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ORIGINAL ARTICLE

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A composite noninvasive index correlates with liver fibrosis scores in post-Fontan patients: Preliminary findings

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Abstract

Objective: We hypothesized that clinic-based, hepatic-ultrasound, elastography measurements, either alone or in combination with other noninvasive variables, might correlate with liver-biopsy fibrosis scores in patients post-Fontan.

Methods: Between March 2012 and February 2017, we identified patients post-Fontan that underwent elective cardiac catheterization and simultaneous transvenous hepatic biopsy. From this group, we selected patients that met inclusion criteria for liver-ultrasound, shear-wave elastography. Utilizing the results of elastography, laboratory testing, and time post-Fontan, we constructed a composite Fontan hepatic index as a sum of elastography measurements in kilopascals, model for end-stage liver disease excluding INR scores, and the square root of the number of years post-Fontan. Further, we analyzed correlations between Fontan hepatic index values and fibrosis scores from hepatic biopsy.

Results: We identified a total of 79 post-Fontan patients that underwent cardiac catheterization and liver biopsy. Of the 79 patients, 53 met inclusion criteria, and 32 consented to undergo hepatic-ultrasound elastography. Of the 32 that underwent elastography, data from 30 patients was used for analysis. We found no statistically significant differences in demographics, laboratory values, or cardiac catheterization data between the 30 included patients and the 21 that did not participate. Utilizing data from the 30 included patients, we found a strong, highly statistically significant correlation between the Fontan hepatic index values and total fibrosis scores ($R = 0.8$, $P < .00001$). However, the cohort size prevented reliable discriminating cut-off values for the range of total fibrosis scores.

Conclusions: In a small cohort of patients post-Fontan, preliminary findings suggest that the composite Fontan hepatic index might be a clinically useful, noninvasive method of serially monitoring for hepatic fibrosis. Further studies, with large patient cohorts, are necessary to validate our findings and develop clinically useful discriminatory cutoff values.

KEYWORDS
Fontan, hepatic fibrosis, shear-wave elastography

1 | INTRODUCTION

Fontan palliation results in chronic, hepatic systemic-venous outflow obstruction, often leading to liver sinusoidal congestion, portal venous hypertension, and liver parenchymal fibrosis.[1–6] Notwithstanding its limitations, secondary to sampling and intraobserver and interobserver variations, liver biopsy is the accepted gold standard for determining the degree of hepatic fibrosis, regardless the etiology[6]; nevertheless, a noninvasive method that correlates with the degree of liver fibrosis would be a more practical clinical approach. Previous, large patient cohort studies report correlations between liver pathology and noninvasive methods, including composite models comprised of multiple patient variables, in those with infectious hepatitis, nonalcoholic fatty liver disease, and alcoholic liver disease.[7–15] However, there are few reports comparing liver biopsy findings with noninvasive approaches in patients with Fontan associated liver disease (FALD); thus, there are no current, useful, clinic-based, noninvasive methods that strongly correlate one with the other.[4,5,16–21] This study reports our experience comparing post-Fontan hepatic biopsy findings with a composite, noninvasive index derived from liver-ultrasound, shear-wave elastography (SWE) measurements, model for end-stage liver disease excluding INR (MELD-XI) scores, and time post-Fontan.

2 | METHODS

The local Institutional Review Board approved this study. We accessed data for this observational, nonrandomized report by inquiring our research database (Epi-InfoTM), a separate Fontan database, and electronic health records. The Children's Heart Center is the sole provider of congenital heart care in Nevada; thus, our databases and EHR contain information on all patients with Fontan procedures seen Southern Nevada. For the searchable parts of our EHR, we used Perspective Software by Lexmark International, Inc. Lexington, Kentucky. Following inquiry of our research database and EHR, we reviewed patient records and collated data for analysis. For statistical analysis, we used SPSS version 13.0 (SPSS Inc., Chicago, Illinois). We used nonparametric testing, and we set a P value of $< .05$ as significant.

We identified patients post-Fontan that underwent transvenous hepatic biopsy between March 2012 and February 2017. From this group, we identified patients eligible for this study. Patients deemed ineligible included those that lived > 50 miles from the testing center, had moved out of state, had developmental delay or psychological issues preventing cooperation with the hepatic elastography testing protocol. To reduce the effects of confounding variables we eliminated patients that had moderate to severe ventricular dysfunction or had moderate to severe atrioventricular valve regurgitation. Further, post liver elastography, we excluded data from patients that had a BMI above the 97th percentile or ≥ 30 kg/m^2 (to avoid the potential additional effect of steatosis[7]) or had acute decompensated ventricular dysfunction, leading to an acute increase in central venous pressure, which may lead to an acute increase in hepatic stiffness unrelated to a change in underlying hepatic fibrosis.

Patients were contacted, scheduled, and consented for hepatic SWE that was undertaken with a Philips EPIQ machine equipped with ElastPQ swear wave technology (Philips Healthcare, Bothell, Washington). Studies were performed at no charge as part of the study protocol. The ElastPQ shear wave method was previously validated.[22] Liver elastography studies were performed by one of three RDMS certified ultrasonographers trained to perform SWE on the Philips EPIQ-ElastPQ system. Ultrasonographers were blinded to patients' hepatic biopsy results. For practical reason due to scheduling, time of day, family travel time, and technician availability, patients were not fasting before elastography.

Ultrasonographers used the C5-1 transducer and placed patients in the supine position with the right side slightly elevated by a pillow underneath with the right arm raised to increase the intercostal space. Intercostal rather than subcostal scanning was used. The best window for the right upper lobe of the liver (segment 7 or 8) was imaged. Rib shadows were avoided by rotating the probe. Technicians obtained a sagittal view of the liver and placed the region of interest (ROI) box in the superior portion of the liver at a depth of about 2 cm. Technicians ensured that the ROI box was in the liver parenchyma and avoided vessels. Patients were asked to cease breathing between normal inhaling and exhaling, avoiding deep inhalation followed by breath holding. The process was repeated, and 15 measurements were obtained and averaged. Calculated values included an average, standard deviation, median, and interquartile range (IQR)/median ratios for each patient. Elastography values with IQR/median ratios of ≤ 0.3 were included.[23] No additional abdominal organ ultrasound imaging or Doppler evaluation was undertaken beyond liver elastography measurements.

During routine Fontan follow-up, we obtained electrocardiograms and echocardiograms for subjective determination of ventricular function and atrioventricular valvar regurgitation. At the time of elective cardiac catheterization and transvenous hepatic biopsy, we obtained complete blood counts with platelet quantification, alanine transaminase (ALT), aspartate transaminase (AST), blood urea nitrogen (BUN), creatinine, and total proteins and albumin. We did not routinely obtain alpha-2-macroglobulin, haptoglobin, apolipoprotein A1, or gamma-glutamyl transferase values, as these variables have been used in hepatic-fibrosis prediction models validated for hepatitis C but not for FALD.[24] We did not perform routine protime values unless patients were on warfarin. We did not obtain routine hepatitis serological testing. We defined protein-losing enteropathy as a serum albumin < 3.5 g/dL, a fecal alpha-1-antitrypsin > 55 mg/dL, or both.[25] We calculated MELD-XI scores from the following equation: MELD-XI $= 5.11$xln(total serum bilirubin mg/dL) $+ 11.76$xln(serum creatinine mg/dL) $+ 9.44$. Serum creatinine and total bilirubin values less than 1.0 mg/dL were rounded to 1.[26] Using average hepatic elastography measurements (E), MELD-XI scores (M) calculated from laboratory values obtained at the time of cardiac catheterization, and the square root of number of years (y) post-Fontan at the time of elastography, we calculated a Fontan hepatic index (FHI): FHI$=(E + M+\sqrt{}y)$.

Congenital cardiologists performed cardiac catheterizations under general anesthesia, and before completion of cardiac catheterization, interventional radiologists performed transvenous-hepatic biopsies using the transjugular route and a 20-gauge biopsy system in patients $\geq$ seven years of age. Liver biopsy specimens were stained with hematoxylin and eosin, trichrome, and reticulin. Two pathologists, with specialty training in gastrointestinal and liver pathology, reviewed each specimen

TABLE 1 Demographic and clinical information

Eligible n = 51	Participants n = 30	Nonparticipants n = 21	*P* value
Male %	63	57	0.38
Current age, years median (range)	20 (8–50)	19 (8–34)	0.59
Oxygen saturation, % median (range)	92 (81–97)	93 (84–97)	0.54
Fontan duration*, years median (range)	15 (1–29)	15 (2–24)	0.62
PLE n (%)	3 (10)	2 (10)	0.78

Abbreviation: PLE, protein losing enteropathy.

independently. The pathologists were blinded to patient characteristics. Semiquantitative analysis was performed for portal fibrosis using the modified Scheuer staging system (0–4) and a previously employed staging system for sinusoidal fibrosis (0–4).[2] If the two pathologists scored a specimen feature differently, then they conferred to arrive at a final score. For each patient, we added the portal fibrosis score to the sinusoidal fibrosis score for a total-fibrosis score (TFS) (0–8).[3]

3 | RESULTS

Between March of 2012 and February of 2017, we identified 79 patients post-Fontan that underwent 86 hepatic biopsies: seven patients each had two catheterization-biopsy procedures, and we used the most current biopsy results for analysis. No liver biopsy specimen demonstrated significant inflammatory changes. Of the 79, only 4 (5%) had either moderate to severe ventricular dysfunction or moderate to severe atrioventricular valve regurgitation. Of the 79 patients; eight lived > 50 miles from the Las Vegas congenital heart testing center; seven had moved out of state; seven had developmental delay or psychological issues that prevented cooperation with hepatic ultrasound elastography; two had died during follow-up; one had moderate atrioventricular valvar regurgitation, and one had moderate ventricular dysfunction, leaving 53 patients eligible for this study. Of the 53 included patients, 32 elected to participate and 21 did not. Of the 32 participating in hepatic elastography, we excluded data from 1 patient that had a BMI > 30 kg/m^2, and one that had acute decompensated congestive heart failure at the time of elastography, leaving data on 30 patients for the analysis. Tables 1–3 lists demographics, laboratory, and cardiac catheterization data, respectively, for both those whose data was

TABLE 2 Laboratory values at time of cardiac catheterization and liver biopsy

Eligible n = 51	Participants n = 30	Nonparticipants n = 21	*P* value
Platelets × 10^3 median (range)	199 (116–423)	203 (118–329)	0.62
ALB g/dL median (range)	3.9 (2.2–5.1)	3.9 (2.0–5.4)	0.76
TP g/dL median (range)	6.4 (3.6–8.6)	6.5 (3.7–8.2)	0.58
ALT (PT)	30 (14–100)	28 (15–75)	0.52
AST (OT)	30 (16–55)	29 (17–54)	0.69
APRi median (range)	0.39 (0.18-0.88)	0.37 (0.12-0.75)	0.46
MELD-XI score median (range)	10.6 (9.4–16)	10.2 (9.4–13.9)	0.37

Abbreviations: ALB, albumin; ALT, alanine transaminase; APRi, aspartate transaminase-to-platelet ratio index platelet ratio; AST, aspartate transaminase; MELD-XI, model for end-stage liver disease excluding INR.

TABLE 3 Cardiac catheterization and liver biopsy information

Eligible n = 51	Participants n = 30	Nonparticipants n = 21	*P* value
Age at BX years median (range)	17 (6–45)	16 (7–32)	0.57
TFS median (range)	2.5 (0–8)	2.7 (0–5)	0.54
IVCP mm Hg median (range)	13 (11–17)	13 (11–17)	0.75
Qs L/min/m^2 median (range)	2.9 (1.9-4.9)	3.0 (2.1–4.5)	0.54
UV EDP mm Hg median (range)	8 (5–11)	9 (6–12)	0.47
PVR Wood units median (range)	1.7 (0.7-2.8)	1.7 (0.6-2.9)	0.85

Abbreviations: BX, biopsy; IVCP, inferior vena caval pressure; PVR, pulmonary vascular resistance; Qs, systemic flow; UV EDP, univentricular end-diastolic pressure.

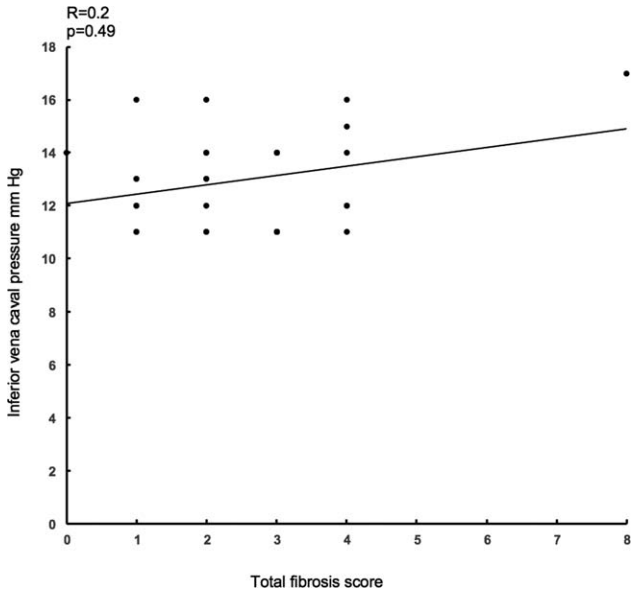

FIGURE 1 Total fibrosis scores versus inferior vena caval pressures

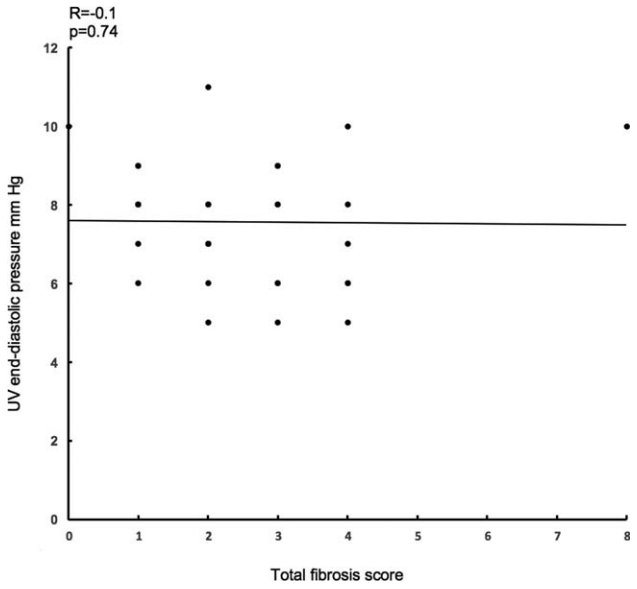

FIGURE 3 Total fibrosis scores versus univentricular end-diastolic pressures. Abbreviation: UV, univentricle

included for analysis and for those that did not elect to undergo hepatic ultrasound elastography. None of the nonparticipants was obese or had acute deterioration in ventricular function. Further, we did not employ VAST scoring, as no patient in the participating or nonparticipating group had varices, ascites, splenomegaly, or thrombocytopenia.[27] Statistical analysis demonstrated no significant differences for any variable between those who underwent elastography versus those who elected not to participate.

Using hemodynamic data acquired during the combined cardiac catheterization and liver biopsy procedures, Figures 1–3 show no significant correlation between TFS and inferior vena caval pressure, pulmonary vascular resistance, or univentricular end-diastolic pressure, respectively. We found no significant correlations between TFS or elastography measurements and APRi (AST to platelet ratio index) scores, individual ALT values, or AST/ALT ratios.[8]

Figures 4 and 5 demonstrate statistically significant correlations respectively between individual sinusoidal and portal fibrosis scores, and hepatic elastography results; nevertheless, Figure 6 shows that the correlation coefficient improved when we compared elastography measurements with the sum of sinusoidal and portal fibrosis scores (total fibrosis scores). Figure 7 demonstrates a statically significant positive correlation between TFS and Fontan duration, a finding previously reported.[3,4]

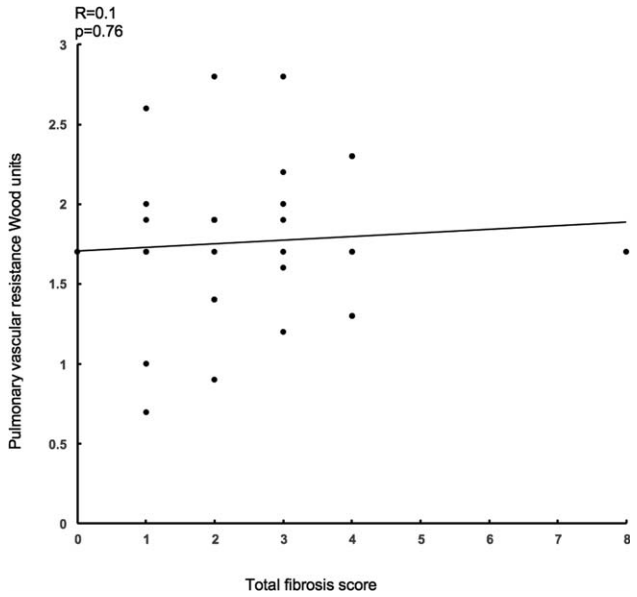

FIGURE 2 Total fibrosis scores versus pulmonary vascular resistance

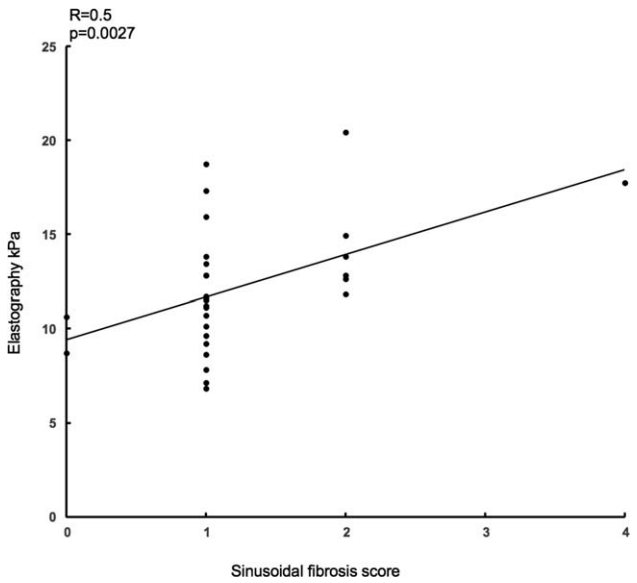

FIGURE 4 Sinusoidal fibrosis scores versus elastography measurements. kPa kilopascals

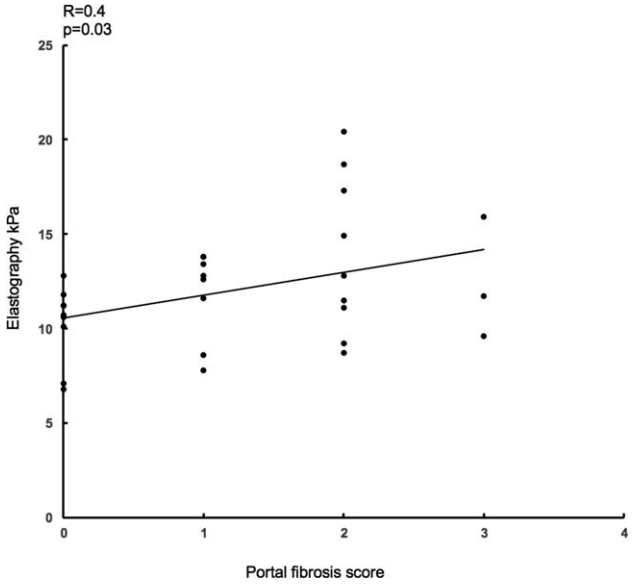

FIGURE 5 Portal fibrosis scores versus elastography measurements. Abbreviation: kPa, kilopascals

Figure 8 shows a highly statistically significant correlation between TFS and sum of hepatic elastography measurements and MELD-XI scores. We previously reported a statistically significant positive correlation between MELD-XI scores and TFS (Figure 9).[19] Further, Figure 10 demonstrates a higher correlation coefficient ($R = .8$, $P = .00001$) for the FHI values versus TFS than the 0.7 correlation coefficient found for Figure 8. If number of years post-Fontan, rather than the square root of the number of years post-Fontan, is substituted in the FHI equation the correlation coefficient with TFS drops to a R value of 0.6. Figure 11 box plot analysis demonstrated a statistically significant difference in mean FHI values associated with a TFS of 1 versus the FHI mean values associated with TFS of 3 and 4 ($P = .004$ for both comparisons).

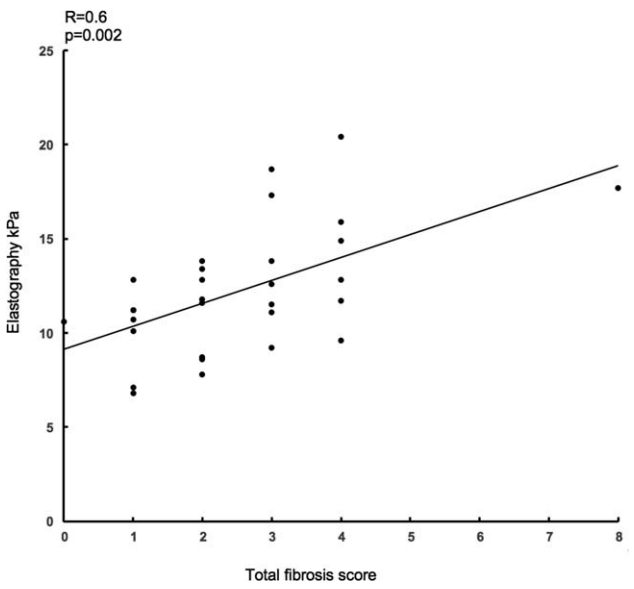

FIGURE 6 Total fibrosis scores versus elastography measurements. Abbreviation: kPa, kilopascals

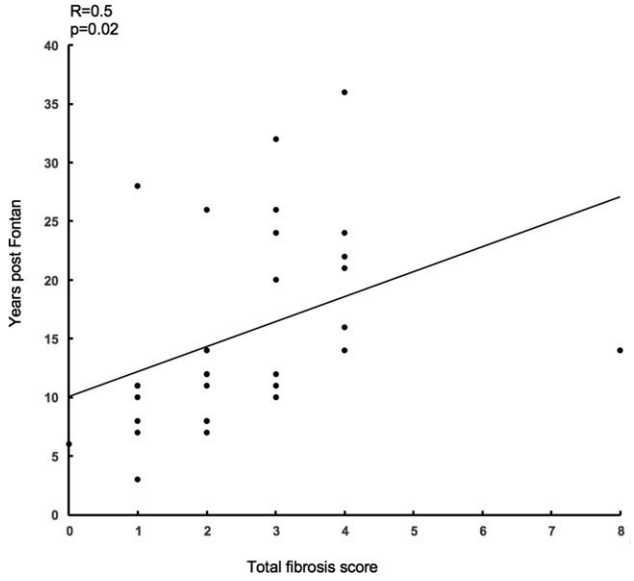

FIGURE 7 Total fibrosis scores versus years post-Fontan

Nevertheless, the small cohort size prevented useful FHI threshold value discrimination by way of receiver operating characteristic (ROC) curve analysis.

4 | DISCUSSION

We developed a noninvasive, composite index, comprised of hepatic ultrasound SWE measurements, MELD-XI scores, and time post-Fontan, which strongly correlated with TFS from liver biopsy. Noninvasive, composite indexes, some with highly complex best-fit equations employing several mathematical transformations, have been previously developed for noninvasively predicting non-Fontan related liver

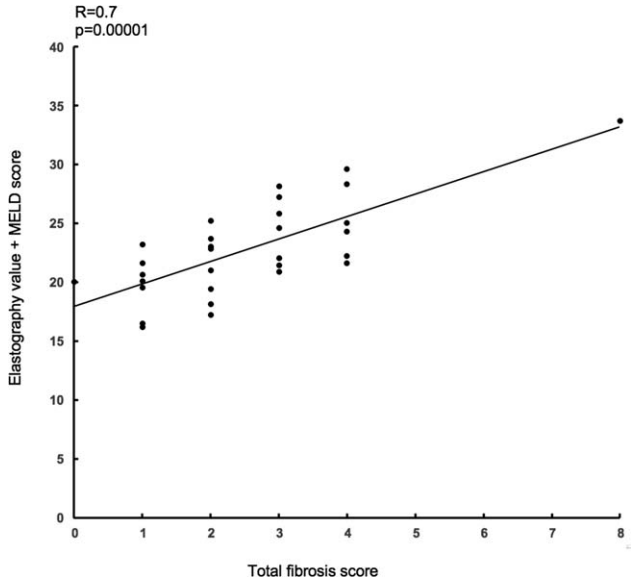

FIGURE 8 Total fibrosis scores versus sum of elastography measurements and MELD-XI scores. Abbreviation: MELD-XI model for end-stage liver disease excluding INR

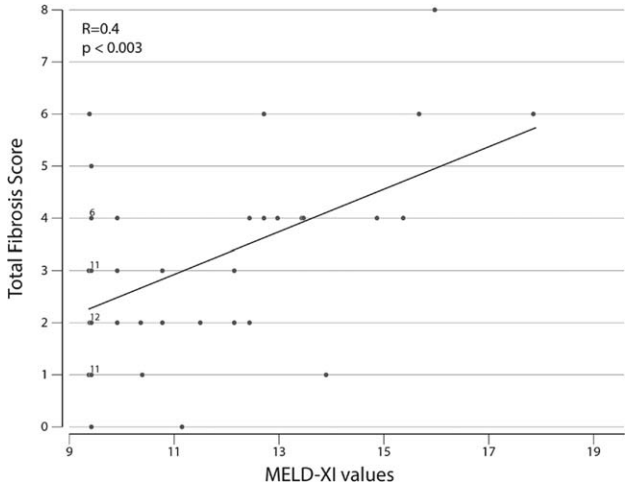

FIGURE 9 Total fibrosis scores versus MELD-XI scores. Abbreviation: MELD-XI model for end-stage liver disease excluding INR

fibrosis, after recognizing that individual markers had poor discriminatory power and limited clinical use in stratifying patients into prognostic subgroups.[8,28]

Fontan associated liver disease (FALD) is inevitable[4]; however, FALD's etiology is complex and likely multifactorial.[5] Post-Fontan liver pathology may be influenced by possible neonatal and even prenatal liver injury, protracted cyanosis, and effects from multiple cardiac surgeries. Following a Fontan procedure, systemic venous pressure is elevated, and such elevation is communicated to the portal venous system. Elevated hepatic venous pressure, both systemic and portal, likely leads to mechanical transduction of hepatic stellate cells that activates collagen-depositing myofibroblasts, coupled with the cellular level proinflammatory effects of increased circumferential vessel wall tension, all leading to fibrosis.[5,29] Routine clinical monitoring for the progression of FALD is challenging, as in contrast to other causes, FALD,

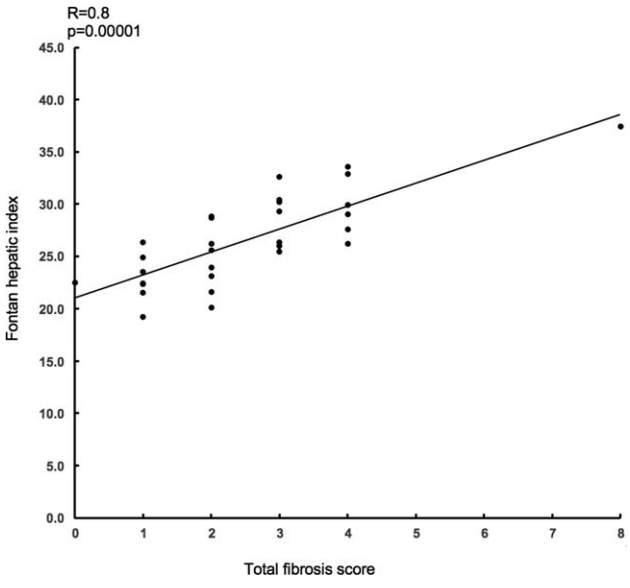

FIGURE 10 Total fibrosis scores versus Fontan hepatic index values

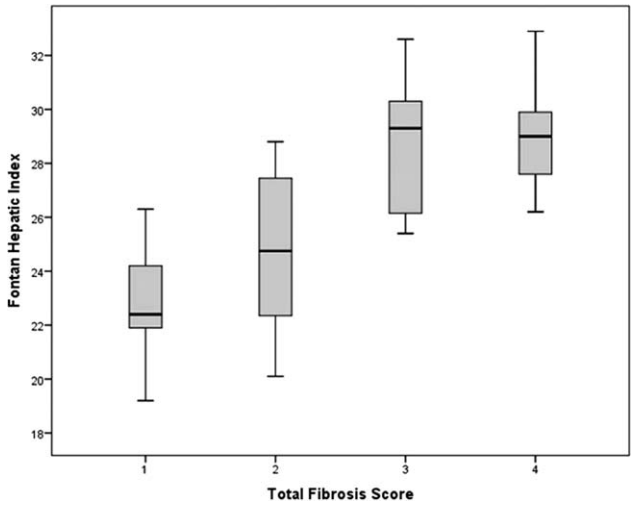

FIGURE 11 Individual total fibrosis score versus Fontan hepatic index values

especially when mild, is often accompanied by normal or near normal liver enzyme serum values.[20,30,31] For example, in this study's cohort, comprised mostly of stable Fontan patients, TFS did not correlate with laboratory values such as ALT, AST to platelet ratios, or AST/ALT ratios. Further, although invasive, hemodynamic parameters recorded at the time of cardiac catheterization also failed to correlate with TFS.

Regardless the challenge of clinically following FALD's progression from no liver fibrosis to cirrhosis, a serial, reproducible, noninvasive, clinic-based method would be preferable to techniques derived from invasive testing or computed tomography/magnetic resonance imaging procedures.[18,21] Further, it is stable Fontan patients that would most be benefited by a reliable noninvasive tracking method for predicting the degree of hepatic fibrosis, as stable patients do not routinely undergo frequent invasive assessments. In both our larger biopsy series and the cohort that underwent elastography, $\geq$ 95% of patients had either normal or at worst mild ventricular dysfunction or had no or at worst mild atrioventricular valve regurgitation.

In patients with infectious hepatitis, nonalcoholic fatty liver disease, and alcoholic liver disease, composite models comprised of laboratory values, patient characteristics, and hepatic elastography either by magnetic resonance or ultrasound, have been developed primarily to predict the presence of cirrhosis.[7–15] However, to the best of our knowledge, there are only two post-Fontan reports, with 10 patients each, that have compared liver biopsy findings with either magnetic resonance or ultrasound hepatic elastography.[18,21] Nevertheless, in FALD patients, liver stiffness may not be directly related to fibrosis, as liver stiffness increases even with Glenn shunting, before Fontan completion.[32] Additionally, liver stiffness further increases immediately have Fontan completion.[33] Nevertheless, liver stiffness changes occurring after Glenn and immediately after Fontan are likely related to liver parenchymal congestion, as liver fibrosis develops slowly over time. Thus, in Fontan patients, liver elastography measurements are elevated even at baseline, blunting the usefulness of comparing Fontan elastography measurements with normal values.[34]

We developed the composite FHI by determining a best-fit model equation. Initially, we set out to investigate whether a correlation existed between hepatic elastography measurements and TFS. We elected SWE because of reported advantages,[16,17,35] and because the technology was available on our current echocardiography equipment used in the congenital cardiac outpatient clinic. By comparing SWE data with individual sinusoidal and portal fibrosis scores, we generated statistically significant correlations; nevertheless, the correlation improved when we compared elastography data with TFS. This analysis supports our previous assumption that TFS are preferable for comparison with other variables, rather than individual sinusoidal or portal fibrosis scores, as hepatic elastography does not discriminate between the two. Also, we previously reported a significant correlation in Fontan patients between TFS and MELD-XI scores.[19] Additionally, past reports, by others and by us, had noted increasing fibrosis scores with time post-Fontan.[21,36,37] Nevertheless, time data had significant variability. Thus, to reduce time's variability but at the same time include its influence as part of our index, we used the square root function, as a method of mathematical transformation.[38]

Limitations of this study include the small number of patients and the retrospective nature of the investigation. Further, patients were not fasting for liver elastography procedures; however, we attempted to eliminate confounding variables by controlling for moderate AVVR, moderate ventricular dysfunction, obesity, and decompensated heart failure. Also, we used data discrepant in time; nevertheless, as the progressive rate of change in hepatic fibrosis in FALD is slow,[3,4,35–37] it was our opinion that an average of 2.5 years between hepatic biopsy and hepatic elastography was acceptable. However, prospectively we intend to use contemporary data in future investigations of the FHI. Despite limitations, our cohort did consist of principally stable patients with only one having cirrhosis. Further, to best of our knowledge, this study includes the largest number of post-Fontan hepatic biopsies in a noninvasive-parameter comparison study that also employed hepatic elastography measurements.

In conclusion, our preliminary findings suggest that the composite FHI might be a useful noninvasive method for serial hepatic-fibrosis monitoring; however, large patient cohort studies will be needed to validate these findings and develop clinically useful discriminatory cut-off values from childhood years, once able to cooperate with elastography, through adulthood.

CONFLICT OF INTEREST

The author(s) declared no conflicts of interest with respect to the research, authorship, and/or publication of this article.

AUTHOR CONTRIBUTIONS

Concept/Design, *Data analysis/interpretation*, *Drafting article*, *Critical revision of article*, *Approval final version*: Evans

Data analysis/interpretation, *Critical revision of article*, *Approval final version*, *Illustration*: Acherman

Data analysis/interpretation, *Critical revision of article*, *Approval final version*: Ciccolo, Carrillo, Galindo, Rothman, Mayman, Adams, Reardon, Winn, Yumiaco, Shimuizu, Inanaga, Deleon

Data analysis/interpretation, *Critical revision of article*, *Approval final version*, *Statistics*: Restrepo

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