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The Splenectomy Paradox in Thalassemia: Reduced Transfusion Requirements vs. Accelerated Hepatic Fibrogenesis

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To the editor.

Rationale and Major Conclusions. Splenectomy is a conventional surgical intervention in transfusion-dependent beta thalassaemia (TDT) to manage symptomatic hypersplenism and reduce annual blood transfusion requirements. While the procedure successfully reduces the immediate volume of transfusions required, it fundamentally alters the patient's ferrokinetic profile by removing a secondary iron storage reservoir. Our study demonstrates that, despite lower transfusion requirements, splenectomy is independently associated with a significant, clinically relevant increase in liver stiffness measurements (LSM), suggesting that the loss of the splenic "iron buffer" may accelerate hepatic fibrogenesis. These findings highlight a critical need for clinicians to prioritize medical management of hypersplenism over surgical intervention when possible and to implement rigorous hepatic monitoring for those who have already undergone the procedure.

Introduction. The spleen plays a multifaceted role in the management of TDT, serving as both an immune organ and the second-largest site for iron sequestration. Although current guidelines prioritize medical management, splenectomy is still indicated when annual transfusion needs increase significantly or when hypersplenism leads to clinical complications.[1,2,3] Following splenectomy, total body iron storage capacity is reduced, forcing excess iron to be redistributed to vital organs, including the heart, liver, and endocrine system.[1,4,5,6]

While the association between splenectomy and myocardial iron overload or endocrinopathies is documented,[4,7,8,9] the long-term impact on the liver remains under-researched. Historical pathology-based studies noted a higher incidence of irregular cirrhosis in liver specimens from splenectomised patients compared to those with an intact spleen.[10] However, these early studies lacked non-invasive, quantitative tools to establish a clear statistical relationship. We utilized transient elastography (FibroScan®) and R2-MRI (FerriScan®) to investigate this association in a modern cohort of TDT patients.

Methods. This study utilized secondary data from a prospective cohort at the North Colombo Teaching Hospital, Sri Lanka. Ethical approval was obtained from the Ethics Review Committee (ERC) of the Faculty of Medicine, University of Kelaniya, Sri Lanka. The study cohort consisted of 45 heavily transfused TDT patients receiving dual intensive chelation: oral deferasirox (40 mg/kg/bw) and subcutaneous deferoxamine (45 mg/kg/bw) 5-7 days per week.

Patients were followed for 2 to 2.5 years. At the end of the study, we assessed LSM using transient elastography (TE; FibroScan® 502 Touch) and liver iron concentration (LIC) using R2-MRI. Drug compliance was monitored using the “Brief Medication Questionnaire” (BMQ), a tool developed by B.L. Svarstad.[11] Statistical analysis included group comparisons based on splenectomy status and a multivariable linear regression to identify factors independently associated with LSM, adjusting for age, gender, BMI, diabetes, and chelation compliance. The distribution of continuous variables was expressed as mean (SD), and group comparisons were made using the Student t-test and Mann-Whitney U test for continuous variables and the chi-square test for categorical variables as appropriate. The data analysis was carried out in R (version 3.4.2), and p-values < 0.05 were considered statistically significant.

Results. Of the 45 patients studied, 33% (n=15) were splenectomised and required significantly less blood (164 ml/kg/year) than the unsplenectomised group (228.6 ml/kg/year; $p < 0.001$). Despite the reduced transfusion burden, splenectomised patients exhibited a

Table 1. Comparison of LIC, LSM, transfusion requirement and biochemical markers between the splenectomised group and the unsplenectomised group.

Variable (unit measure)	Total study group; n=45 Mean (SD)	Un-splenectomised group (n=30) Mean (SD)	Splenectomy group (n=15) Mean (SD)	P value
AST (IU/L)	43.50 (27)	35.57 (24.00)	59.38 (26.50)	0.001†
ALT (IU/L)	54.95 (52)	48.47 (59.00)	67.92 (33.21)	0.016†
Platelet count (cells/*10^3mm^3)	380.00 (189)	287.30 (108.00)	570.70 (175.47)	<0.001†
FIB-4 score	0.43 (0.24)	0.42 (0.19)	0.42 (0.33)	0.366†
Mean Pre Hb	8.70 (0.47)	8.64 (0.49)	8.80 (0.45)	0.311†
No of transfusions	248.00 (57)	238.00 (59.00)	269.00 (50.00)	0.074 ‡
Blood requirement ml/kg/yr. (during the immediate past year)	207.10 (53.78)	228.60 (50.38)	164.00 (29.07)	<0.001†
Serum ferritin (ng/mL)	2662.00 (1820)	2497.00 (1952.00)	2991.00 (1534.00)	0.173†
LIC (mg Fe/g dw)	16.60 (14.03)	14.77 (14.00)	20.27 (13.75)	0.117†
LSM (kPa)	11.92 (13.42)	6.94 (2.37)	21.87 (19.88)	<0.001†
Drug compliance	gc = 23 (51%) mc= 12(27%) pc =10 (22%)	gc = 17 (37.7%) mc=8(17.7%) pc =5(11.1%)	gc= 6 (13.3%) mc =4 (8.8%) pc=5(11.1%)	0.408±

SD, standard deviation; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IU/L = international units per litre; kPa, kilopascal;LIC, Liver iron concentration; LSM, Liver stiffness measurement; mg Fe/g dw**,** milligrams of iron per gram of dry tissue;ng/mL, nanograms per millilitre; gc=good compliance, *both drugs were taken >5days /wk*; mc=moderate compliance, *both drugs were taken ≥3-5days /wk*; pc=poor compliance, *both drugs were taken<3 days /wk*. Unless otherwise stated, data are mean (SD) or n/N(%).‡T-test assuming equal variance in both groups, †Wilcoxon Sign Rank Test.± chi-square test

Table 2. Multiple Variable Analysis for Liver Stiffness Measurement (LSM).

Variable	Parameter estimate	SE (standard error)	Z value	P value
Individual variable analysis with simple linear regression for liver fibrosis	**Individual variable analysis with simple linear regression for liver fibrosis**	**Individual variable analysis with simple linear regression for liver fibrosis**	**Individual variable analysis with simple linear regression for liver fibrosis**	**Individual variable analysis with simple linear regression for liver fibrosis**
Age	1.283	0.385	3.327	0.002
Gender (male)	5.279	3.967	1.331	0.190
CAP	0.096	0.043	2.208	0.033
BMI	1.157	0.629	1.839	0.073
Ferriscan	0.160	0.144	1.110	0.273
Drug Compliance (pc) Drug Compliance (mc)	11.750 1.892	4.8684.576	2.4140.413	0.020 0.681
DM	12.288	4.052	3.032	0.004
Hypogonadism	6.696	4.346	1.541	0.131
Splenectomy	14.927	3.639	4.101	<0.001
No of blood transfusions	0.051	0.035	1.456	0.153
Liver fibrosis model (Multiple variable analysis)	**Liver fibrosis model (Multiple variable analysis)**	**Liver fibrosis model (Multiple variable analysis)**	**Liver fibrosis model (Multiple variable analysis)**	**Liver fibrosis model (Multiple variable analysis)**
(Intercept)	-10.886	7.104	-1.532	0.134
Age	2.862	0.708	4.041	<0.001
Splenectomy	9.512	3.283	2.897	0.006
Drug compliance (pc) Drug compliance (mc)	7.079 -0.126	3.8433.413	1.842 -0.037	0.073 0.971
No of blood transfusions	-0.172	0.058	-2.949	0.005

BMI= Body Mass Index, DM= Diabetes mellites, CAP= Controlled attenuation parameter, SE = standard Error, LIC= liver iron concentration. gc=good compliance, *both drugs were taken >5days /wk*; mc=moderate compliance, *both drugs were taken ≥3-5days /wk*; pc=poor compliance, *both drugs were taken<3 days /wk.*

dramatically higher mean LSM of 21.87 kPa compared to 6.94 kPa in those with an intact spleen ($p < 0.001$). Interestingly, LIC was higher in the splenectomy group (20.27 vs. 14.77 mg Fe/g dw), while this difference did not reach statistical significance ($p = 0.117$). Detailed laboratory results are provided in **Table 1**.

Multivariable regression analysis confirmed that splenectomy was a powerful independent predictor of liver stiffness, associated with a 9.51 kPa rise in LSM in splenectomised patients compared to the unsplenectomised group ($p = 0.006$) (**Table 2**).

Discussion. The strong association between splenectomy and increased liver stiffness in our contemporary cohort identifies a significant clinical paradox: surgery intended to reduce iron loading through transfusions may actually accelerate liver injury

The "LIC-LSM Paradox" — where stiffness is significantly higher despite similar steady-state iron concentrations — suggests that the liver in splenectomised patients is subject to a higher iron flux once the splenic buffer is removed. This higher rate of hepatocyte iron loading likely drives oxidative stress and fibrogenesis more aggressively than absolute concentration alone.[1]

Furthermore, the significant thrombocytosis observed in our cohort (570.7 vs. 287.3 cells/*10^3mm^3) points toward vascular drivers of injury (**Table 1**). Chronic microthrombi in the portal circulation, a known complication post-splenectomy, may cause congestive stiffness, which elastography records as a high kPa value.[3] Importantly, our regression model adjusted for the total lifetime number of blood transfusions. This confirms that the observed fibrosis is not merely a consequence of "more severe disease" or higher iron intake,[12] but is independently linked to the absence of the spleen.

Conclusions. Splenectomy is an independent risk factor for increased liver stiffness in TDT patients. These results emphasize that the surgical reduction of transfusion burden is not a surrogate for organ protection. Careful long-term monitoring of hepatic outcomes is mandatory for this high-risk subgroup.

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