# Correlation of Transient Elastography With MRI T2* and Serum Ferritin Levels in Children With Transfusion-Dependent Thalassemia

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**Objectives**: We investigated the correlation of transient elastography (TE) with MRI R2* values and serum ferritin in patients with transfusion-dependent thalassemia (TDT) **Methods**: We reviewed hospital records of 59 patients with TDT aged ≥8 years without any evidence of chronic liver disease and who had fibroscan within 3 months of MRI T2*, who seen at our center between January, 2014 and December, 2019. Spearman correlation and linear regression analysis were used to evaluate the correlation between TE liver stiffness measurements and R2* MRI values and with serum ferritin. **Results**: Mean (SD) age of the subjects was 13.0 (3.1) years and body mass index was 16.6 (2.3) kg/m$^2$. Mean liver stiffness measurement, MRI T2*(3T), corresponding MRI R2*(3T), and ferritin values were 6.55 (3.10) kPa, 3.4 (4.6) milliseconds, 616.20 (383.9) Hz, and 2874.69 (1570.7) ng/mL, respectively. TE measurements correlated with MRI R2* values ($r$=0.61; $P$=0.001) and with serum ferritin level ($r$=0.59, $P$=0.001). **Conclusion:** TE is a reliable tool to estimate hepatic iron overload in patients with TDT.

**Keywords**: *Fibroscan, Iron overload, Liver iron, Prognosis.*

Iron overload mediated damage to various vital organs including liver, heart, and endocrine glands is the major cause of mortality and morbidity in patients with transfusion- dependent thalassemia (TDT) [1]. The liver is considered to be the first and major site of iron overload. The total body iron stores correlate well with the liver iron concentration (LIC), therefore LIC is often considered representative of overall iron overload in TDT patients [2].

Estimation of LIC by liver biopsy was previously regarded as the gold standard modality of iron overload estimation. However, being an invasive procedure and due to uneven distribution of iron, this method is now abandoned [3]. Being cheap and easily accessible, serum ferritin is the most practical method of estimation of iron overload in these patients. However, serum ferritin does not correlate with LIC, and being an acute phase reactant, gets affected by various systemic conditions such as infection, cancers, inflammatory states, and oxidative stress [4]. Presently, magnetic resonance imaging (MRI) T2* is considered as investigation of choice for iron estimation due to its high specificity and sensitivity [5]. However, MRI T2* has its own limitation like availability, affordability and also because of its poor ability to accurately ascertain very fast R2* signal decay occurring at very high overload [6]. Transient elastography (TE), a widely available, non-invasive, and relatively inexpensive tool to measure liver stiffness due to fibrosis, is emerging as a promising tool in estimating iron overload mediated liver fibrosis [7-9]. This study was conducted to evaluate the utility of TE in assessment of liver iron overload and also to correlate it with the serum ferritin, and liver MRI R2* values.

## METHODS

This was a review of hospital records at our public sector pediatric tertiary care hospital on patients evaluated between January, 2014 and December, 2019. Approval was obtained from the institutional ethics committee.

Data of TDT patients was retrieved from the hospital records. Patients aged ≥8 years with TDT and who had undergone fibroscan within three months of MRI T2* were enrolled for the study. All participants were receiving oral iron chelators regularly. At our center, monitoring of iron status is done with serum ferritin every three monthly and MRI T2* annually (starting at the age of 10 years or earlier, if persistent transaminitis and high serum ferritin).

Patients, who were hepatitis B antigen (HBsAg) positive, anti-HCV positive, human immune deficiency virus (HIV) positive or had any other chronic liver disease, were excluded. Obese children with BMI > 95th percentile for age and sex were also excluded. Any patient with any evidence of cirrhosis (imaging evidence, bilirubin >5 mg/dL, ascites, encephalo-pathy or variceal bleed), and cardiac insufficiency (which can increase venous pressure) were also excluded.

Data including anthropometry, hemoglobin, annual transfusion requirement (ATR), serum bilirubin (total and indirect), aspartate transaminase, alanine transaminase (AST, ALT), serum ferritin, hepatitis B surface antigen, anti-HCV antibody, ultrasonography of abdomen (if done), MRI T2* values, and fibroscan values were retrieved from records.

All TDT patients at our center undergo 3.0T MRI T2* (Philips Acheiva 3.0T, Philips Medical Systems) yearly. Liver iron overload was defined as mild, moderate and severe when T2* (1.5T) values (ms) were 4.5-15.4, 2.1- 4.5 and less than 2.1, respectively [10]. Corresponding R2*(1.5T) values (Hz) were 65-224, 224- 475 and more than 475, respectively.

Tissue elastography (Fibroscan 402, Echosens) was carried out by an experienced examiner in all patients (with at least 6 hours of fasting) in supine position in midaxillary line with right arm in full abduction. Median value of the 10 successful measurements fulfilling the criteria (success rate of greater than 60% and interquartile range / median ratio of <30%) were noted in kilo Pascals (kPa). Measure-ments that did not have a correct vibration shape or a correct follow up of the vibration propagation were automatically rejected by the software.

Serum ferritin was analyzed by chemiluminescence immunoassay (Beckman Coulter Unicel DX1\ 600 Serum).

*Statistical analysis*: Spearman correlation test and linear regression analysis were used to check for correlation between TE mean liver stiffness (LSM) values and R2*MRI, ferritin and LIC. Characteristics of four groups (no, mild, moderate and severe iron overload) were compared using one-way analysis of variance (ANOVA) test. Statistical significance was considered as $P$ <0.05. All analyses were done using SPSS software.

## RESULTS

Out of 102 patients with TDT (≥8 years of age), 97 were eligible for the study (3 patients who were HCV reactive and 2 patients who were HBsAg positive were excluded). Out of those 97 patients, 38 patients in whom the duration between MRI T2* and fibroscan was >3 months were also excluded from study. Finally, 59 patients (34 males) meeting the inclusion criteria were identified to participate in the study.

The mean (SD) age was 12.9 (3.1) years. The median time interval between the fibroscan and MRI T2* was 60 days (range 0-90 days). Baseline characteristics of patients are outlined in **Table I**. LSM, MRI T2*(3T), corresponding MRI R2*(3T), and serum ferritin values were 6.55 (3.1) kPa, 3.4 (4.6) milliseconds, 616.2 (383.9) Hz, 2874.7 (1570.9) ng/mL respectively (**Table I**).

Liver iron overload was defined on the basis of MRI R2* values, and was present in 96.6 % of patients. Based on MRI analysis, 8 patients (13.6 %) had mild iron overload, 10 patients (17%) had moderate iron overload, and 39 (66 %) patients had severe iron overload (**Table I**).

Mean LSM value (Kpa) was 6.55 (3.10). Using the Spearman correlation test, positive linear correlation was found between MRI R2* and LSM values by TE (correlation coefficient ($r$)=0.615; $P$=0.001) (**Fig. 1a**). We found significant correlation between serum ferritin and LSM values ($r$=0.587, $P$=0.001) (**Fig. 1b**).

Patients were stratified according to the degree of iron overload determined on the basis of MRI R2* values into four groups (**Table II**). Liver stiffness measurements (LPA) were 4.2 (0.8), 5.3 (1.3), 4.2 (1.01) and 7.5 (3.3) in patients with no, mild, moderate, and severe overload, respectively. Since the number of patients in no, mild and moderate group was very small hence correlation of LSM with the MRI T2* and ferritin values in each group could not be assessed.

## DISCUSSION

Transient elastography consists of an ultrasound transducer mounted on the axis of the vibrator, which produces vibration of a mild amplitude and low frequency (50 Hz), consequently inducing an elastic shear wave that

**Table I Baseline Characteristics of Children With Transfusion-Dependent Thalassemia Enrolled in the Study (*N*=59)**

| *Characteristics* | *Value* |
|---|---|
| Age (y) | 13.0 (3.1) |
| Body mass index | 16.6 (2.3) |
| Male sex[a] | 34 (57.6) |
| Hemoglobin (g/dL) | 9.3 (0.6) |
| Aspartate transaminase (U/L) | 53.1 (39.3) |
| Alanine transaminase (U/L) | 57.3 (52.1) |
| Annual transfusion requirement (mL/kg/y) | 136 (18) |
| Serum ferritin (ng/mL) | 2874.7 (1570.9) |
| MRI T2* liver (Hz) | 3.4 (4.6) |
| MRI R2* liver (Hz) | 616.2 (383.9) |
| Liver iron concentration (MRI T2*) | 18.9 (11.8) |
| Fibroscan (kPa) | 6.6 (3.1) |
| Cardiac MRI T2* (Hz) | 25.2 (10.7) |
| *Iron overload[a]* | |
| Mild | 8 (13.6) |
| Moderate | 10 (17) |
| Severe | 39 (66) |

*Data expressed as mean (SD) or [a]no. (%). MRI: magnetic resonance imaging.*

**Table II Profile of Iron Overload Documented by Magnetic Resonance Imaging in Children With Transfusion-Dependent Thalassemia (*N*=59)**

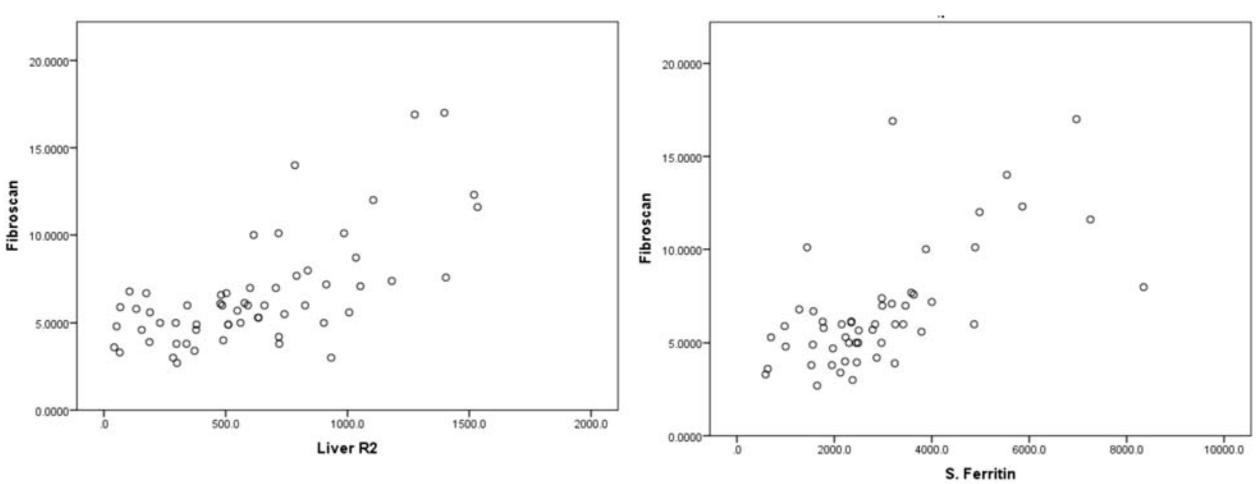
| *Parameter* | *No overload (n= 2)* | *Mild (n=8)* | *Moderate (n=10)* | *Severe (n=39)* | *P value* |
|---|---|---|---|---|---|
| Age (y) | 15.3 (2.8) | 12.8 (2.9) | 12.8 (2.5) | 12.8 (3.4) | 0.42 |
| Hemoglobin (g/dL) | 9.5 (0.6) | 9.4 (0.5) | 9.4 (0.5) | 9.3 (0.7) | 0.27 |
| Serum bilirubin, total (mg/dL) | 2.0 (1.4) | 1.1 (0.4) | 1.0 (0.4) | 1.2 (0.9) | 0.63 |
| Serum bilirubin, indirect (mg/dL) | 1.8 (0.9) | 1 (0) | 0.6 (0.6) | 0.7 (0.9) | 0.52 |
| Alanine transaminase (U/L) | 22.5 (11.4) | 23.8 (7.6) | 39.7 (29.8) | 76.1 (59.4) | 0.01 |
| Aspartate transaminase (U/L) | 27 (15.6) | 30.6 (10.5) | 41.7 (20.4) | 65.9 (45.8) | 0.02 |
| Serum ferritin (ng/mL) | 800.1 (220.1) | 1898.5 (636.9) | 2394.5 (807.0) | 3532.1 (1649.5) | 0.01 |
| MRI L2* (Hz) | 18.6 (3.9) | 5.5 (2.6) | 2.9 (0.9) | 1.3 (0.5) | <0.001 |
| MRI R2* (Hz) | 56.5 (11.7) | 255 (204.2) | 386.5 (134.2) | 854.9 (307.5) | <0.001 |
| LIC (MRI T2*) | 1.8 (0.5) | 7.8 (6.5) | 11.8 (4.5) | 26.3 (9.3) | <0.001 |
| Fibroscan (kPa) | 4.4 (1.9) | 6.1 (1.2) | 4.7 (1.3) | 7.6 (3.5) | 0.01 |
| ATR (mL/kg) | 134.8 (16.6) | 127 (11.3) | 135.6 (8.9) | 138.5 (21.5) | 0.24 |
| Body mass index (kg/m$^2$) | 17.5 (1.9) | 16.2 (2.2) | 16.2 (2.4) | 16.7 (2.4) | 0.76 |

*All values in mean (SD). MRI: magnetic resonance imaging; LIC: liver iron concentration; ATR: annual transfusion requirement.*

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, and is faster in fibrotic liver than normal liver [9].

Transient elastography; thus, is able to detect fibrosis and may indirectly assess the degree of iron overload. Fraquelli, et al. [8] demonstrated that TE is a reliable tool for assessing liver cirrhosis. Alavian, et al. [11], in a similar study, conducted on patients with TDT and hepatitis C, observed that fibroscan is an accurate and reliable method to diagnose liver fibrosis.

Our study showed that there is a significant correlation between TE and MRI R2* and also significant correlation between serum ferritin and TE values. Similar results have been also reported previously [7]. These authors [7] also found that TE is cheaper and more readily available than MRI, and might be used to estimate hepatic iron overload; however, they did not find any correlation between serum ferritin and LSM) values [7]. Similar results were also seen in other studies [12-14]. Atmakusuma, et al. [15], from their study on 45 patients with thalassemia intermedia from Indonesia, demonstrated that liver stiffness correlated with serum ferritin, liver MRI T2* and LIC and concluded that serum ferritin, liver MRI T2*and LIC correlated with liver elastography [15]. In contrast to our study results, no




(*a*) (*b*)

**Fig. 1** Scatter plot showing correlation between mean liver stiffness measurement values (LSM) measured by fibroscan and (*a*) MRI R2* ($r$=0.615, $P$= 0.001) and (*b*) serum ferritin ($r$=0.587, $P$= 0.001).

**WHAT THIS STUDY ADDS?**

- Transient elastography can be a useful adjunct to MRI T2* in assessment of iron overload related liver fibrosis in transfusion-dependent thalassemia.

correlation between LIC and TE war reported by Qu, et al. [16], who suggested that TE may not be sensitive enough to detect subtle changes in the hepatic parenchymal stiffness associated with liver iron deposition.

A small sample size is the major limitation of our study. We could not demonstrate a significant correlation of fibroscan values in different groups with no, mild, or moderate based on MRI T2* values as the number of patients in these different sub groups was very small. Moreover, applicability of our findings in children less than 8 years is uncertain.

We conclude that TE is a potential modality to estimate hepatic iron overload in patients with TDT.

*Ethics clearance*: Institutional Ethics Committee, Kalawati Saran Children's Hospital; No.LHMC/IEC/2020/57, dated August 19, 2020.

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