Nutrition 63–64 (2019) 134–140

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Applied nutritional investigation

Intestinal failure-associated liver disease in patients with short bowel syndrome: Evaluation by transient elastography

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ARTICLE INFO

Article History:
Received 1 September 2018
Received in revised form 27 December 2018
Accepted 11 February 2019

Keywords:
Short bowel syndrome
Long-term parenteral nutrition
Intestinal failure-associated liver disease
Transient elastography
Controlled attenuation parameter
Liver fibrosis
Steatosis

ABSTRACT

Objective: Patients with short bowel syndrome (SBS) receiving long-term parenteral nutrition (PN) are at risk for intestinal failure-associated liver disease (IFALD). The aim of the present study was to evaluate dynamic changes of liver fibrosis and steatosis within 12 mo by transient elastography (TE), including controlled attenuation parameter (CAP) in a cohort of patients with SBS receiving long-term PN.
Methods: Twenty-five adult patients with SBS and PN requirement for ≥3 mo consecutively were included and prospectively followed. Liver stiffness by FibroScan (Echosens, Paris, France) and CAP measurement were done at study entry and after 12 mo. Clinical parameters, as well as data on underlying bowel disease and nutrition composition, were collected. Bioelectrical impedance analysis was performed in all patients.
Results: FibroScan and CAP did not show any significant differences after 12 mo (5.2 kPa [2.8–16.2 kPa]; 223 dB/m [101–366 dB/m]) compared with study entry (5.3 kPa [2.7–12.3 kPa]; 237 dB/m [100–344 dB/m]). There was no significant correlation between FibroScan and CAP and elevated transaminase levels. CAP significantly correlated with triacylglyceride levels ($r = 0.411$; $P = 0.042$) and body mass index ($r = 0.468$; $P = 0.016$). Patients with a remnant small bowel <100 cm showed a significantly higher stiffness value by FibroScan than those having a remnant length ≥100 cm (6.1 versus 4.7 kPa; $P = 0.028$).
Conclusion: In the present study cohort, prevalence of advanced fibrosis or cirrhosis was low (<10%) without significant dynamic within the 12-mo follow-up. Short intestinal remnant length <100 cm appeared to be a risk factor for development of fibrosis.

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Introduction

Short bowel syndrome (SBS) in adults is usually caused by surgical resection of a large portion of the functional small intestine [1]. The most common underlying diseases are inflammatory bowel disease, postsurgical complications, mesenteric vascular disease, radiation enteritis, and chronic small bowel disease with severe malabsorption and dysmotility syndromes [2]. Patients with SBS are at risk for hepatobiliary complications such as liver cirrhosis or end-stage liver disease, especially if receiving long-term parenteral nutrition (PN) [3,4]. Intestinal failure-associated liver disease (IFALD) has multifactorial origins with a number of involved pathogenic mechanisms. Among several factors, the underlying disease, composition of PN, length of remnant intestine, and patient age play an important role in disease progression [5,6]. However, there are only few data concerning IFALD in adults. Most studies focus on children dependent on PN, including infants under the age of 6 mo. In the pediatric population, beginning PN at an early stage, particularly in the neonatal period, was associated with greater mortality [7,8]. Patients with SBS requiring PN frequently present with elevated liver enzymes [9]. Little published data exist on the reliability of increased liver values for the degree of

VK and MFR conceived of and designed the study. VK, SCN, SM, EH, TP, and MFR were responsible for the generation, collection, assembly, analysis, or interpretation of data. All authors approved the final version of the manuscript. MFR has received speaker honorarium from Echosens and Siemens and has performed research collaboration with Echosens, Siemens, and Hitachi. TP is the inventor of FibroTest and SteatoTest and founder of BioPredictive; the patents belong to the public organization Assistance Publique Hôpitaux de Paris. The remaining authors have no conflicts of interest to declare.

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https://doi.org/10.1016/j.nut.2019.02.001
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histopathologic damage in form of fibrosis or cirrhosis. A study by Naini et al. could demonstrate that histologic evidence of portal inflammation, ductopenia, portal and penivenular fibrosis, cholestasis, and steatosis were characteristic markers of IFALD [10]. The authors concluded that neither duration of PN nor biochemical parameters were good predictors for severity of histologic damage. It is mandatory to detect severe fibrosis or cirrhosis early to monitor these patients more closely for signs and symptoms of hepatic decompensation.

Liver biopsy, the gold standard for staging of fibrosis, is invasive, and the accuracy is even somehow questionable owing to sampling variations, inadequate specimen size, and observer variability [11]. Over the last few years, non-invasive methods have been evaluated for the assessment of liver fibrosis. Several meta-analyses have focused on the ultrasound-based transient elastography (TE; FibroScan, Echosens, Paris, France), and it is now a well-established non-invasive technique for the staging liver fibrosis worldwide, especially in patients with chronic viral hepatitis and non-alcoholic steatohepatitis [12–14]. Controlled attenuation parameter (CAP) implemented on FibroScan has been developed to quantify the degree of ultrasound attenuation owing to hepatic fat. The use of CAP as a means for detecting steatosis was originally proposed by Sasso et al. [15], who demonstrated an area under receiver operative characteristic curve (AUROC) of 0.91 and 0.95 for the detection of >10% and 33% of steatosis.

To our knowledge, liver stiffness values in patients with IFALD have been examined in only a few adult patients [16]. It could be shown that TE values were significantly correlated to serum bilirubin level and severity of histologic cholestasis and aspartate aminotransferase to platelet ratio index (APRI) and fibrosis-4 (FIB-4) scores [16–18].

The aim of the present study was to evaluate dynamic changes of liver fibrosis and steatosis within 12 mo by TE including CAP in a cohort of adult patients with SBS receiving long-term PN.

Material and methods

Patients and study design

This was a prospective ultrasound trial conducted between January 2014 and September 2016 at a German tertiary center and was approved by the local ethics committee according to the latest Declaration of Helsinki and the International Conference on Harmonisation/Committee for Proprietary Medicinal Products guidelines "Good Clinical Practice." All patients provided written informed consent.

Adult men and women with SBS and PN requirement for ≥3 mo consecutively were included. They all had a malabsorption disorder caused by small intestinal dysfunction. Main exclusion criteria were other causes of liver disease such as autoimmune disorders, chronic viral hepatitis, Wilson's disease, hemochromatosis, hepatic metastases, hepatocellular carcinoma, presence of ascites, preexisting severe psychiatric conditions, significant alcohol consumption (≥40 g/d in women and ≥60 g/d in men), pregnancy, and presence of cardiac defibrillator. The primary endpoint of the study was assessment of fibrosis stage within 12 mo by TE in a cohort of patients with SBS receiving long-term PN. Secondary study endpoints were as follows:

1. evaluation of steatosis by CAP;
2. evaluation of fibrosis and steatosis by serum markers such as FibroTest and SteatoTest [19,20];
3. estimation of body composition by bioelectrical impedance analysis (BIA); and
4. evaluation of risk factors associated with chronic liver disease in patients with SBS receiving long-term PN.

Clinical and laboratory assessments and liver stiffness measurement by TE were performed at study entry and after 1 y. Furthermore, spleen diameter, hepatic perfusion, and the presence or absence of cholestasis were estimated by conventional abdominal ultrasound.

Laboratory data

Laboratory tests, including serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), γ-glutamyl transferase (GGT), bilirubin, albumin, creatinine levels, platelet count, prothrombin time, cholesterol, and ferritin were obtained at study entry and after 12 mo. In addition, APRI score: aspartate aminotransferase level (upper limit of normal)/(platelet counts (109/l) × 100) [17], FibroTest [19], SteatoTest [20], and FIB-4 index [18] were calculated.

Transient elastography

Transient liver elastography was assessed with the FibroScan device, which incorporates an ultrasound transducer probe mounted on the axis of a vibrator. The vibrator generates a completely painless vibration with a frequency of 50 Hz, which leads to an elastic shear wave propagating through the skin and the subcutaneous tissue to the liver. The share wave velocity (expressed in kilopascal, kPa) is directly related to the stiffness of the tissue [21]. Stiffness measurements were performed with a 3.5-MHz transducer (M-probe) in patients with a skin capsule distance ≤25 mm and a 2.5-MHz transducer (XL-probe) in patients with a skin capsule distance >25 mm, respectively. The fasting interval between last food intake and measurement was assigned to ≥4 h [22]. Ten measurements were obtained. Unreliable measurements were defined as an interquartile range to median value ratio >30% or a success rate <60%. These thresholds were chosen because they were reported to improve inter- and intravariability discrepancies [22,24].

The following cutoff values were chosen to define different fibrosis stages:

- significant fibrosis (F2): ≥7kPa to <8.7 kPa;
- advanced fibrosis (F3): ≥8.7 kPa to <10.3 kPa; and
- liver cirrhosis (F4): ≥10.3 kPa [25].

Hepatic steatosis was assessed by CAP using signals acquired by FibroScan. CAP measures ultrasonic attenuation in the liver at 3.5 MHz at a depth between 25 and 65 mm [15,26]. The final CAP value, which ranges from 100 to 400 dB/m, represents the median of individual measurements.

Bioelectrical impedance analysis

BIA is a commonly used method for estimating body composition. BIA measurements were obtained in the supine position using a multifrequency impedance device (2000-M BIA; Data Input, Pöcking, Germany). Current-injector gel electrodes (Bianostic AT) were placed below the phalangeal-metacarpal joint in the middle of the dorsal side of the right hand and below the metatarsal arch on the superior side of the right foot. Detector electrodes were placed on the posterior side of the right wrist, midline to the pisiform bone of the medial (fifth phalangeal) side with the wrist semi flexed. Impedance was measured using 1, 5, 50, and 100 kHz at oscillating current. An undisclosed proprietary equation developed by the manufacturer (NutriPlus 5.4.1) calculated total body water (TBW) using the impedance at 5, 50, and 100 kHz and body weight, height, age, and sex. Hence, TBW is the calculated variable from measured impedance values (height^2 / resistance). The lean body mass (LBM) is defined to contain 73% of water, and therefore, the calculation looks as follows:

$$LBM = TBW/0.73.$$

LBM, fat mass (FM) and percent body fat (%BF) values are calculated using TBW and body weight. BIA was performed at study entry and after 1 y in all patients.

Statistical analyses

Continuous variables are given as median and range and categorical variables as frequency and percentage. Wilcoxon test and *t* test were used for comparison of two paired groups. Spearman's and Pearson's rank correlations were calculated with several baseline variables. Differences between two or more groups referring to TE were analyzed by Jonckheere–Terpstra test. All tests were two-sided, and $P < 0.05$ was considered significant. All statistical analyses were carried out using the statistical software package SPSS version 22 for Windows (IBM, Armonk, NY, USA) BIAS version 11.05 and Microsoft Excel 2016.

Results

Patient characteristics

Between January 2014 and September 2015, we screened 26 patients receiving long-term PN (median 30 mo). One of the 26 patients was not eligible because of concomitant chronic hepatitis C infection. Follow-up data after 12 mo (FU12) were available from 22 of 25 patients. Two patients died within the study period and one was lost to follow-up. In a subgroup of patients, FibroTest (n = 13) and SteatoTest (n = 12) were additionally calculated at

baseline and after 12 mo. Baseline characteristics of patients included in the final evaluation are shown in Table 1.

Characteristics of PN

At study entry, detailed information on composition and duration of PN was obtained from each patient and are shown in Table 2. After 12 mo, 4 of 22 patients (18%) could abstain from PN by initiating enteral feeding. One patient received continuous total PN, whereas 17 patients were treated with a combination of PN and enteral nutrition (EN; Table 2).

Liver stiffness and CAP by FibroScan

Prevalence of significant or advanced fibrosis or cirrhosis (≥7 kPa) was low (4 of 22 patients) at FU12. There was no significant elevation of liver stiffness assessed by FibroScan between baseline (median [range], 5.3 [2.7–12.3] kPa) and FU12 (median [range], 5.2 [2.8–16.2] kPa; Fig. 1A). In detail, 18 of 22 patients (82%) showed no change of fibrosis stage at FU12, whereas 4 patients (18%) achieved reduction of liver stiffness. Overall, prevalence of advanced fibrosis and cirrhosis (≥8.7 kPa) was low (2 of 22 patients) at FU12.

Steatosis (≥222 dB/m) could be detected in 15 of 25 patients at study entry. CAP measurement did not reveal any significant difference after 12 mo (median [range], 223 ([101–366] dB/m) compared with baseline (median [range], 237 [100–344] dB/m; Fig. 1B). In particular, 5 of 22 patients (23%) showed improved CAP values at FU12, whereas in another 23%, steatosis deteriorated. Overall, prevalence of severe steatosis (≥290 dB/m) was documented in 6 of 22 patients.

Non-invasive assessment of fibrosis and steatosis by serum markers

APRI score, FIB-4 index, FibroTest, and SteatoTest were performed at study entry and after 12 mo. Neither fibrosis nor steatosis assessment by serum markers showed any significant difference between baseline and FU12 (Table 3).

Table 1
Baseline characteristics of patients

Baseline characteristics	Patients (N = 25)
Male/Female, n	13/12
Age, y, median (range)	49 (19–83)
BMI, kg/m^2, median (range)	19 (11–28)
Ethnicity	
Caucasian, n (%)	23 (92.6)
Asian, n (%)	2 (7.4)
Indication for surgical treatment	
Crohn's disease, n (%)	8 (32)
Ulcerative colitis, n (%)	1 (4)
CIPO, n (%)	3 (12)
FAP, n (%)	1 (4)
Others, n (%)	12 (48)
Remnant small bowel length, cm, median (range)	95 (0–350)
Remnant colon length, cm, median (range)	75 (0–131)
PN duration, mo, median (range)	30 (3–350)
Bilirubin, mg/dL, median (range)	0.4 (0.2–3.2)
AST, U/L, median (range)	28 (14–202)
ALT, U/L, median (range)	32 (9–294)
Cholesterol, mg/dL, median (range)	119 (72–255)
Triacylglycerides, mg/dL, median (range)	85 (35–224)
FibroScan (liver stiffness), kPa, median (range)	5.25 (2.7–12.3)
CAP, dB/m, median (range)	237 (100–344)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; CIPO, chronic intestinal pseudo-obstruction; FAP, familial adenomatous polyposis; PN, parenteral nutrition;

Changes in BMI and body composition

There was no significant change in body mass index (BMI) between baseline and FU12 (median [range], 19.7 [11.9–28.3] kg/m^2) and FU12 (median [range], 19.3 [12.5–28.5] kg/m^2).

In 2 of 22 patients, BIA showed invalid values. In the remaining patients, no significant differences of phase angle (median [range], 5.3° [2.3–7.2°] versus 5.7° [3.5–6.8°]) and fat mass (median [range], 15.6% [2.9–41.7%] versus 18.5% [7.8–35%]) were documented between study entry and FU12, respectively.

Correlation between TE including CAP and clinical parameters at baseline

Liver stiffness assessed by FibroScan and CAP were profoundly correlated with biochemical scores and metabolic factors. In detail, FibroScan was positively correlated with FibroTest (F0–F3 versus F4, $P < 0.0001$; F0–F2 versus F3–F4, $P = 0.045$) at baseline (Table 4). CAP showed a positive correlation with SteatoTest ($P = 0.002$), BMI ($P = 0.016$), and triacylglycerides ($P = 0.042$; Table 5) at baseline. Thus, there was no significant correlation between FibroScan and CAP.

Risk factors for development of fibrosis assessed by TE

Patients with remnant small bowel length <100 cm were shown to have higher stiffness factors by FibroScan than those having a remnant length ≥100 cm (6.1 versus 4.7 kPa; $P = 0.028$). There was no significant difference in liver stiffness concerning BMI (19 versus 19–25 versus >25 kg/m^2), type of small bowel resection (jejunum versus ileum), underlying bowel disease (Crohn's disease versus ulcerative colitis versus familial adenomatous polyposis versus chronic intestinal pseudo-obstruction), oral food intake (<1000 versus >1000 kcal/d), and type of nutrition (PN versus EN versus combined PN and EN).

Discussion

In the present study, we investigated liver fibrosis and steatosis within 12 mo by ultrasound-based TE including CAP in patients with SBS receiving long-term PN. Overall, prevalence of advanced fibrosis or cirrhosis measured by TE was low (<10%) without significant dynamic changes within 12 mo follow-up. Short intestinal remnant length (<100 cm) turned out to be a risk factor for fibrosis development.

In contrast, prevalence of steatosis measured by CAP was considerably higher (50%) without significant progression during the 12 -mo follow-up. Salvino et al. demonstrated in a previous study that the number of patients with severe liver dysfunction was rather small [27].

FibroScan is a well-established non-invasive method for assessing liver fibrosis in patients with viral hepatitis, non-alcoholic steatohepatitis, or biliary disease; however, on research evaluation, there are only two studies investigating TE in patients with IFALD [12,16,23,28]. Hukkinen et al. analyzed 57 children with intestinal failure (IF) and PN duration ≥3 mo using liver biopsy as a reference [28]. The authors demonstrated that TE predicted any liver histopathology (fibrosis, cholestasis, or steatosis) with AUROC of 0.86. For prediction of ≥F1 and ≥F2 fibrosis, AUROC values were 0.78 and 0.73. The only study among adult IF patients using TE to evaluate severity of liver disease was performed by van Gossum et al. [16]. It revealed no correlation between TE and the stages of histologic fibrosis, but TE values were significantly correlated to serum bilirubin levels and the severity of histologic cholestasis. It is well known

Table 2
Characteristics of parenteral nutrition regime at baseline and after 12 mo

	Patients (N = 25)	Patients (N = 22)	*P*-value
	at baseline	after 12 mo	
Type of nutrition, n (%)			0.038
Combined PN/EN	20 (80)	17 (77)	
PN	5 (20)	1 (5)	
EN	0 (0)	4 (18)*	
Composition of PN, n (%)			0.317
Smofkabiven	10 (40)	7 (39)	
Aminomix	1 (4)	1 (6)	
Individual PN mixture	14 (56)	10 (56)	
PN total volume, mL·kg·d^{-1}, median (range)	23.2 (8.9–34.1)	16 (0.86–52.6)†	0.072
		15.29‡	
		16.03 (0.86–52.6)§	
PN total energy, kcal·kg·d^{-1}, median (range)	19.6 (2.9–47.8)	14.8 (0.96–37)‖	0.035
		16.56¶	
		12.93 (0.96–37)#	
Compounds of PN, median (range)			
Glucose, g·kg·d^{-1}	1.9 (0.5–4.6)	1.82 (0.11–4.6)	0.077
Amino acids, g·kg·d^{-1}	0.9 (0.23–2.3)	0.66 (0–2.4)	0.026
Fatty acids, g·kg·d^{-1}	0.7 (0–2.4)	0.57 (0–1.8)	0.134

EN, enteral nutrition; FU12, follow-up after 12 mo; PN, parentral nutrition.
*Patients stopped PN after 1 (1 patient), 2 (2 patients), and 6 (1 patient) mo, respectively.
†PN total volume of all patients (N = 22) at FU12.
‡PN total volume of 1 of 22 patients with PN at FU12.
§PN total volume of 17 of 22 patients with combined PN/EN at FU12.
‖PN total energy of all patients (N = 22) at FU12.
¶PN total energy of 1 of 22 patients with PN at FU12.
#PN total volume of 17 of 22 patients with combined PN/EN at FU12.

that cholestasis leads to an overestimation of liver fibrosis using TE because TE measures liver stiffness and not liver fibrosis [29]. We could not find evidence of relevant cholestasis in our patients. In the present study, with a median of 30 mo of PN, the prevalence of advanced liver fibrosis and cirrhosis assessed with TE was low (<10%) without significant dynamic changes within 12 mo follow-up.

To our knowledge, this is the first study to analyze degree of steatosis by ultrasound-based elastography in adult patients with IFALD. Half of our patients had presence of steatosis measured by CAP without significant progression during the 12-mo follow-up. In the present study, CAP values were significantly associated with metabolic parameters such as BMI and triacylglycerides, but not with liver stiffness. In a recent study by Huijbers et al., liver fat content was quantified by proton magnetic resonance spectroscopy (1 H-MRS) in adult patients with chronic IF owing to PN. 1 H-MRS analysis revealed steatosis in 5 of 15 patients receiving PN for >6 mo. However, a limitation of using 1 H-MRS is that no information is obtained on fibrosis. Moreover, 1 H-MRS cannot be performed in all patients (e.g., in those with claustrophobia) [30]. Earlier studies of pediatric patients documented variable degrees of steatosis ranging from 22% to 58% assessed by liver biopsy [10,28,31].

Hence, we do not conclude that there is a close association between pathogenesis of steatohepatitis and its progression to liver fibrosis. The exact mechanism is most likely multifactorial. In our study cohort, short intestinal remnant length (<100 cm) appeared to be a risk factor for development of fibrosis. This was in line with a study by Cazals-Hatem et al. who could demonstrate by liver biopsy that an ultra-short bowel was an independent risk factor for fibrosis in adults requiring PN [32]. A retrospective analysis by Luman et al. noted that length of small bowel of <100 cm was significantly associated with deranged liver function tests in patients with long-term PN, and the reason for this observation could be due to higher parenteral caloric intake [33]. However, in the present study, we could not find any correlation between total energy intake and higher stiffness values by TE. Experimental data obtained in a piglet SBS model suggest that dysbiosis combined with a decrease in overall bacterial diversity in the colon generates colonic mucosal inflammation and liver damage [34]. In a mouse model of IF, PN-induced increase in intestinal permeability promotes Toll-like receptor 4-dependent Kupffer cell activation and liver injury, presumably caused by bacterial translocation [35].

Serum fibrosis markers, mainly the APRI score, were evaluated in previous trials with patients receiving long-term PN taking liver biopsy as reference [16,27,36–39]. The majority of these studies could demonstrate a significant correlation between histologic fibrosis stage and serum test, particularly in cirrhotic patients. Van Gossum et al. reported a significant correlation of TE with APRI and FIB-4 score [16], whereas in our study FibroTest turned out to be the only serum fibrosis marker correlated with TE values. As outlined previously, this discrepancy might be due to minor severity of liver injury in our study population.

Cavicchi et al. showed that longer exposure to PN was associated with a higher prevalence of complicated liver disease, with clinical manifestations occurring at a median of 17 mo and histologic features of severe liver disease arising at a median of 27 mo after PN was initiated [40]. The present results did not show an association between duration of PN and fibrosis. Compared with the present study, Cavicchi et al. included patients who had preexisting risk factors for liver disease, which makes it difficult to assess how much of the liver damage was induced by intravenous feeding itself. Moreover, we could not detect any difference of liver stiffness between patients receiving exclusively PN and those who were treated with mixed PN and oral nutrition or EN. However, the number of patients was limited.

To our knowledge, few studies to date have used BIA for the assessment of nutritional status and body composition in patients with SBS [41–43]. However, its reliability in individual patients cannot be assured. Frequency of PN infusions varied between three to seven times per week in our study cohort. Thus, some of our patients had been investigated after a longer interval without PN than others, and therefore the hydration status might have

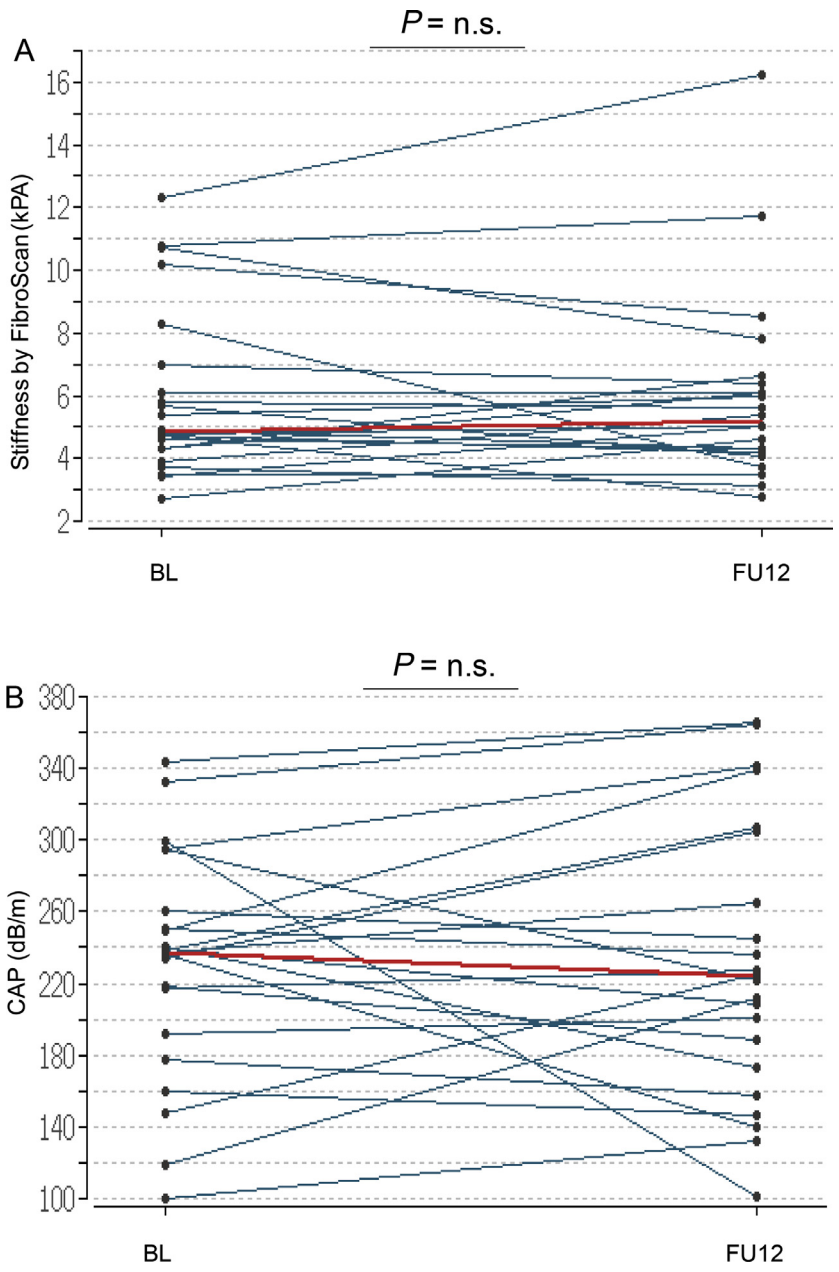

Fig. 1. (**A**) Liver stiffness by FibroScan at BL and after FU12 in 22 patients. (**B**) CAP at and after FU12 in 22 patients. Red line indicates the median. BL, baseline; CAP, controlled attenuated parameter; FU12, follow-up after 12 mo.

differed. This affected the calculation of body composition. Our study did not reveal any significant change of phase angle nor FM during the follow-up period. This was consistent with stability of BMI within study duration.

Table 3
Non-invasive assessment of fibrosis and steatosis by serum markers at baseline and at FU12

Serum markers	Baseline	FU12	*P*-value
APRI score, median (range)	0.3 (0.1–5.2)	0.3 (0.1–2.2)	n.s.
FIB-4 index, median (range)	1.33 (0.6–8.76)	1.31 (0.59–5.22)	n.s.
FibroTest*, median (range)	0.26 (0.03–0.92)	0.36 (0.02–0.89)	n.s.
SteatoTest†, median (range)	0.23 (0.07–0.73)	0.21 (0.04–0.78)	n.s.

FU12, follow-up after 12 mo; n.s., not significant.
*Complete data of FibroTest were available in 13 patients.
†Complete data of Steatotest were available in 12 patients.

Table 4
Correlation between FibroScan and clinical parameters at baseline

Baseline variables*	*r*†	*P*-value‡
FibroTest (F0–F3 vs F4)	0.791	<0.0001
FibroTest (F0–F2 vs F3–F4)	0.478	0.045
PN duration	0.233	0.241
ALT	−0.098	0.626
BMI	0.097	0.632
AP	0.073	0.717
GGT	−0.041	0.838
AST	0.024	0.907
Bilirubin	0.006	0.977

ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; BMI body mass index; GGT, γ-glutamyl transferase; PN, parenteral nutrition.
*Variables are sorted with respect to increasing overall *P*-value.
†Spearman's rank correlation coefficient.
‡*P*-value for comparison of baseline FibroScan with clinical variables at baseline.

Table 5
Correlation between CAP and clinical parameters at baseline

Baseline variables*	*r*	*P*-value†
SteatoTest	0.7‡	0.002
BMI	0.468§	0.016
Triacylglycerides	0.411§	0.042
HDL	−0.396‡	0.05
PN duration	0.153‡	0.457
LDL	−0.072§	0.732

BMI, body mass index; CAP, controlled attenuation parameter; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PN, parenteral nutrition.
*Variables are sorted with respect to increasing overall *P*-values.
†*P*-value for comparison of baseline CAP.
‡Spearman's rank correlation coefficient with clinical variables at baseline.
§Pearson's rank correlation coefficient.

There were some limitations to our study. The present study was conducted at a single center and patients had no liver biopsy taken as reference. Non-invasive methods as FibroScan including CAP and serum markers are not validated yet in large cohorts with patients receiving PN. The low number of patients analyzed in a short follow-up time does not allow us to draw a conclusion on long-term prognosis of liver injury. Nevertheless, the median duration of PN at inclusion was 2.5 y. Because decompensated liver disease was an exclusion criterion, we did not follow up with patients in the advanced stage.

Conclusions

The results of the present study clearly demonstrate that prevalence of advanced liver disease was low without significant dynamic changes of liver fibrosis and steatosis within 12 mo. TE including CAP is a promising method for monitoring the development and progression of liver injury in patients receiving long-term PN. However, further studies with extended observation time are required to assess long-time risk for chronic liver disease.

References

[1] Buchmann AL, Scolapio J, Fryer J. AGA technical review on short bowel syndrome and intestinal transplantation. Gastroenterology 2003;124:1111–34.
[2] Nightingale JM. Management of patients with a short bowel. World J Gastroenterol 2001;7:741–51.
[3] Buchmann AL. Complications of long-term home total parenteral nutrition: their identifications, prevention and treatment. Dig Dis Sci 2001;46:1–18.
[4] Tomar BS. Hepatobiliary abnormalities and parenteral nutrition. Indian J Pediatr 2000;67:695–701.
[5] Kelly D. Intestinal failure associated liver disease: what do we know today? Gastroenterology 2006;130:70–7.
[6] Kubota A, Yonekura T, Hoki M, Oyanagi H, Kawahara H, Yagi M, et al. Total parenteral nutrition-associated intrahepatic cholestasis in infants: 25 years experience. J Pediatr Surgery 2000;25:1049–51.
[7] Colomb V, Dabbas-Tyan M, Taupin P, Talbotec C, Révillon Y, Jan D, et al. Long-term outcome of children receiving home parenteral nutrition: a 20-year single-center experience in 302 patients. J Pediatr Gastroenterol Nutr 2007;44:347–53.
[8] Bueno J, Ohwada S, Kocoshis S, Mazariegos GV, Dvorchik I, Sigurdsson L, et al. Factors impacting the survival of children with intestinal failure referred for intestinal transplantation. J Pediatr Surg 1999;34:27–32.
[9] Freund HR. Abnormalities of liver function and hepatic damage associated with total parenteral nutrition. Nutrition 1991;7:1–6.
[10] Naini BV, Lassman CR. Total parenteral nutrition therapy and liver injury: a histopathologic study with clinical correlation. Human Pathology 2012;43:826–33.
[11] Rockey DC, Caldwell SH, Goodman ZD, Nelson RC, Smith AD. Liver biopsy. Hepatology 2009;49. 1077–44.
[12] Friedrich-Rust M, Ong MF, Martens S, Sarrazin C, Bojunga J, Zeuzem S, et al. Performance of transient elastography for the staging of liver fibrosis: a meta-analysis. Gastroenterology 2008;134:960–74.
[13] Talwalker JA, Kurtz DM, Schoenleber SJ, West CP, Montori VM. Ultrasound-based transient elastography for the detection of hepatic fibrosis: systematic review and meta-analysis. Clin Gastroenterol Hepatol 2007;5:1214–20.
[14] Stebbing J, Farouk L, Panos G, Anderson M, Jiao LR, Mandalia S, et al. A meta-analysis of transient elastography for the detection of hepatic fibrosis. J Clin Gastroenterol 2010;44:214–9.
[15] Sasso M, Beaugrand M, de Ledinghen V, Douvin C, Marcellin P, Poupon R, et al. Controlled attenuation parameter (CAP): a novel VCTE guided ultrasonic attenuation measurement for the evaluation of hepatic steatosis: a preliminary study and validation in a cohort of patients with chronic liver disease from various causes. Ultrasound Med Biol 2010;36:1825–35.
[16] Van Gossum A, Pironi L, Messing B, Moreno C, Colecchia A, D'Errico A, et al. Transient elastography (FibroScan) is not correlated with liver fibrosis, but with cholestasis in patients with long-term home parenteral nutrition. JPEN J Parenter Enteral Nutr 2015;39:719–24.
[17] Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology 2003;8:518–26.
[18] Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/ HCV coinfection. Hepatology 2006;43:1317–25.
[19] Halfon P, Imbert-Bismut F, Messous D, Antoniotti G, Benchetrit D, Cart-Lamy P, et al. A prospective assessment of the inter-laboratory variability of biochemical markers of fibrosis (FibroTest) and activity (ActiTest) in patients with chronic liver disease. Comp Hepatol 2002;1:3.
[20] Poynard T, Ratziu V, Naveau S, Thabut D, Charlotte F, Messous D, et al. The diagnostic value of biomarkers (SteatoTest) for the prediction of liver steatosis. Comp Hepatol 2005;4:10.
[21] Sandrin L, Fourquet B, Hasquenoph JM, Yon S, Fournier C, Mal F, et al. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. Ultrasound Med Biol 2003;29:1705–13.
[22] Mederacke I, Wursthorn K, Kirschner J, Rifai K, Manns MP, Wedemeyer H, et al. Food intake increases liver stiffness in patients with chronic or resolved hepatitis C virus infection. Liver Liver International 2009;29:1500–6.
[23] Castera L, Foucher J, Bernard PH, Carvalho F, Allaix D, Merrouche W, et al. Pitfalls of liver stiffness measurement: a 5-year prospective study of 13,369 examinations. Hepatology 2010;51:828–35.
[24] Castera L, Forns X, Alberti A. Non-invasive evaluation of liver fibrosis using transient elastography. J Hepatol 2008;48:835–47.
[25] Wong VWS, Vergniol J, Wong GLH, Foucher J, Chan HLY, Le Bail B, et al. Diagnosis of fibrosis and cirrhosis using liver stiffness measurement in nonalcoholic fatty liver disease. Hepatology 2010;51:454–62.
[26] Sasso M, Miette V, Sandrin L, Beaugrand M. The controlled attenuation parameter (CAP): a novel tool for the noninvasive evaluation of steatosis using FibroScan. Clin Res Hepatol Gastroenterol 2012;36:13–20.
[27] Salvino R, Ghanta R, Seidner DL, Mascha E, Xu Y, Steiger E. Liver failure is uncommon in adults receiving long-term parenteral nutrition. JPEN J Parenter Enteral Nutr 2006;30:202–8.
[28] Hukkinen M, Kivisaari R, Lohi J, Heikkilä P, Mutanen A, Merras-Salmio L, et al. Transient elastography and aspartate aminotransferase to platelet ratio predict liver injury in paediatric intestinal failure. Liver International 2016;36:361–9.
[29] Millonig G, Reimann FM, Friedrich S, Fonouni H, Mehrabi A, Büchler MW, et al. Extrahepatic cholestasis increases liver stiffness (FibroScan) irrespective of fibrosis. Hepatology 2008;48:1718–23.
[30] Huijbers A, Wanten G, Dekker HM, van der Graaf M. Noninvasive quantitative assessment of hepatic steatosis by proton magnetic resonance spectroscopy among adult patients receiving home parenteral nutrition. JPEN J Parenter Enteral Nutr 2018;42:778–85.
[31] Mutanen A, Lohi J, Heikkilä P, Koivusalo AI, Rintala RJ, Pakarinen MP. Persistent abnormal liver fibrosis after weaning off parenteral nutrition in pediatric intestinal failure. Hepatology 2013;58:729–38.
[32] Cazals-Hatem D, Billiauws L, Rautou PE, Bondjemah V, Poté N, Corcos O, et al. Ultra-short bowel is an independent risk factor for liver fibrosis in adults with home parenteral nutrition. Liver Int 2018;38:174–82.
[33] Luman W, Shaffer JL. Prevalence, outcome and associated factors of deranged liver function tests in patients on home parenteral nutrition. Clin Nutr 2002;21:337–43.
[34] Lapthorne S, Pereira-Fantini PM, Fouhy F, Wilson G, Thomas SL, Dellios NL, et al. Gut microbial diversity is reduced and is associated with colonic inflammation in a piglet model of short bowel syndrome. Gut Microbes 2013;4:212–21.
[35] El Kasmi KC, Anderson AL, Devereaux MW, Fillon SA, Harris JK, Lovell MA, et al. Toll-like receptor 4-dependent Kupffer cell activation and liver injury in a novel mouse model of parenteral nutrition and intestinal failure. Hepatology 2012;55:1518–28.
[36] Diaz JJ, Gura KM, Roda J, Perez-Atayde AR, Duggan C, Jaksic T, et al. Aspartate aminotransferase to platelet ratio index correlates with hepatic cirrhosis, but not with fibrosis in pediatric patients with intestinal failure. J Pediatr Gastroenterol Nutr 2013;57:367–71.
[37] Mangus RS, O`Connor MG, Tector AJ, Lim JD, Vianna RM. Use of the aspartate aminotransferase to platelet ratio index to follow liver fibrosis progression in infants with short gut. J Pediatr Surg 2010;45:1266–73.

[38] O'Connor M, Mangus RS, Tector AJ, Fridell JA, Vianna RM. Utility of liver function tests including aminotransferase-to-platelet ratio index in monitoring liver dysfunction in short-gut infants of varying ages and intestinal lengths. J Pediatr Surg 2011;46:1057–63.
[39] Rumbo C, Martinez MI, Cabanne A, Trentadue J, Fernández A, Gondolesi G. Utility of aminotransferase/ platelet ratio index to predict liver fibrosis in intestinal failure-associated liver disease in pediatric patients. JPEN J Parenter Enteral Nutr 2017;41:884–9.
[40] Cavicchi M, Beau P, Crenn P, Degott C, Messing B. Prevalence of liver disease and contributing factors in patients receiving home parenteral nutrition for permanent intestinal failure. Ann Intern Med 2000;132:525–32.
[41] Bizari L, Da Silva Santos AF, Marchini JS, Marques Miguel Suen V. Anthropometric, food intake differences and applicability of low-cost instruments for the measurement of body composition in two distinct groups of individuals with short bowel syndrome. Nutr Hosp 2014;30:205–12.
[42] Mehta NM, Raphael B, Guteirrez I, Quinn N, Mitchell PD, Litman HJ, et al. Comparison of body composition assessment methods in pediatric intestinal failure. J Pediatr Gastroenterol Nutr 2014;59:99–105.
[43] Fassini PG, Nicoletti CF, Pfrimer K, Nonino CB, Marchini JS, Ferriolli E. Bioelectrical impedance vector analysis as a useful predictor of nutritional status in patients with short bowel syndrome. Clin Nutr 2017: 1117–21.