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Original Article

Correlation of Transient Elastography with Liver Iron Concentration and Serum Ferritin Levels in Patients with Transfusion-Dependent Thalassemia Major from Oman

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Competing interests: The authors declare no conflict of Interest.

Abstract. ***Aims*: In a longitudinal study, we aimed to assess the correlation between ultrasound transient elastography (TE), serum ferritin (SF), liver iron content (LIC) by magnetic resonance imaging (MRI) T2* along with the fibrosis-4 (FIB-4) score as a screening tool to detect significant liver fibrosis among chronically transfusion-dependent beta-thalassemia (TDT) patients.**
***Methods*: The study was conducted at a tertiary health center treating TDT patients. Transient elastography was performed within 3 months of Liver MRI T2* examinations at the radiology department over a median of one-year duration. T-test for independent data or Mann-Whitney U test was used to analyze group differences. Spearman correlation with linear regression analysis was used to evaluate the correlation between TE liver stiffness measurements, Liver MRI T2* values, and SF levels.**
***Results*: In this study on 91 patients, the median age (IQR) of the subjects was 33 (9) years, and the median (IQR) body mass index was 23.8 (6.1) kg/m^2. Median (IQR) TE by fibroscan, MRI T2*(3T), Liver iron concentration (LIC) by MRI Liver T2*, and SF levels were 6.38 (2.6) kPa, 32.4 (18) milliseconds, 7(9) g/dry wt., and 1881 (2969) ng/mL, respectively. TE measurements correlated with LIC g/dry wt. (rS =0.39, p=0.0001) and with SF level (rS =0.43, P=0.001) but not with MRI T2* values (rS =-0.24; P=0.98).**
***Conclusion*: In TDT patients, liver stiffness measured as TE decreased significantly with improved iron overload measured as LIC by MRI and SF levels. However, there was no correlation of TE with the fibrosis-4 (FIB-4) score.**

Keywords: Serum ferritin; Fibrosis-4; Transfusion-dependent beta-thalassemia; Transient elastography; Magnetic resonance imaging.

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Introduction. The major cause of morbidity and mortality in patients with transfusion-dependent thalassemia (TDT) is iron overload,[1] which is essentially due to the currently recommended practice of regular blood transfusions with iron chelation.[2] Despite optimal compliance monitoring to chelation, iron overload-

mediated damage occurs in these patients to the vital organs, including the liver, heart, and endocrine glands. Interestingly, the liver is the first and the major site of transfusional iron overload, further augmented by the increased iron absorption from the gastrointestinal tract.[3] Also, since the total body iron stores correlate well with the liver iron concentration (LIC), estimation of LIC is now the method of choice to monitor iron overload in TDT patients, especially by the time serum ferritin (SF) levels are above 1000 ng/mL.[4] Presently, iron overload assessment is essentially done by magnetic resonance imaging (MRI) T2* as it is considered the investigation of choice for tissue iron estimation owing to its high specificity and sensitivity.[5] However, MRI T2* has limitations like availability, affordability, and its poor ability to accurately ascertain very fast R2* signal decay that occurs in very high overload conditions.[6]

Although the estimation of LIC by liver biopsy has been the gold standard for evaluating iron overload, it is an invasive procedure and can be associated with local complications and, due to the uneven distribution of iron, may not provide accurate results either.[7] Moreover, SF estimation, being inexpensive and easily accessible, is the most practical method to study iron overload in these patients, especially when performed serially. The only drawback of SF is that it, being an acute phase reactant, is affected by various systemic conditions such as infection, inflammatory conditions, and oxidative stress.[8]

Although liver biopsy remains a gold standard for evaluating hepatic fibrosis, several approaches, such as the Fibrosis-4 (FIB-4), the Lok index, the Fibro test, and the aspartate aminotransferase (AST)-to-platelet ratio index (APRI), have been used by investigators and compared with liver biopsy, showing varying degrees of accuracy in evaluating liver fibrosis.[9,10] FIB-4 measures four biomarkers: age, platelet count, albumin level, and aspartate aminotransferase (AST) level, and the score is calculated by adding the individual values of these biomarkers. A higher FIB-4 score indicates a higher likelihood of liver fibrosis. However, currently, transient elastography (TE) is another approach that has also been used as a reliable, noninvasive tool for evaluating liver fibrosis and is a relatively inexpensive technique that shows comparable results to liver biopsy, especially in patients with chronic viral hepatitis and cirrhosis.[11,12] A higher liver stiffness measurement indicates a higher likelihood of liver fibrosis. Nonetheless, despite being simple, safe and efficient, routine use of TE is restricted by the cost of the equipment, especially in developing countries.

The role of TE in patients with beta-thalassemia has yet to be extensively investigated as there is a paucity of literature studies on TE's performance in assessing liver fibrosis in multi-transfused TDT patients.[9,13,14] The present study is thus aimed to evaluate TE's role in assessing hepatic fibrosis and correlate the same with FIB-4 and iron overload parameters in the liver and cardiac tissues in adult TDT patients with antecedent iron overload from Oman.

Materials and Methods. This longitudinal study was conducted in the Department of Hematology, Sultan Qaboos University Hospital, Oman, by enrolling the current cohort of adult patients with TDT (n=91 over a median period of one year. All participants' height, weight, and body mass index (BMI) were measured by standard techniques. During their daycare visits for blood transfusion, these patients underwent evaluation for ultrasound transient elastography (FibroScan©, EchoSens, Paris, France) in addition to the routine full blood counts, SF levels, and blood chemistry studies. Liver function tests, renal function tests, serum electrolytes, serum calcium, phosphorous, and alkaline phosphatase were tested by spectrophotometric methods using the fully automated clinical chemistry analyzer (COBAS C 501 analyzer). Iron overload was also assessed by the in-house 3 Tesla MRI machine (Siemens LTD, MAGNETOM Vida), and the cardiac and liver T2* values were calculated using the licensed CMR tools software.[15]

Statistical Analysis. Clinical and laboratory parameters were compared, and quantitative data were expressed as mean ± standard deviation and range. The student's t-test was used to compare means, but the Wilcoxon–Mann-Whitney test was used when data was not normally distributed and expressed as median with interquartile range. Spearman's rank of correlation coefficient (rS) and linear regression analysis were used to study TE's correlations with other iron overload parameters like the SF levels, LIC, and MRI T2* values. A correlation was considered poor if rS was <0.4, moderate if rS was between 0.4-0.6, good or substantial if rS was between 0.6-0.8, and excellent if rS was >0.8. Multiple means were compared using the ANOVA test, and a p-value <0.05 was considered statistically significant. All data recording, statistical analysis, and results extraction were achieved using Statistical Package for the Social Sciences (IBM SPSS, USA, version 23).

Results. In this study on 91 patients, the median age (IQR) of the subjects was 33 (9) years, and BMI was 23.8 (6.1) kg/m^2. BMI is classified as underweight (under 18.5 kg/m^2), normal weight (18.5 to 24.9), overweight (25 to 29.9), and obese (30 or more).[16] The baseline demographic characteristics of ninety-one TDT patients are outlined in **Table 1**. Two subgroups, namely 31 patients who had undergone splenectomy and 35 patients who had exposure to the hepatitis C virus with positive serology, have been analyzed separately. The median age (IQR) was 33 (9) years. However, there was a significant

Table 1. Demography and Laboratory characteristics, FIB-4, TE scores and Iron overload parameters in the study cohort (n=91).

Parameters	Splenectomised (n=31) Median (IQR)	Unsplenectomised (n=60) Median (IQR)	p-value	Hepatitis C Exposed (n=35) Median (IQR)	Hepatitis C negative (n=56) Median (IQR)	p value
Age (years)	36(34-41)	31(27-35)	<0.001*	36(34-41)	31(26-35)	<0.001*
BMI (kg/m^2)	26(22.6-29.8)	22.4(19.5-25)	0.004*	25(21.5-29.3)	22.7(19.6-25.9)	0.07*
AST (U/L)	23(20-42)	23(16-30)	0.2*	23(18-39)	23(17-31)	0.8*
ALT (U/L)	29(17-66)	24.5(13-47)	0.16*	23(17-50)	28(15-47)	0.8*
Platelets (X10^9/L)	522(453-637)	298(241-412)	<0.001*	453(277-521)	351(251-506)	0.1*
FIB-4 score	0.41(0.31-0.46)	0.46(0.3-0.6)	0.11**	0.42(0.36-0.57)	0.3(0.25-0.58)	0.9**
TE score (kPa)	9.3(7.6-10.8)	8(7.1-9.6)	0.04**	8.2(7.1-10.1)	9.1(7.3-10.6)	0.6**
Pre-Transfusion Hb (g/dL)	9.5(9.3-10)	9.4(9.1-9.8)	0.12*	9.5(9.2-10)	9.4(9.2-9.8)	0.25*
Blood Requirement Index (mL/kg/year)	174(156-190)	216(186-232)	<0.001*	179(158-214)	211(182-232)	0.005*
Mean SF (ng/mL)	2644(1472-4814)	1973(1348-2639)	0.005*	1957(1341-3823)	2206(1374-2935)	0.24*

Key. * Students T test; ** Wilcoxon–Mann-Whitney test.

difference in the ages of patients who underwent splenectomy as well as those who were exposed to hepatitis virus C (p<0.001, Students t-test).

The patients who had undergone splenectomy showed a significantly higher median BMI kg/m^2 (26 v/s 22.4, p=0.004), higher median platelet counts, X10^9/L (522 v/s 298, p<0.001), and higher median fibroscan scores in kilopascals (kPa) (9.3 v/s 8, p=0.04) while lower median blood requirement index ml/kg/year (174 v/s 216, p<0.001) respectively. The splenectomized group also had higher median SF levels ng/mL (2644 v/s 1973, p=0.005).

Almost half of this cohort (49.5%) received Deferasirox (DFX) in the recommended range with a median of 24.7 mg/kg/day. 32% of this patient cohort is on Deferiprone (DFP) treatment with a median treatment dose of 95.7mg/kg/day, and almost one-fifth (18.5%) of the patients are on double agent treatment with DFX and DFP. None of these patients are currently on Inj. Desferral. Liver iron overload was evaluated on the basis of serial SF levels as well as LIC and cardiac MRI T2* (**Table 2A**). The median SF levels (ng/mL) showed a statistically significant rise during treatment evaluation from 1309 to 1881 (p=0.045). This iron overload was also significantly noticeable in the LIC data derived from Liver MRI T2* values (g/dry wt.), initially going up from 10.2 to 14.2 and coming down to 7 as the chelation treatment effects were seen (p<0.017, ANOVA). Improved cardiac iron load status was also noticeable, with the cardiac MRI T2* (ms) improving from 25.6 to 32.4 (p<0.0007, Wilcoxon–Mann-Whitney test). Lastly, the repeat fibroscan studies also showed a statistically significant improvement in the hepatic stiffness, with the median TE (kPa) decreasing from 8.4 to 6.4 (p<0.001, Wilcoxon–Mann-Whitney test). This cohort's median ejection fraction (IQR) was 61 % (58%-65%). **Table 2B**

Table 2A. Correlation between TE and SF; LIC, MRI T2* values in the study Cohort.

Parameters	Entire Cohort **(n=91)** Median (IQR)	p value	Spearmans Correlation of TE rS	p value
First Timeline TE score (kPa)	8.4(7.2-10)	<0.001$^{\#}$		
Second Timeline TE Score (kPa)	6.4(5.5-8.1)			
First Timeline SF (ng/mL)	1309(754-2698)	0.045$^{\#}$	0.43$^{\$}$	<0.001
Second Timeline SF (ng/mL)	1881(820-3789)			
First Timeline Cardiac T2*MRI (ms)	25.6(13.6-34.5)	0.0007$^{\#}$	-0.24$^{\$}$	0.98
Second Timeline Cardiac T2*MRI (ms)	32.4(22-40)			
First Timeline Liver T2* MRI LIC (gm/ dry wt.)	10.2(4.8-17.9)	0.017$^{\#\#}$	0.39$^{\$}$	0.0001
Highest LiverT2* MRI LIC (gm/dry wt.)	14.2(6.9-21.4)			
Second Timeline Liver T2* MRI LIC (gm/ dry wt.)	7(3.4-12.3)			
Ejection Fraction (%)	61(58-65)			

Key. # - Wilcoxon–Mann-Whitney test; ## - ANOVA; $ -Spearman's Correlation Coefficient (rS).

Table 2B. Comparison between TE and SF; LIC, MRI T2* values in splenectomised versus non-splenectomised patients.

Parameters	Splenectomised (n=31)	p value	Non-Splenectomised (n=60)	p value
First Timeline TE score (kPa)	9.3(7.6-10.8)	0.0009#	8(7.1-9.6)	<0.001#
Second Timeline TE Score (kPa)	6.4(5.8-8.1)		6.23(5.4-8.1)	
First Timeline SF (ng/mL)	1221(540-2982)	NS	1556(876-2399)	0.02#
Second Timeline SF (ng/mL)	1426(514-2889)		2060(1087-3794)	
First Timeline Cardiac T2*MRI (ms)	21(10.8-31.4)	0.012#	25.9(16.5-36.4)	0.016#
Second Timeline Cardiac T2*MRI (ms)	31.5(18.7-38.9)		33.1(22-40.3)	
First Timeline Liver T2* MRI LIC (gm/ dry wt.)	11.6(5-22.9)	<0.001#	10.2(4.75-17.3)	0.016#
Second Timeline Liver T2* MRI LIC (gm/ dry wt.)	5.7(3.1-10)		7.3(4.2-16.1)	
Ejection Fraction (%)	60(57-63)		62(58-65.5)	NS

Key. # - Wilcoxon–Mann-Whitney test; NS – Not Significant.

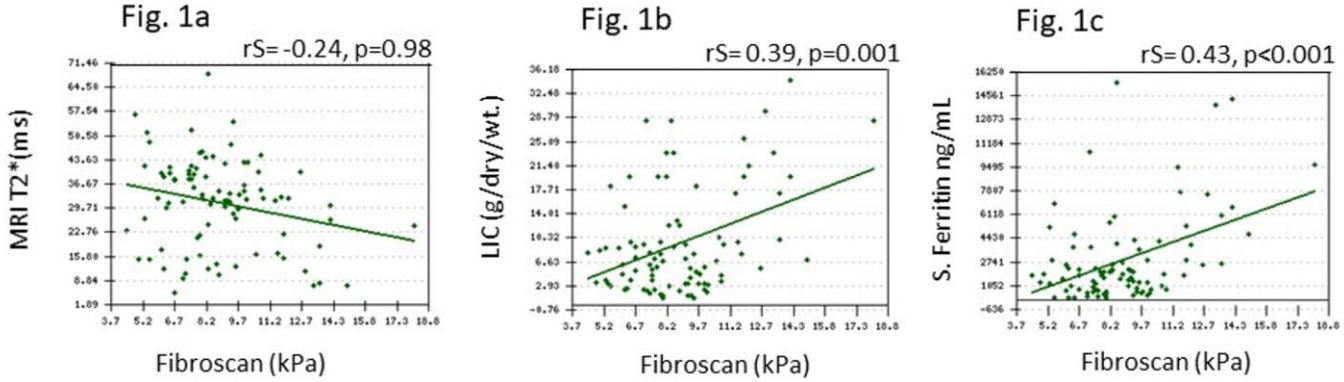

Figure 1. Scatter plot showing correlation between median TE (kPa) measured by ultrasound elastography (fibroscan) and (a) MRI T2* (r = -0.24, P = 0.98) and (b) LIC g/dw (r = 0.39, p = 0.001) and (c) serum ferritin (r = 0.43, P<0.001).

compares serial SF levels and LIC and cardiac MRI T2* between TDT patients with and without splenectomy, which did not reveal any bias due to splenectomy.

Spearman correlation test and linear regression analysis revealed a positive linear correlation between TE measurements (kPa) and LIC g/dry wt. (rS =0.39, p=0.0001) and with SF level (rS =0.43, P=0.001) but not with MRI T2* values (rS =-0.24; P=0.98) (**Figure 1**).

Discussion. Although infections and cardiac failure are the leading causes of death among TDT patients, the liver is the most important target organ susceptible to damage.[17] It is believed that chronic exposure to excess iron leads to toxic reactive oxygen species generation, which in turn activate myofibroblasts and secrete extracellular matrix protein, predominantly collagen type I and III, assisting in scar tissue formation, which leads to liver fibrosis.[18] Despite regular chelation with blood transfusions, we observed a significant iron overload with rising SF levels and LIC measurements by MRI technique. The median SF levels rose from 1309 at the start of chelation to 1881 ng/mL, which was statistically significant. There was also a comparable and statistically significant rise in the LIC from a median level of 10.2 to 14.2 g/dry wt. of liver. However, with sustained patient education and compliance monitoring, it was encouraging to see the results of sustained chelation efforts, with the median LIC decreasing significantly to 7 g/dry wt. at the last follow-up.

This study aimed to evaluate TE as an indicator of liver involvement and correlate it to iron overload or to the associated complications such as viral hepatitis. A literature review indicates that transfusional iron overload and transfusion-transmitted hepatitis infections are the leading causes of hepatic fibrosis, producing liver cell dysfunction in these patients.[19,20] We were concerned that the rise in iron overload would lead to hepatic fibrosis; however, our study provided evidence that efficient and optimal chelation therapy effectively reverses the elevated TE values over time and that this process seems reversible. Similar results were reported by D. Maria et al., who show that patients would benefit from regular assessment of liver fibrosis by TE to monitor treatment adequacy and therapeutic compliance, ensuring optimal chelation therapy.[21]

The FIB-4 score is a simple, inexpensive point-of-care test based on biochemical parameters like alanine aminotransferase (ALT), aspartate aminotransferase (AST), platelet count, and the patient's age.[22,23] This test was initially developed in patients with HIV and Hepatitis C Virus (HCV) coinfection to predict liver fibrosis and has been validated in HCV and non-

alcoholic fatty liver disease (NAFLD) patients. Incidentally, the FIB-4 score was not significantly different in our patients with or without exposure to the hepatitis C virus. Even Hamidieh et al. reported that the TE scores in their study on TDT patients were superior to FIB-4 in the assessment of liver fibrosis.[24] It is important to understand that the correlation between FIB-4 values and TE will vary depending on the patient's age, sex, and underlying liver disease. We believe that in our cohort, this was because most of our patients exposed to the hepatitis C virus had received the recommended antiviral therapy at baseline and are currently stable with normal liver transaminases and negative for viral RNA studies, although positive for hepatitis IgG serology tests. Further, the FIB-4 score was also not significantly different in our TDT patients with or without splenectomy, an observation also reported by Padeniya et al.[25]

Splenectomy was performed in a small section of our TDT patients as their blood transfusion requirements were initially observed to be high. However, following splenectomy, although the pretransfusion Hb was no different, the blood requirement index became lower in this group (174 v/s 216, p<0.001). Also, this cohort showed a significantly higher median age, higher median BMI, higher median platelet counts, and higher TE score that was significantly higher than the unsplenectomised group. However, there were significant differences in liver stiffness measured as TE, which decreased significantly with improved iron overload as measured by LIC and MRI and SF levels between TDT patients with and without splenectomy, indicating that splenectomy played no role in the observed putative differences.

Transient elastography (TE) estimates liver fibrosis/stiffness non-invasively. This technology was first introduced by Sandrin et al.[11] and is a rapid bedside tool with remarkable reproducibility. Ultrasound transducer generates vibration of a mild amplitude and low frequency (50 Hz), which consequently induces an elastic shear wave that propagates through the liver. Pulse-echo ultrasound follows the propagation of the shear wave and measures its velocity, which is related to liver tissue stiffness, being faster in fibrotic liver than in normal liver, and is expressed in kPa.[11] The "rule of 4" is a commonly used guideline for interpreting the results of transient elastography ultrasound. According to the rule of 4, a liver stiffness measurement of less than 5 kPa is considered normal, a measurement of 5-9 kPa is considered to be within the range of uncertainty, and a measurement of more than 9 kPa is considered to be indicative of significant liver fibrosis.[11] The ability to indirectly assess liver iron overload and correlate the same with indolent liver fibrosis in TDT patients has been reported by several investigators.[9,10,26] Further, Pipaliya N et al. reported that TE is cheaper and more readily available.[27] Elalfy et al. reported that, with active hepatitis C infection, their cohort of TDT patients had significant hepatic cirrhosis or fibrosis at a young age when accompanied by hepatic siderosis.[20] In our setup, we had the advantage that both these investigative techniques were available for monitoring the degree of iron overload. Thus, we could report here the benefit of repeating the TE study after a year, which showed that the median TE values significantly dropped from 8.4 to 6.4 kPa (p<0.001, Wilcoxon–Mann-Whitney test). Furthermore, TE measurements also showed a positive correlation with LIC g/dry wt. (rS =0.39, p=0.0001) and with serum ferritin level (rS =0.43, P<0.001) but not with MRI T2* values (rS =-0.24; P=0.98). These data indicated that as the tissue iron overload increased in the liver, there were corresponding higher TE values as higher median kilopascals. Nevertheless, with improved chelation and strong motivation and compliance, there was a trend in lowering the LIC (g/dry wt), reflected in a correspondingly lower TE value. Moreover, these results also highlight the dynamic relationship between compliance and robust monitoring of chelation that resulted in a significant fall in SF, LIC, and TE levels with progressive follow-up.

Conclusions. Although the study population is small, the present study demonstrated that TE plays a pivotal role in dynamically assessing the degree of hepatic fibrosis and correlates well with other measurements of tissue iron overload, namely the serial SF and MRI T2* measurements. It also shows the reversibility of liver fibrosis with improved optimal chelation. Furthermore, these results were apparent over a median follow-up of one year. However, we did not find that FIB-4 estimations correlated with any other iron overload parameters for liver and cardiac tissues in our adult TDT patients with antecedent iron overload.

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