormal lymphocytes. These tests were performed within 3 days before or after FibroTouch examinations. Clinical information and routine biochemical examination results were also collected. After 25-30 days, patients with IM undergoing treatment underwent another blood test and FibroTouch examination. BMI was calculated using the following equation: BMI = body weight (kg)/height (m^2). APRI score was calculated as follows: (AST/upper limit of normal * 100)/PLT (10^9/L). Fibrosis index based on the 4 factor (FIB-4) score was calculated using the following equation: age (years) * AST (IU/L)/(PLT (10^9/L) * $ALT^{1/2}$ (IU/L)).

Liver stiffness measurement and fat attenuation parameter

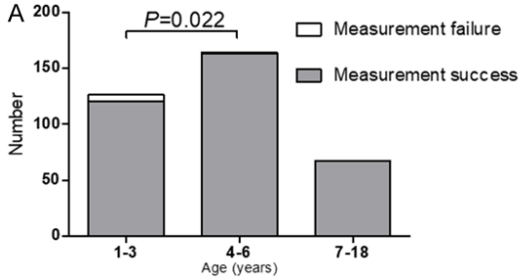
TE was performed by a well-trained and certified physician using FibroTouch, according to manufacturer instructions. FibroTouch was used to measure both LSM (kPa) and FAP (dB/m). LSM and FAP were considered reliable parameters only if 10 successful measurements were obtained, with an IQR/median (M) of < 30% and success rate (SR) > 60% [7]. Subjects with unsuccessful examinations were excluded. LSM > 6.47 kPa indicated liver fibrosis in children [11].

Liver ultrasonography

Ultrasound examinations were performed by an experienced ultrasonographer. Sizes of livers were compared with the same age and healthy children's livers under ultrasound. During ultrasound examinations, attention was paid to the size and morphology of livers. The primary objective of the present study was to evaluate the feasibility of FibroTouch, with a secondary objective of identifying risk factors for liver fibrosis in IM children.

Statistical analyses

Quantitative variables are expressed as mean ± SD or median (interquartile) and were com-



B

	The number of measurement success	The number of measurement failure	The success rate (%)
1.0-3.0years	120	6	95.2
4.0-6.0years	163	1	99.4
7.0-18.0years	67	0	100.0

Figure 2. A. Age distribution of patients examined using FibroTouch. B. Success rates for patients of different ages examined using FibroTouch. A total of 357 children and adolescents (age, 1.1–17.3 years; 209 males) were examined using FibroTouch. A total of 350 patients (gray bars) were examined successfully; the evaluation was unsuccessful in the remaining 7 patients (white bars). The number of measurement failures in 1.0-3.0 years age group was six and in 4.0-6.0 years age group was one, with a significant difference (P=0.022).

Table 2. Characteristics of the 350 patients in the study

	All	Control group	IM group	*P* value
N	350	238	112	
Age, years	4.0 (3.0, 6.0)	4.0 (3.0, 6.0)	4.0 (3.0, 7.0)	0.976
Gender (male, %)	209 (59.7)	142 (59.7)	67 (59.8)	0.978
BMI percentile	35.9 (11.5, 69.1)	40.4 (14.3, 71.1)	30.3 (7.8, 57.0)	0.064
AST, U/L	22.0 (15.0, 39.0)	16.0 (11.4, 23.0)	61.0 (37.3, 131.3)	< 0.001
ALT, U/L	25.0 (18.5, 36.0)	21.0 (16.0, 28.0)	96.0 (30.3, 189.3)	< 0.001
GGT, U/L	11.0 (9.0, 21.0)	10.0 (8.0, 12.0)	40.0 (15.3, 100.8)	< 0.001
ALB, g/L	41.6 (40.1, 43.4)	42.5 (41.3, 43.5)	39.3 (36.5, 41.4)	< 0.001
ALP, U/L	199.0 (163.0, 245.0)	204.5 (169.0, 245.0)	185.0 (141.3, 248.0)	0.019
TB, μmol/L	8.0 (5.2, 10.0)	8.5 (6.2, 10.4)	5.3 (4.3, 7.7)	< 0.001
DB, μmol/L	3.2 (2.2, 5.2)	4.0 (2.6, 5.2)	2.5 (1.8, 3.8)	< 0.001
Blood glucose, mmol/L	5.2 (4.8, 5.9)	5.2 (4.8, 5.6)	5.7 (4.9, 6.3)	0.001
PLT * 10^9/L	300.5 (238.0, 369.5)	326 (269.0, 412.8)	218.5 (178.5, 278.3)	< 0.001
EBV DNA load, cps/mL	3790.0 (739.8, 16,650.0)		3790.0 (739.8, 16,650.0)	
APRI	0.1 (0.1, 0.3)	0.1 (0.1, 0.1)	0.8 (0.7, 1.1)	< 0.001
FIB-4	1.2 (0.6, 2.4)	0.8 (0.5, 1.4)	2.4 (1.7, 4.1)	< 0.001
LSM, kPa	5.2 (4.8, 5.9)	3.3 (2.4, 4.2)	4.9 (3.6, 6.5)	< 0.001
N (LSM > 6.5) (%)	39 (11.1)	9 (3.8)	30 (26.8)	< 0.001
FAP, dB/m	183.2 (170.8, 203.5)	178.1 (168.3, 195.4)	198.0 (181.2, 211.1)	< 0.001
Size of liver				
Hepatomegaly (%)	68 (19.4)	0	68 (60.7)	< 0.001
Normal (%)	282 (80.6)	238 (100.0)	44 (39.3)	< 0.001
Percentage of abnormal lymphocytes (%)	13.5 (7.3, 21.0)	0	13.5 (7.3, 21.0)	< 0.001
Serum ferritin, μmol/L	213.5 (144.9, 269.0)		213.5 (144.9, 269.0)	

Note: BMI, body mass index; AST, aspartate aminotransferase; ALT, aminotransferase; GGT, glutamyl transpeptidase; ALB, serum albumin; ALP, alkaline phosphatase; TB, total bilirubin; DB, direct bilirubin; PLT, platelet; EBV, Epstein-Bar virus; APRI, aspartate aminotransferase-to-platelet ratio index; FIB-4, fibrosis index based on the 4 factors; LSM, liver stiffness measurement; FAP, fat attenuation parameter.

pared using t-test or Mann-Whitney's U-test. Count and categorical variables are expressed as percentage and were compared using Chi-square test. Variables with *P* values of 0.1 or less in univariate analyses were subjected to multivariable regression analysis. Quantitative variables of biochemical indicators were converted into rank variables according to cutoff points in clinical application. Multiple logistic regression models were built to explore the relationship between BMI percentile, ALT, GGT, ALB, DB, EBV DNA load, FAP and LSM (**Table 1**). P < 0.05 was considered statistically significant. All statistical analyses were performed with IBM SPSS Statistics (version 22; IBM, Java).

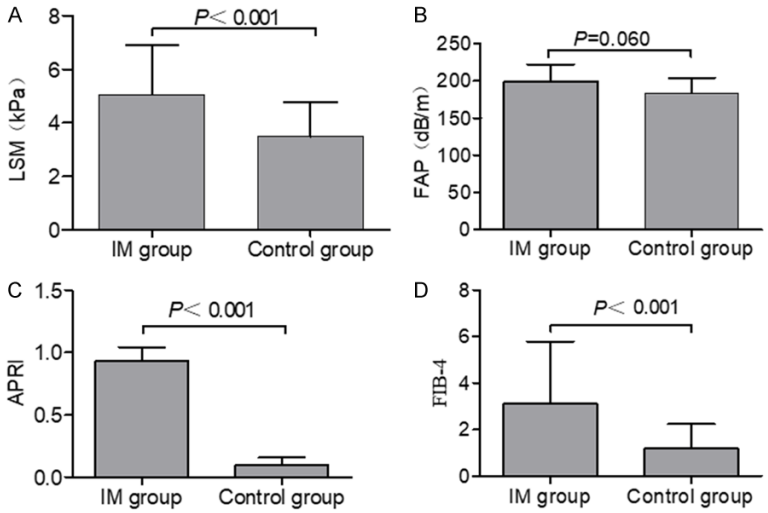


Figure 3. LSM, FAP, APRI and FIB-4 values in the IM and control groups. A. LSM value was significantly higher in the IM group (P < 0.001). B. FAP value was not significantly different between the IM group and control group (P=0.060). C. APRI value was significantly higher in the IM group (P < 0.001). D. FIB-4 value was significantly higher in the IM group (P < 0.001).

Results

FibroTouch is feasible regardless of age of children

Of the 357 children (1.1-17.3 years old; 213 males, **Figure 2**) assessed by TE using FibroTouch, 350 (98.0%; median age, 4.0 years; range, 1.1-17.3 years; 209 males) had valid measurements with SR > 60.0% and IQR/M < 30.0%. The proportion of valid measurements by TE using FibroTouch was 98.0% (350/357 patients). Evaluations were not successful in the remaining 7 children (2.0%; median age, 2.0 years; 4 males) because of small intercostal spaces in two children (1.2 and 1.6 years old, respectively) and poor cooperation from five children (1.3, 2.0, 2.2, 3.6 and 6.0 years old, respectively). Therefore, FibroTouch is feasible in children of different ages.

AST, ALT, GGT levels, APRI and FIB-4 in IM and control groups

Clinical and biochemical profiles of each group are summarized in **Table 2**. AST, ALT, GGT, APRI, and FIB-4 values were significantly higher in the IM group than the control group (all P < 0.05). ALB, ALP, TB, DB, and PLT values decreased significantly in the IM group (all P < 0.05). Age, gender, and BMI percentile were not statistically different between the two groups.

Liver stiffness in IM and control groups

LSM value increased significantly in the IM group (5.1±1.8 kPa) compared to the control group (3.5±1.3 kPa; P < 0.001). FAP values showed no significant differences between the IM group (198.9±23.1 dB/m) and control group (183.6±19.9 dB/m, P=0.060). APRI value was significantly higher in the IM group (0.9±0.1) than the control group (0.1±0.1; P < 0.001). FIB-4 value was significantly higher in the IM group (3.1±0.3) than the control group (1.2±0.1, P < 0.001) (**Figure 3**). The value of liver fibrosis at baseline (LSM > 6.5 kPa) in children has been previously reported [11]. In this study, 26.8% of the patients with IM were found to have liver fibrosis. Thus, liver fibrosis is partly present in the pediatric IM population.

Factors associated with liver fibrosis in the IM group

Univariate analysis demonstrated that group (P < 0.001), age (P < 0.001), ALT (P < 0.001), GGT (P < 0.001), ALB (P < 0.001), DB (P < 0.001), FAP (P < 0.001), and size of liver (P=0.040) were associated with liver fibrosis. Regarding multivariable analysis, ALT > 40 U/L (OR=3.277, P=0.046) and DB > 7 μmol/L (OR=1.230, P=0.008) were regarded as independent factors relevant with liver fibrosis (**Table 3**).

For univariate analysis in the IM group, BMI percentile (P=0.011), ALB (P=0.007), EBV DNA load (P=0.045), and FAP (P=0.036) were associated with liver fibrosis. In multivariable analysis, BMI percentile ≥ 90% (OR=0.976, P=0.013), ALB < 40 g/L (OR=0.866, P=0.028), and FAP > 249 dB/m (OR=1.022, P=0.039) were regarded as independent factors associated with liver fibrosis (**Table 4**).

LSM in patients with IM after treatment

Children with IM received the same treatment for 7-10 days. FibroTouch examinations were

Table 3. Factors associated with fibrosis in the two groups

Variables	Univariate analysis			Multivariable analysis		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Group (control, IM)	0.107	0.049-0.236	< 0.001	3.188	0.782-13.001	0.106
Age, years	1.171	1.074-1.278	< 0.001	1.084	0.961-1.223	0.191
Gender	1.165	0.595-2.283	0.656			
BMI percentile	1.255	0.423-2.722	0.683			
ALT*, U/L	0.090	0.043-0.186	< 0.001	3.277	0.933-11.515	0.046
GGT, U/L	1.011	1.006-1.01 5	< 0.001	0.999	0.992-1.005	0.702
ALB, g/L	6.979	3.447-14.131	< 0.001	0.471	0.177-1.258	0.133
DB#, μmol/L	1.248	1.120-1.390	< 0.001	1.230	1.054-1.435	0.008
PLT, 10^9/L	1.611	0.183-14.153	0.667			
FAP, dB/m	0.108	0.033-0.355	< 0.001	2.941	0.485-17.856	0.241
Size of liver	0.382	0.153-0.956	0.04	1.408	0.416-4.767	0.582

Note: BMI, body mass index; ALT, aminotransferase; GGT, glutamyl transpeptidase; ALB, serum albumin; DB, direct bilirubin; PLT, platelet; FAP, fat attenuation parameter. In multivariable analysis, ALT* > 40 U/L and DB# > 7 μmol/L were variables.

Table 4. Factors associated with fibrosis in the IM group

Variables	Univariate analysis			Multivariable analysis		
	OR	95% CI	*P* value	Adjusted OR	95% CI	*P* value
Age, years	1.073	0.960-1.198	0.214			
Gender	0.837	0.359-1.953	0.681			
BMI percentile	0.978	0.961-0.995	0.011	0.976	0.957-0.995	0.013
ALT, U/L	0.659	0.283-1.537	0.335			
GGT, U/L	1.001	0.995-1.006	0.821			
ALB, g/L	0.855	0.762-0.959	0.007	0.866	0.762-0.985	0.028
DB, μmol/L	1.035	0.953-1.124	0.413			
PLT 10^9/L	1.000	0.996-1.004	0.917			
EBV DNA load, cps/Ml	1.000	1.000-1.000	0.045	1.000	1.000-1.000	0.290
FAP, dB/m	1.020	1.001-1.039	0.036	1.022	1.001-1.044	0.039
Size of liver	1.727	0.720-4.141	0.221			
Percentage of abnormal lymphocytes, %	0.978	0.935-1.024	0.347			
Serum ferritin, μmol/L	1.000	0.999-1.001	0.597			

Note: BMI, body mass index; ALT, aminotransferase; GGT, glutamyl transpeptidase; ALB, serum albumin; DB, direct bilirubin; PLT, platelet; EBV, Epstein-Bar virus; FAP, fat attenuation parameter.

performed after 25-30 days. LSM before treatment (5.1±1.8 kPa) decreased after treatment (4.2±1.0 kPa), showing significant differences (P < 0.001). After treatment, the percentage of patients with liver fibrosis (LSM > 6.5 kPa) decreased from 26.8% to 1.8%, with statistical differences (P < 0.001) (**Figure 4**).

Discussion

FibroTouch can simultaneously obtain LSM and FAP data in adults. However, the suitability of FibroTouch and reliable indicators for its application in the pediatric population has remained uncertain. This present study mainly demonstrated the feasibility of FibroTouch in Chinese children of different ages. This study also revealed that liver stiffness in Chinese children with IM, especially those with elevated ALT levels, increased in the early stage and decreased in the recovery period.

Moreover, this study demonstrated that Chinese children and adolescents with IM had increased LSM values compared with the control group in the early stage. Therefore, FibroTouch enables simultaneous determination of LSM and FAP values, perhaps playing a vital role in hepatic evaluation, particularly in children with liver diseases. However, LSM val-

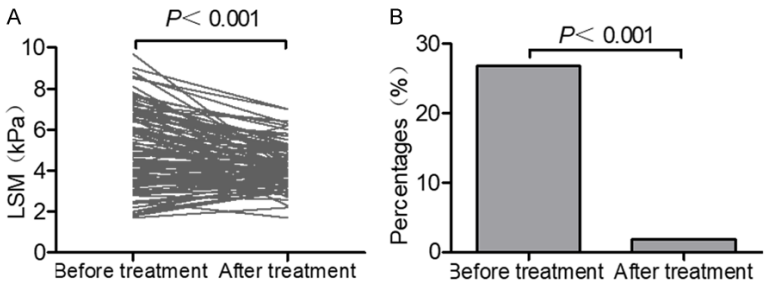


Figure 4. Changes of LSM in the IM group. A. After treatment, LSM of children with IM decreased (P < 0.001). B. After treatment, the percentage of patients with liver fibrosis (LSM > 6.5 kPa) decreased (P < 0.001).

ues were influenced by certain factors [15]. In some studies, LSM increased mildly in patients with steatohepatitis, possibly due to inflammation [16, 17]. In the present study, liver stiffness in children with IM was associated with BMI percentile, EBV DNA load, and FAP. Hence, these factors should be considered during evaluations.

Furthermore, results of this study showed that pediatric and adolescent IM were associated with BMI percentile, EBV DNA load, FAP and ALB. Elevated BMI percentile, reduced ALB, and increased FAP were regarded as independent factors associated with liver fibrosis in the IM group. Thus, ALB was the primary laboratory abnormality in patients with IM. Obese children with IM may have higher liver stiffness. It was reported that obese children usually have higher LSM and FAP, consistent with a previous study [7]. Some studies have found that the load of hepatitis B virus was positively correlated with liver stiffness in the infectious phase of hepatitis B virus [17, 18]. In this present study, EBV DNA load was relevant with liver stiffness in a pediatric IM population. To the best of our knowledge, this is the first time that a clear link to IM has been revealed.

In addition, this study found that liver stiffness in some children with IM decreased significantly during follow up. Results suggested that changes in liver stiffness due to IM were temporary and would not lead to permanent liver damage. It could be attributed to the liver fibrosis mechanism that failed to be initiated by EBV. Previous studies have reported that increased liver stiffness is mostly due to viruses and recovery is not easy [19]. However, this present report showed that increasing liver stiffness in IM children was transient, possibly explaining why IM is not serious in most children.

FibroTouch is feasible in children from different age groups. The present study showed that FibroTouch could be carried out successfully in patients ranging from 1.0 to 18.0 years. However, 2.0% of the measurements were invalid for the 357 consecutive examinations. Previous studies using FibroTouch have reported a failure rate of 0% in adults. A pediatric study reported a failure rate of 6.1% in children using FibroScan [7]. The highest failure rate for children was less than 5 years [7]. In this study, the failure rate was mainly attributed to patients less than 3 years old, consistent with a previous report [7]. Factors independently associated with FibroTouch measurement failure in adults included high BMI, female sex, and metabolic syndrome [20].

In the present study, measurement failure was primarily attributed to poor cooperation of the young children (1.3, 2.0, 2.2, 3.6 and 6.0 years old) and small intercostal spaces (1.2 and 1.6 years old). Since patients must be immobile during FibroTouch imaging, young children, especially those < 3.0 years old, might require sedation. Moreover, small intercostal space was important as a risk factor for measurement failure. Therefore, more research is necessary. Previous findings and results from this study indicate that FibroTouch imaging is feasible in pediatric subjects of different ages. However, risk factors for measurement failure, poor cooperation, and small intercostal space in young children should be considered.

FibroTouch is painless and harmless. It is, therefore, suitable for repeated examinations in children. Since non-invasiveness is a key feature of diagnostic modalities in children, the non-radiative and painless characteristics of FibroTouch combined with its applicability to a broad age range make it suitable for pediatric patients, particularly.

There are several limitations to the present research. First, subjects were pediatric patients visiting our hospital, not from the general population. Therefore, FibroTouch results may differ

between control patients and healthy individuals in the general population. Second, the sample size was quite small. Third, the duration of follow up for patients with IM was short. However, this study was still able to identify changes in data and show that liver fibrosis was transient after liver damage in children with IM. Nevertheless, this study focused on liver profile differences between the IM group and control group, showing that FibroTouch testing should focus on liver stiffness in patients with liver disease. The findings of this present study provide additional evidence regarding the usefulness of FibroTouch testing in a hospital-based pediatric population.

In summary, this study demonstrates that FibroTouch is feasible in Chinese children across a wide range of ages. FibroTouch imaging, simultaneously determining FAP and LSM values, is a non-invasive and effective screening method for measuring hepatic steatosis and liver stiffness in Chinese children, especially those with liver diseases. Liver stiffness increases transiently in children with IM but decreases after treatment.

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Disclosure of conflict of interest

None.

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References

[1] Sayyahfar S, Lavasani A, Nateghian A, Karimi A. Evaluation of lipid profile changes in pediatric patients with acute mononucleosis. Infect Chemother 2017; 49: 44-50.

[2] González Saldaña N, Monroy Colín VA, Piña Ruiz G, Juárez Olguín H. Clinical and laboratory characteristics of infectious mononucleosis by Epstein-Barr virus in Mexican children. BMC Res Notes 2012; 5: 361.

[3] Janani MK, Malathi J, Appaswamy A, Singha NR, Madhavan HN. A hospital based pilot study on Epstein-Barr virus in suspected infectious mononucleosis pediatric patients in India. J Infect Dev Ctries 2015; 9: 1133-8.

[4] Morshed SA, Nishioka M, Saito I, Komiyama K, Moro I. Increased expression of Epstein-Barr virus in primary biliary cirrhosis patients. Gastroenterol Jpn 1992; 27: 751-8.

[5] Ariad S, Yanai I, Sobel R. Chronic infection with Epstein-Barr virus, chlamydia and hepatitis a virus, terminating in cirrhosis and nasopharyngeal carcinoma. Isr J Med Sci 1989; 25: 328-31.

[6] Afdhal NH, Bacon BR, Patel K, Lawitz EJ, Gordon SC, Nelson DR, Challies TL, Nasser I, Garg J, Wei LJ, McHutchison JG. Accuracy of fibroscan, compared with histology, in analysis of liver fibrosis in patients with hepatitis B or C: a united states multicenter study. Clin Gastroenterol Hepatol 2015; 13: 772-9, e1-3.

[7] Cho Y, Tokuhara D, Morikawa H, Kuwae Y, Hayashi E, Hirose M, Hamazaki T, Tanaka A, Kawamura T, Kawada N, Shintaku H. Transient elastography-based liver profiles in a hospital-based pediatric population in Japan. PLoS One 2015; 10: e0137239.

[8] Nobili V, Monti L, Alisi A, Lo Zupone C, Pietrobattista A, Tomà P. Transient elastography for assessment of fibrosis in paediatric liver disease. Pediatr Radiol 2011; 41: 1232-8.

[9] de Lédinghen V, Vergniol J, Capdepont M, Chermak F, Hiriart JB, Cassinotto C, Merrouche W, Foucher J, Brigitte le B. Controlled attenuation parameter (CAP) for the diagnosis of steatosis: a prospective study of 5323 examinations. J Hepatol 2014; 60: 1026-31.

[10] Goldschmidt I, Streckenbach C, Dingemann C, Pfister ED, di Nanni A, Zapf A, Baumann U. Application and limitations of transient liver elastography in children. J Pediatr Gastroenterol Nutr 2013; 57: 109-13.

[11] Engelmann G, Gebhardt C, Wenning D, Wühl E, Hoffmann GF, Selmi B, Grulich-Henn J, Schenk JP, Teufel U. Feasibility study and control values of transient elastography in healthy children. Eur J Pediatr 2012; 171: 353-60.

[12] Alkhouri N, Sedki E, Alisi A, Lopez R, Pinzani M, Feldstein AE, Nobili V. Combined paediatric NAFLD fibrosis index and transient elastography to predict clinically significant fibrosis in children with fatty liver disease. Liver Int 2013; 33: 79-85.

[13] Chen GF, Ping J, Gu HT, Zhao ZM, Zhou Y, Xing F, Tao YY, Mu YP, Liu P, Liu CH. Correlation of liver stiffness measured by FibroTouch and FibroScan with Ishak fibrosis score in patients with chronic hepatitis B. Chin J Hepatol 2017; 25: 145-150.

[14] Huang Y, Wei C, Zheng K, Zhao D. The impact of serological features in Chinese children with primary or past Epstein-Barr virus infections. Virol J 2013; 10: 55.

[15] Shan R, Yin H, Yang W, Li J, Zhang M, Zhao M, Shao J, Wang A. Influencing factors of transient elastography in detecting liver stiffness. Exp Ther Med 2016; 12: 2302-2306.

[16] Tana MM, Zhao X, Bradshaw A, Moon MS, Page S, Turner T, Rivera E, Kleiner DE, Heller T. Factors associated with the platelet count in patients with chronic hepatitis C. Thromb Res 2015; 135: 823-8.

[17] Tseng TC, Liu CJ, Yang HC, Su TH, Wang CC, Chen CL, Hsu CA, Kuo SF, Liu CH, Chen PJ, Chen DS, Kao JH. Serum hepatitis B surface antigen levels help predict disease progression in patients with low hepatitis B virus loads. Hepatology 2013; 57: 441-50.

[18] Liang LB, Zhu X, Yan LB, Du LY, Liu C, Chen LY, Liao J, Tang H. Serum hepatitis B surface antigen titer and transient elastography in screening for insignificant fibrosis in HBeAg-positive chronic hepatitis B patients. Ther Clin Risk Manag 2015; 11: 229-35.

[19] Cepeda JA, Thomas DL, Astemborski J, Sulkowski MS, Kirk GD, Mehta SH. Increased mortality among persons with chronic hepatitis C with moderate or severe liver disease: a cohort study. Clin Infect Dis 2017; 65: 235-243.

[20] Deng H, Wang CL, Lai J, Yu SL, Xie DY, Gao ZL. Noninvasive diagnosis of hepatic steatosis using fat attenuation parameter measured by FibroTouch and a new algorithm in CHB patients. Hepat Mon 2016; 16: e40263.