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ORIGINAL ARTICLE

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FibroSURE and elastography poorly predict the severity of liver fibrosis in Fontan-associated liver disease

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Abstract

Objective: As the population of patients with Fontan circulation surviving into adulthood increases, hepatic cirrhosis has grown to be a significant cause of morbidity and mortality. Early detection of advanced hepatic fibrosis is imperative for proper intervention and consideration for heart or combined heart/liver transplantation. Noninvasive biomarkers and elastography have been evaluated for their diagnostic utility with variable results in the Fontan population.

Design: The cohort included 14 patients age 26.4 SD 7.5 who underwent Fontan surgery. All patients were evaluated with FibroSURE, shear wave elastography (SWE), hepatic duplex sonography, and liver biopsy. Liver fibrosis on biopsy was evaluated according to the congestive hepatic fibrosis system.

Results: In our cohort, 100% of patients had fibrosis with 36% demonstrating advanced fibrosis. FibroSURE agreed with liver biopsy in only 5 out of 14 cases (36%): underestimating in 7 and overestimating in 2 individuals. SWE agreed with liver biopsy in 0% of cases: overestimating in 10 and underestimating in 4 cases. None of the duplex sonography indices predicted the presence or severity of liver fibrosis.

Conclusion: This study demonstrates that children who have undergone a Fontan procedure universally develop some hepatic fibrosis and a significant number have advanced fibrosis by adulthood. The FibroSURE blood test, SWE, and hepatic duplex sonography were unable to accurately predict the presence or severity of hepatic fibrosis when compared with liver biopsy. Further studies are needed to investigate novel noninvasive methods and/or biomarkers that can adequately detect advanced hepatic fibrosis before the development of cirrhosis and hepatic decompensation.

KEYWORDS

adult Fontan, elastography, FibroSure, liver fibrosis

1 | INTRODUCTION

Due to advances in medical care and surgical techniques, the population of adults with congenital heart disease (CHD) has been growing exponentially since the 1950s.[1] Survivorship to adulthood is estimated to be greater than 90% of children born with congenital heart disease; with over 1 million adults living in the United States with CHD.[2–4] One of the more severe forms of CHD is that of functional single ventricle, including hypoplastic left or right heart syndrome, tricuspid, or pulmonary atresia. Without palliative surgery, the life expectancy of neonates born with single ventricle physiology is extremely poor with mortality reaching more than 90% within the first year of life.[5] The Fontan procedure, first performed in 1968 as a palliative surgery for tricuspid atresia, has been widely implemented

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as a staged palliative surgery for single ventricle patients. Although there has been a significant decrease in mortality in the first 25 years post-Fontan,[6] it has been associated with significant cardiac and noncardiac complications resulting in delayed morbidity and mortality in young adults.

The Fontan procedure allows for passive pulmonary blood flow by creating a direct connection with the inferior and superior vena cava to the lungs.[5] Over time, there is an increase in both pulmonary vascular resistance and ventricular end-diastolic pressure. The pathophysiology of hepatic fibrosis likely shares similarities with typical cardiac hepatopathy with downstream effects causing hepatic venous and sinusoidal congestion resulting in hepatic fibrosis and possible cirrhosis.[7–9] Hepatic dysfunction has been well documented among adults with Fontan physiology[6,9–11] with outcomes worsening as a patient is farther out from the surgical intervention.[8,11–14]

Currently, liver biopsy is the only validated method for evaluating liver damage in Fontan patients, or Fontan-associated liver disease (FALD). However, this is an invasive procedure that is limited by the risk of procedural complications, observer variability, and sampling error.[15,16] Institutions throughout the world continue to strive to predict hepatic fibrosis through noninvasive modalities with conflicting results.[17–23]

Serologic biomarkers, such as FibroSURE (LabCorp, Burlington, North Carolina), and transient elastography (TE), have been validated in the use of screening for other causes of chronic liver disease, such as chronic hepatitis C.[16] To date, there has been no study comparing serum FibroSURE, elastography, and hepatic duplex sonography to the "gold standard," liver biopsy. Therefore, we sought out to determine if these noninvasive methods could reliably predict the presence or severity of hepatic fibrosis in FALD.

2 | METHODS

2.1 | Patients

Fourteen out of 15 (93%) consecutive individuals' with single ventricle physiology followed in the Adult Congenital Heart Disease Clinic of Greenville Health System (GHS) agreed to participate. These individuals had a blood sample sent for routine labs and FibroSURE analysis, ultrasound imaging for shear wave elastography (SWE) and duplex sonography as well as a liver biopsy. The study protocol was approved by the GHS institutional review board in accordance with the ethical guidelines of the 1975 Declaration of Helsinki. IRB approval was obtained prior to all subjects consenting to participate in our study.

2.2 | FibroSURE

FibroSURE (LabCorp) serology includes alanine aminotransaminase (ALT), α2-macroglobulin, apolipoprotein A1, total bilirubin, γ-glutamyl transferase (GGT), haptoglobin, patient's age, and gender. A range of values predict the histologic stages of fibrosis, F0 none < 0.21; F1 mild > 0.21-0.31; F2 moderate > 0.31-0.58; F3 advanced fibrosis > 0.58-0.72, and F4 cirrhosis > 0.72.

2.3 | Shear wave elastography

Two-dimensional (2D) SWE was performed using a General Electric LOGIQ E9 scanner (GE, Milwaukee, Wisconsin). Patients were asked to lie supine, with their right hand in the maximal abduction position. Patients were asked to hold their breath for 5 s; acoustic shear waves were generated, and 10 acceptable values were obtained in the right hepatic lobe per patient with IQR (interquartile ratio)/median value less than 0.3 for all patients. The GE LOGIQ E9 system uses the R5 software version and the C1-6-D probe. The results were generated by measuring average liver stiffness expressed in terms of the Young modulus (a mechanical property of linear elastic solid material that defines the relation between stress and strain in a material). Mean and median elasticity was reported using kilopascals (kPa). The GE-LOGIQ E9 kPa cutoff values for predicting liver fibrosis are F0: <5.48, F1: 5.49–8.28, F2: 8.29–9.39, F3: 9.40–11.8, and F4: >11.9.[24]

2.4 | Duplex ultrasonography

Duplex ultrasound used grayscale imaging of the liver with hepatic Doppler examinations in all patients. Examination of the portal vein (PV) was performed at the hepatic hilum. Portal vein diameter (mm), portal vein cross-sectional diameter (mm), portal vein peak velocity (cm/sec), and portal vein pulsatility index were measured in each patient. Pulsatility index of the PV = peak systolic velocity-end diastolic velocity/timed average velocity which has been suggested to better correlate with right heart failure than the congestive index.[25] The congestive index (CI) of the portal vein was determined by the ratio of the cross-sectional area (cm^2) and blood flow (cm/s).[26] The CI is suggested to correlate with portal venous hypertension. The hepatic artery was interrogated at the hepatic hilum and hepatic artery peak systolic velocity (cm/s) was recorded. Doppler angle for hepatic artery and portal vein velocity measurements was set to less than 60°. Of note, the splenic vein was interrogated to determine the patency as part of the ultrasound protocol but the splenic size was not measured. Two well-trained and experienced sonographers performed elastography and duplex sonography blinded to clinical and liver biopsy results. A single radiologist blinded to clinical and liver biopsy results interpreted all sonographic exams.

2.5 | Liver biopsy

Ultrasound-guided percutaneous core liver biopsies were performed using an 18-gauge needle by a single operator. Biopsies were completed within two months of FibroSURE and shear wave elastography. We used the congestive hepatic fibrosis (CHF) score to assess the presence and severity of portal and sinusoidal liver fibrosis as well as sinusoidal dilatation.[27] We compared the CHF score to the simpler METAVIR scoring system. Liver biopsies

were interpreted by a single hepatopathologist blinded to all data. Finally, we analyzed our results comparing all noninvasive modalities into either none/mild fibrosis (F0-F2) or advanced fibrosis (F3-F4).

2.6 | Statistical analysis

Continuous variables are reported as the mean ± standard deviation or median (interquartile range) and discrete variables are reported as N (%). Descriptive statistics are provided along a concordance analysis of the FibroSURE versus CHF score, and Elastography versus CHF score, which were tested using Cohen's kappa. Additionally, differences in various continuous measurements were stratified by advanced CHF (Stages 3 and 4) versus nonadvanced CHF (Stages 2-0) and were tested using Wilcoxon rank-sum tests. *P* values < .05 were considered indicative of statistical significance. All data analyses were completed using R statistical software (R Version 3.0.2; R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

Demographics of our single ventricle physiologic cohort (Table 1) consisted of 5 females/9 males with a mean age of 26.4 years (range 19–43 years); mean years from Fontan surgery to liver biopsy was 24.7 SD 6.2; New York Heart Association (NYHA) class I in 12/14, two NyHA class II. Liver transaminases ALT and aspartate aminotransferase (AST) were normal in 12/14 subjects (2 with minimal ALT elevation 52 IU/ml and 45 IU/ml). Echocardiograms were normal in seven, low normal five, and mildly depressed in two cases. Seven subjects had a history of arrhythmia. Doppler US values and median time from FibroSURE, SWE and US to liver biopsy are also noted in Table 1. Median time for FibroSURE and SWE testing to obtaining the liver biopsy was less than two months.

All percutaneous liver biopsy samples were considered adequate (length 25 SD 8 mm, portal tracts 14 SD 3) and obtained without complications. Using the CHF score all 14 subjects had some degree of liver fibrosis, 2 (F1), 7 (F2), and 5 (F3-4). The CHF score demonstrated excellent correlation with the METAVIR fibrosis scale (r = 0.938). There was no correlation between the degree of sinusoidal dilatation and sinusoidal fibrosis (r = −0.269); however, a moderate correlation was noted between sinusoidal dilatation and overall CHF score (r = 0.679).

FibroSURE staging only agreed with CHF scores in five cases (35.7%), while it underestimated in seven (n = 2 by two stages, n = 1 by three stages) and overestimated in two cases (kappa = 0.016) (Table 2). SWE never agreed with CHF staging (0/14 cases) with underestimation in 4 cases and overestimation in 10 cases (kappa = −0.21) (Table 3).

SWE did not identify our single patient with cirrhosis, estimating only F1 mild fibrosis (Table 3). In the 10 subjects that elastography overestimated liver fibrosis, the mean kPa values were significantly greater than the underestimated group (13.58 SD 1.82 vs 7.69 SD 1.30, *P* = 0.0001). However, comparing subjects with mild versus moderate sinusoidal dilatation, no elastography differences were noted (12.89 SD 3.2 versus 10.91 SD 3.1, *P* = 0.26).

All duplex measurements (hepatic artery peak systolic velocity, portal vein diameter, portal vein cross sectional diameter, portal vein peak systolic velocity, portal vein pulsatility, and congestive index) demonstrated poor correlations with the presence of liver fibrosis.

TABLE 1 Demographics

N	14
Age, mean SD (years)	26.4 SD 7.5
Years since surgery, mean SD	24.7 SD 6.2
ALT, mean SD (units/L)	28.0 SD 10.9
AST, mean SD (units/L)	25.9 SD 6.9
Echo, N (%)	
Normal	7 (50%)
Low-normal	5 (35.71%)
Mildly decreasing	2 (14.29%)
NYHA class	
I	12 (85.71%)
II	2 (14.29%)
Oxygen saturation, mean SD	94.6 SD 2.8
Arrhythmia history, N (%)	7 (50%)
Hepatic artery velocity (cm/sec), mean SD	82.4 SD 21.6
Portal vein, mean SD	
Main diameter (mm)	8.8 SD 1.8
Velocity (cm/sec)	25.4 SD 4.3
Cross-section diameter (cm^2)	0.77 SD 0.26
Pulsatility index	0.53 SD 0.23
Congestive index	0.05 SD 0.33
Time, median (IQR)	
US and SWE to liver biopsy (months)	1.97 (1.41, 3.78)
FibroSURE to liver biopsy (months)	1.15 (0.82, 2.12)
Surgery to liver biopsy (years)	22 (21, 31)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; echo, echocardiogram; IQR, interquartile range; N, number; NYHA, New York Heart Association; SD, standard deviation; SWE, shear wave elastography; US, ultrasonography.

TABLE 2 Correlation of CHF score versus FibroSURE

	CHF Score			
FibroSURE	1	2	3	4
0	0	1	1	0
1	1	1	0	0
2	1	4	3	1
4	0	1	0	0

Kappa 0.0071 (−0.21, 0.23)
Weighted K 0.043 (−0.32, 0.40)

TABLE 3 Correlation of CHF score versus elastography

	CHF score			
Elastography	1	2	3	4
1	0	1	0	1
2	0	0	2	0
3	0	2	0	0
4	2	4	2	0

Kappa −0.21 (−0.35, −0.07)
Weighted Kappa −0.36 (−0.79, 0.08)

TABLE 4 Correlated and associations, tested against advanced CHF score

	Advanced CHF	Advanced CHF	
	Yes	No	*P* values
N	5	9	
Composite FibroSURE	0.5 (0.47, 0.50)	0.44 (0.29, 0.56)	1
Elastography, kPA	8.8 (8.7, 14.9)	13.4 (11.3, 14.3)	0.699
Hepatic artery, (cm/s)	72.9 (64.2, 92.0)	87.1 (69.0, 92.0)	0.739
PV, main diameter, (mm)	7.1 (6.8, 8.0)	10.0 (8.2, 10.1)	0.16
PV, velocity (cm/s)	25.0 (24.6, 25.2)	22.5 (22.0, 25.1)	0.256
PV, pulsatility index	0.46 (0.41, 0.74)	0.53 (0.38, 0.75)	1
Congestive index	0.02 (0.02, 0.03)	0.04 (0.03, 0.05)	0.188
PV, cross-diameter (cm^2)	0.67 (0.53, 0.68)	0.8 (0.61, 1.03)	0.548
Age (years)	21 (21, 29)	24 (21, 33)	0.585
Years since surgery	22.0 (21.0, 29.0)	22.0 (20.0, 32.0)	1
O_2 saturation (%)	94 (93, 94)	96 (95, 97)	0.249

All values medians (IQR = 25th, 75th percentiles) wilcoxon rank-sum Tests.
Abbreviation: kPA, kilopascals; PV, portal vein.

We evaluated each of the noninvasive techniques between mild/moderate fibrosis (F0-2) to advanced fibrosis (F3-4) since advanced fibrosis leads to liver morbidity and mortality. All noninvasive measurements, FibroSURE, SWE, and duplex measurements, were statistically insignificant (Table 4).

4 | DISCUSSION

In this study, we explored serologic and radiologic studies used for evaluation of hepatic fibrosis in correlation with liver biopsy in adult patients with Fontan physiology. Our goal was to determine the diagnostic accuracy of these noninvasive studies in predicting the stages of liver fibrosis. To our knowledge, this is the first study to have compared all three modalities of FibroSURE, SWE, and duplex US to liver biopsy in this population. Unfortunately, our results were unable to demonstrate, either alone or in combination, a useful diagnostic prediction between any of these noninvasive modalities with the severity of hepatic fibrosis when using the liver biopsy as the gold standard.

4.1 | Role of liver biopsy

Presently, a liver biopsy remains the "gold standard" to assess liver fibrosis. However, there have been numerous studies demonstrating the heterogeneity that can be encountered in correctly staging liver fibrosis. In a study conducted by Abdi et al, three consecutive liver biopsy samples were obtained from 118 patients' postmortem immediately prior to autopsy. Of the 20 subjects with cirrhosis, they detected cirrhosis in only 80% on first biopsy.[28] Additionally, both Bedossa et al[15] and Rousselet et al[29] found discrepancies in accuracy and reproducibility of scoring liver fibrosis based on the size of the histologic specimen, and the experience of the pathologist respectively. Therefore, a minimum of 10–12 portal tracts and a 2-cm length of tissue are considered necessary for an adequate interpretation. The mean size and number of portal tracts in our cohort met these requirements and were deemed acceptable for interpretation.

4.1.1 | CHF scores

Various scoring systems have been developed for staging liver fibrosis. This includes the METAVIR fibrosis scale, which was originally developed, evaluated and validated for use in chronic hepatitis C,[30] though it has never been validated in assessing congestive hepatopathy.

Dai et al developed the CHF scoring system in patients with congestive hepatopathy.[27] The CHF method is a useful indicator of the clinical severity of liver disease, correlating well with echocardiographic and hemodynamic parameters that reflect the severity of heart disease.

In our study, we used the CHF method as our standard and compared it to the METAVIR fibrosis scale demonstrating an excellent correlation with regards to stages of fibrosis (r = 0.94). The advantage of the CHF scoring system is that it includes degrees of sinusoidal fibrosis as well as sinusoidal dilation whereas METAVIR focus is on portal-based fibrosis. Of note, there was a good correlation (r = 0.68) between the sinusoidal dilatation and the overall CHF score however there was a poor correlation between sinusoidal dilation and sinusoidal fibrosis.

4.2 | Noninvasive techniques for detecting fibrosis in the Fontan patient

FibroSURE and transient elastography (TE) alone or in combination are well-known and widely validated noninvasive techniques to diagnose hepatic fibrosis or cirrhosis in viral, alcohol, and fatty liver disease.[16,31–33] Previous studies in the adult Fontan population have demonstrated inconsistent results.

4.2.1 | FibroSURE

In our cohort, FibroSURE correctly staged only 5/14 (35.7%) subjects, in the remaining 9 individuals 2/9 were overestimated, but more importantly 7/9 (78%) underestimated the extent of fibrosis. Additionally it failed to detect our single subject with cirrhosis underestimating the extent of fibrosis by two stages. This underestimation of liver fibrosis emphasizes the hazard of using FibroSURE as the sole diagnostic method for screening the Fontan patient for FALD.

Similar to our results, Wu et al recently investigated 27 adult subjects with FibroSURE and hyaluronic acid and correlated these results with liver biopsy.[19] They demonstrated that neither test correlated with the degree of histologic hepatic fibrosis and did not predict cirrhosis. Ofei et al also noted in 10 patients who had FibroSURE testing and a liver biopsy, FibroSURE overestimated in 3 and underestimated in 2 subjects.[34]

Taken together, it is not surprising that the FibroSURE serology is a poor predictor for hepatic fibrosis since several markers used in this model include ALT, GGT and total bilirubin levels that are elevated in conditions associated with hepatocellular injury such as viral and cholestatic hepatitis. However, FALD subjects usually have normal serologic liver tests and hepatic histology is primarily a non-inflammatory histopathologic entity.

4.2.2 | Shear wave elastography

It is worth noting that, in our study, we used the SWE imaging modality as opposed to TE to measure liver stiffness. These methods are similar, yet distinct, with real-time SWE being a two-dimensional transient elastography.[35] SWE has been noted to have an advantage over TE with higher accuracy for mild and intermediate stages of liver fibrosis in hepatitis C.[36] Furthermore, Poynard et al[35] found that SWE had significantly higher applicability than TE when diagnosing liver fibrosis in the more progressive stages of fibrosis. Disadvantages to SWE are lack of diagnostic threshold standardization across manufacturers in addition to the imaging being operator dependent.[37]

Fidai et al[38] used both TE with FibroSURE to assess for signs of FALD in a group of children and adults. They noted a significant correlation between the degree of liver stiffness and time post-Fontan. They concluded that TE might have a role in following individuals' early post-Fontan though they never validated the liver stiffness values with a liver biopsy.

Kutty et al[20] and Wu et al[22] both evaluated the Fontan patient comparing elastography to liver biopsy. Kutty et al studied 10 Fontan patients and SWE overestimated liver fibrosis in 4 subjects (40%) suggesting cirrhosis in those with only minimal fibrosis. Wu et al investigated 10 post-Fontan subjects and TE overestimated fibrosis by at least one stage in 70% and two stages in 50% of subjects.

Consistent with these studies, our results demonstrated that SWE did not agree with the CHF score in any of the 14 subjects. It overestimated the degree of fibrosis in 71% of the cohort. Of note, it also underestimated our single subject with cirrhosis by three stages of fibrosis.

The majority of the above studies, including ours, evaluating elastography mostly overestimate the degree of liver fibrosis. This may be explained by congestive hepatopathy which can cause liver stiffness due to a decrease in elasticity from excessive blood within the sinusoids. Elastography evaluating liver stiffness, per se, cannot differentiate blood from fibrosis. Our results did show a good correlation between the degree of sinusoidal dilation and the overall severity of liver fibrosis. However no significant differences were identified between mild versus moderate degrees of sinusoidal dilation and mean liver stiffness values to explain the overestimation of elastography. Magnetic resonance elastography correlates well with liver fibrosis and portal hypertension in viral hepatitis and fatty liver disease.[39] Serai et al have demonstrated a moderate correlation in MRE and the year's post-Fontan[40] warranting future investigations to determine if MRE more accurately predicts the stages of liver fibrosis.

4.2.3 | Duplex ultrasonography

While Doppler US is commonly utilized in patients with normal cardiac anatomy in assessment of portal hypertension, the utility of this technique in Fontan circulation is unclear.[11] Kiesewetter et al described a significant correlation between hepatic vein pressures and the severity of cirrhotic changes identified on liver histology in adult Fontans.[8] Kutty et al[20] similarly found a positive correlation between liver stiffness and main portal vein (MPV) diameter ($P = 0.01$) in addition to patient age and duration of the palliation.

We investigated multiple measurements of the hepatic and portal system including hepatic artery flow; PV diameter, PV velocity as well as the PV pulsatility index and congestive index and were unable to identify any of these measurements to be associated with the severity of liver fibrosis.

4.3 | Significance of early recognition of FALD

The recognition of advanced hepatic fibrosis may be especially important if early cardiac transplantation is an option, thereby decreasing future liver morbidity and mortality from cirrhosis, clinical decompensation such as ascites, variceal hemorrhage, hepatic encephalopathy, and hepatocellular carcinoma.

The presence of liver cirrhosis is considered to be a relative or even an absolute contraindication to heart transplantation, with recommendations that patients with abnormal liver function tests not be listed for heart transplantation until cirrhosis has been excluded.[41] Conversely, Hsu et al in an overview of heart transplantation in patients with cirrhosis, suggests that while mortality and morbidity in the Fontan population may be increased in patients undergoing cardiac transplantation, it is still recommended to consider transplantation in those with cirrhosis due

to the likelihood of regression of liver fibrosis with treatment.[42] Additionally, Crespo-Leiro et al described a case of a 52-year-old with a history of idiopathic dilated cardiomyopathy, 10 years following orthotopic heart transplant, had complete reversal of her cardiac cirrhosis.[43]

4.4 | Study limitations

Our study included a small cohort of 14 adult patients, limiting the generalization of our results in post-Fontan adults. However, our cohort in addition to the three studies above that have compared either FibroSURE or Elastography to a liver biopsy now include a total of 61 subjects all demonstrating the limitations in both of these modalities in predicting the severity of liver fibrosis. Importantly, a liver biopsy continues to be considered the "gold standard," however, as mentioned above there is considerable heterogeneity and sampling error therefore mild stages of liver fibrosis on biopsy may underestimate the overall architecture.

5 | CONCLUSION

Current noninvasive tests for liver fibrosis are inadequate in adults with SVP post Fontan. Screening for early recognition of liver fibrosis with a liver biopsy may be warranted but the initial timing and serial surveillance is undefined. Further research into the mechanism of FALD is necessary to identify novel biomarkers that will accurately detect the severity of liver fibrosis and to develop innovative therapeutic medications.

CONFLICT OF INTEREST

The authors report no relationships that could be construed as a conflict of interest.

AUTHOR CONTRIBUTIONS

All authors read and approved the final version of the manuscript.

Study concept, design, and planning: Abrams, Patel.

Data collection: Patel, Horton, Devane, Ewing, Abrams,.

Interpretation of data: Schachter, Patel, Horton, Devane, Ewing, Abrams.

Carried out initial literature search: Abrams, Schachter.

Initial drafting of article: Schachter.

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