

Original Article

Cardiac iron overload following liver transplantation in patients without hereditary hemochromatosis or severe hepatic iron deposition



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ABSTRACT

Background: Cardiac iron overload following liver transplantation in patients without hemochromatosis but with severe hepatic iron deposition has been reported to result in heart failure and/or death in case reports and small case series. However, the frequency and causes of cardiac iron overload following liver transplantation and its relationship to cardiac dysfunction in patients without severe hepatic iron deposition are unclear.

Methods: The primary inclusion criteria for this study were liver transplantation followed by autopsy or cardiac transplantation within 1 year. Cases of known hemochromatosis were excluded. Iron stains were performed on left ventricular myocardium from either the autopsy or surgically resected heart, as well as the surgically resected liver.

Results: Nineteen cases met the study criteria: 18 autopsies and 1 case of cardiac transplantation. None of the resected livers evaluated showed severe iron deposition. Myocardial iron deposition was identified in 7 (37%) of the cases. The presence of myocardial iron deposition was not significantly associated with the grade of hepatic iron deposition, or the pre-liver transplantation serum iron or ferritin levels. However, in the patients with myocardial iron deposition, there were trends toward higher pretransplant transferrin saturation (TSAT) and more units of red blood cells transfused (uRBC). The product of the TSAT multiplied by the uRBC was significantly greater in the patients with myocardial iron deposition [4700 (3100–9800) vs. 680 (400–2300), median (interquartile range), $P=.003$]. New reduced left ventricular ejection fraction (<50%) following liver transplantation occurred in four of five patients with myocardial iron deposition, compared with zero of eight patients without myocardial iron deposition ($P=.007$).

Conclusions: In this series of patients without severe hepatic iron deposition, cardiac iron overload was associated with cardiac dysfunction following liver transplantation and was related to the product of the pre-liver transplant TSAT multiplied by the number of uRBC transfused during and following the surgery.

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1. Introduction

Patients with cirrhosis but without genetic hemochromatosis are at increased risk for iron overload, including cardiac iron overload [1–4]. It is thought that chronic liver failure can result in iron overload due to decreased hepatic hepcidin secretion [5–7]. Thus, these patients may be iron overloaded at the time of evaluation for liver transplantation. The liver transplantation procedure is often associated with the transfusion of significant amounts of red blood cells (RBCs), which can contribute to iron overload following liver transplantation in these patients. Also, the liver graft may be dysfunctional following liver transplantation, and the resulting deficiency of hepatic hepcidin might exacerbate iron overload

in the post-liver transplant setting. For these reasons, iron overload can occur in the setting of liver failure and liver transplantation even in the absence of genetic hemochromatosis.

One of the most serious complications of systemic iron overload is heart failure from cardiac iron overload. In fact, cardiac iron overload in patients without hemochromatosis but with severe hepatic iron deposition has been reported to result in heart failure and/or death following liver transplantation in case reports and small case series [8]. Some centers routinely perform endomyocardial biopsies to evaluate for cardiac iron overload in any patient with severe hepatic iron deposition prior to liver transplantation [9]. Patients with cardiac iron overload may be excluded from liver transplantation due to the risk of heart failure following the procedure. This approach targets those patients with existing cardiac iron overload prior to liver transplantation.

Given that liver transplantation is often associated with the transfusion of relatively large amounts of RBCs and can be associated with posttransplant hepatic dysfunctions, it remains possible that cardiac

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iron overload could occur following liver transplantation in the absence of preexisting severe hepatic iron overload. However, the frequency and causes of cardiac iron overload following liver transplantation in patients without severe hepatic iron deposition and its relationship to cardiac dysfunction in this setting are unclear. This study examined the presence of cardiac iron overload in patients who underwent cardiac transplantation or autopsy within 1 year of liver transplantation to ascertain the relationship between cardiac iron deposition in this setting and heart failure and to identify risk factors for cardiac iron deposition following liver transplantation in the absence of severe hepatic iron deposition.

2. Materials and methods

2.1. Case selection and medical history

The primary inclusion criteria for this study were liver transplantation between 2000 and 2016 followed by autopsy or cardiac transplantation within 1 year. Cases of known genetic hemochromatosis were excluded, as were cases of combined heart/liver transplantation for preexisting heart failure. Laboratory values, transfusion history, results of genetic testing, and echocardiographic evidence of left ventricular dysfunction were obtained from the medical records. Model for end-stage liver disease (MELD) scores were calculated using the serum levels of bilirubin, creatinine, and sodium; the prothrombin international normalized ratio; and the requirement for dialysis, following the guidelines in the Organ Procurement and Transplantation Network Executive Committee policy statement dated November 23, 2015 (https://optn.transplant.hrsa.gov/media/1575/policynotice_20151101.pdf). The study was approved by the hospital's human subjects institutional review board.

2.2. Gross heart assessments

The heart weight and left ventricular free wall thickness were obtained from the pathology reports. The upper limit of normal for the autopsy heart weight based on the patient's height was obtained as previously described [10,11]. The degree of coronary artery atherosclerosis was graded as described previously [12] using a semiquantitative scale based on the assessment in the pathology report: grade 1, 0%–30% estimated stenosis (mild stenosis); grade 2, 31%–74% estimated stenosis (moderate stenosis); and grade 3, 75%–100% estimated stenosis (severe stenosis). The highest score from the individual coronary arteries was used as the overall atherosclerosis score for each patient.

2.3. Tissue iron stains

Iron (Prussian blue) stains were performed on left ventricular myocardium from either the autopsy or surgically resected heart [13], as well as the surgically resected liver. The degree of iron deposition in the resected liver was scored by a liver pathologist (R.M.), who was blinded to the presence of cardiac iron deposition, using a semiquantitative scoring system: grade 0: none (no iron staining); grade 1: minimal (<5% of hepatocytes); grade 2: mild (5%–30% of hepatocytes); grade 3: moderate (30%–60% of hepatocytes); grade 4: marked (>60% of hepatocytes) [14]. The same scoring system was used to grade the cardiac iron deposition based on the percentage of cardiac myocytes staining positively for iron.

2.4. Statistical analyses

Patients with cardiac iron deposition were compared to the patients without cardiac iron deposition. Data were compared using Fisher exact test, chi-square test, or Wilcoxon test as appropriate. Where indicated in the text, the *P* values were corrected for multiple assessments using the Benjamini–Hochberg method (P_{BH}). *P* values less than .05, after

any necessary adjustment for multiple comparisons, were considered significant.

3. Results

There were 19 patients identified who met the study criteria: 18 autopsies and 1 case of cardiac transplantation. Myocardial iron deposition was identified in 7 (37%) of the patients. The cardiac iron overload group consisted of one surgically explanted heart for heart failure (Fig. 1) and six autopsies in which the causes of death were infection ($n=3$), hepatic failure ($n=2$), and congestive heart failure ($n=1$). Four patients were grade 1 for myocardial iron deposition, two patients were grade 2, and one patient was grade 3. The control group consisted of 12 autopsies in which the causes of death were hepatic failure ($n=6$), infection ($n=3$), hemorrhage ($n=2$), and pulmonary hypertension ($n=1$). The patient characteristics and general cardiac pathology findings are listed in Table 1. There was no difference between the two groups in regards to age, gender, year of liver transplantation, MELD score prior to liver transplantation, cause of liver failure prior to liver transplantation, or time interval to death or heart transplantation. There was also no statistically significant difference between the two groups in terms of the weight of the hearts at autopsy, the left ventricular wall thickness, or the degree of coronary artery atherosclerosis. There

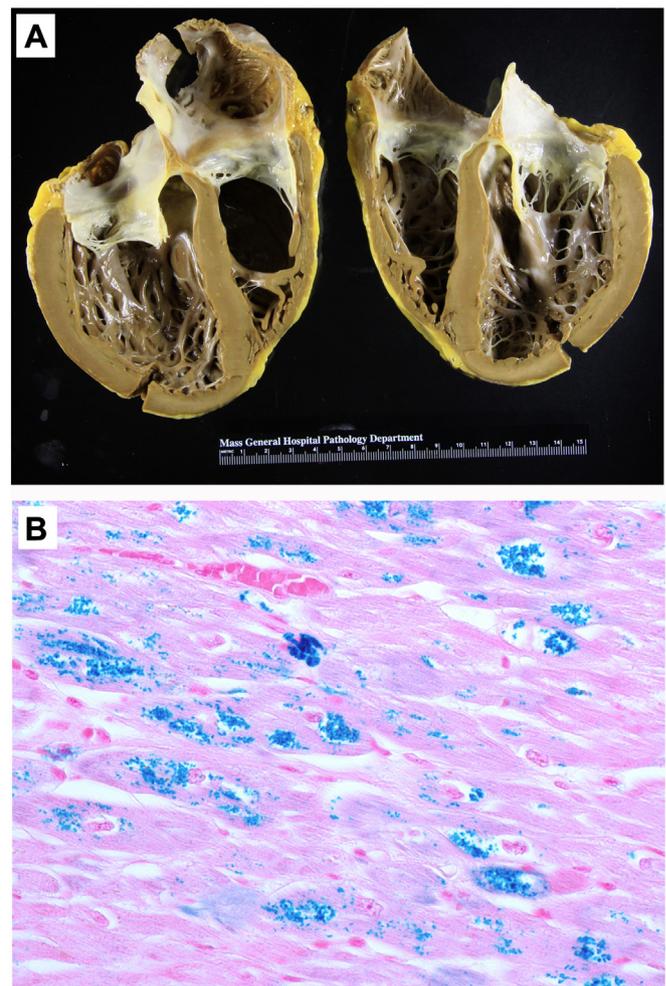


Fig. 1. Resected heart due to heart failure with reduced ejection fraction following liver transplantation. (A) The heart resected from a patient who underwent heart transplantation 4 months after liver transplantation showed dilated left and right ventricles. (B) A myocardial iron stain on this heart demonstrated iron deposition within the cardiac myocytes (blue color).

Table 1
Patient characteristics and cardiac pathology findings

	Iron positive	Iron negative	P
Number of patients	7	12	
Autopsy/heart transplant	6/1	12/0	.37
Age ^a	52 (46–57)	54 (49–58)	.90
Male gender ^b	6 (86)	6 (50)	.17
Year of liver transplantation ^a	2010 (2002–2015)	2004 (2003–2011)	.31
MELD score prior to LT ^a	32 (25–40)	23 (15–33)	.19
Cause of liver failure ^b			.64
Cirrhosis with hepatitis C	5 (71)	9 (75)	
Cirrhosis without hepatitis C	2 (29)	2 (17)	
Fulminant hepatic failure	0 (0)	1 (8)	
Interval to death or HT (days) ^a	134 (19–246)	71 (7–220)	.77
Autopsy heart weight (g) ^c	538±73 (n=5)	449±32 (n=11)	.21
Heart weight/upper limit of normal ^c	1.27±0.18 (n=5)	1.08±0.07 (n=11)	.44
Left ventricular free wall thickness (mm) ^a	16 (15–18)	14 (13–16)	.22
Coronary artery atherosclerosis score ^c	1.2±0.2 (n=6)	1.2±0.1 (n=11)	1.00

Data expressed as median (interquartile range),^a n (%),^b or mean ± standard error.^c HT, heart transplantation; LT, liver transplantation. The total number of patients in each group is listed on the top line. On the following lines, the number (n) of patients with an available variable is indicated when the variable was not available for all patients in the group.

were nonsignificant trends toward increasing heart weight and left ventricular wall thickness in the cardiac iron overload group.

None of the patients in either group were felt clinically to have genetic hemochromatosis. Of the seven patients with cardiac iron overload, two were negative on HFE gene mutation analysis and one was found to be heterozygous for C282Y, which is not sufficient to cause hemochromatosis. The other four patients with cardiac iron overload did not have HFE gene mutation analysis, but all had normal serum ferritin levels upon initial presentation. None of the patients in either group were treated with chelation therapy.

In order to gain insight into potential clinical predictors and etiologies of cardiac iron overload in this setting, assessments of the pre-liver transplant iron status and amount of red blood cell transfusions during and after the liver transplantation procedure were compared between the two groups (Table 2). There was no difference between the two groups in the serum iron or ferritin levels. Explanted liver tissue was available for assessment of iron deposition for all 7 patients with cardiac iron deposition and for 10 of 12 patients without cardiac iron deposition. There was no difference in the degree of iron deposition in the resected livers between the two groups (Table 2, Fig. 2). In the cardiac iron overload group, one patient had grade 3 hepatic iron deposition, four patients had grade 2 hepatic iron deposition, one patient had grade 1 hepatic iron deposition, and one of the patients had no iron deposition in the explanted liver.

Table 2
Association of transfusions and pre-liver transplant iron status with post-liver transplant cardiac iron overload

	Iron positive	Iron negative	P
Number of patients	7	12	
Serum iron (µg/dl) ^a	146 (74–187)	99 (73–156) n=9	1.00
Iron binding capacity < 220 (µg/dl) ^b	6/7 (86%)	3/9 (33%)	.06
Ferritin (µg/L) ^a	439 (204–734) n=6	323 (109–929) n=8	.85
TSAT (%) ^a	100 (83–100)	69 (28–89) n=9	.13
Resected liver iron score ^c	1.7±0.4	1.7±0.4 (n=10)	.88
uRBC ^a	72 (33–128)	21 (13–58)	.035
TSAT-uRBC ^a	4700 (3100–9800)	680 (400–2300) n=9	.003

Data expressed as median (interquartile range),^a n over total (%),^b or mean ± standard error.^c The total number of patients in each group is listed on the top line. On the following lines, the number (n) of patients with an available variable is indicated when the variable was not available for all patients in the group.

In the patients with myocardial iron deposition, there was a trend toward a higher pre-liver transplant transferrin saturation (TSAT, median 100% vs. 69%, $P=.13$). The patients with cardiac iron overload also tended to have received more units of red blood cells (uRBC) (median 72 U vs. 21 U, $P=.035$, $P_{BH}=.12$) during and after the liver transplantation (Table 1). The product of the TSAT multiplied by the uRBC (TSAT-uRBC) was significantly greater in the patients with myocardial iron deposition [4700 (3100–9800) vs. 680 (400–2300), median (interquartile range), $P=.003$, $P_{BH}=.02$]. In terms of predicting cardiac iron overload following liver transplantation, a TSAT-uRBC of ≥ 3000 had a positive predictive value of 88%, and a TSAT-uRBC of < 3000 had a negative predictive value of 100% (Fig. 3).

Post-liver transplant echocardiography was performed on 13 of the 19 patients. New reduced left ventricular ejection fraction ($< 50\%$) following liver transplantation occurred in four of five patients with myocardial iron deposition compared with zero of eight patients without myocardial iron deposition ($P=.007$). For the four patients with reduced left ventricular ejection fraction, one had grade 3 cardiac iron deposition, one had grade 2 cardiac iron deposition, and two had grade 1 cardiac iron deposition. One patient with grade 2 cardiac iron deposition at autopsy did not have a detectable reduction in left ventricular ejection fraction at the time of the echocardiography study.

4. Discussion

The degree of hepatic iron overload at the time of liver transplantation is associated with decreased posttransplant survival even in the absence of classic homozygous or compound heterozygous HFE gene mutations [15]. Fenton et al. described a series of such patients who underwent liver transplantation, were found to have severe (4+) hepatic iron deposition, and subsequently developed heart failure within 5 months of liver transplantation from cardiac iron overload [8]. In one autopsy series of patients with cirrhosis without classic homozygous or compound heterozygous HFE gene mutations, five of six patients with severe 4+ hepatic iron deposition also displayed cardiac iron overload [4]. While the patients in these two studies did not have classic homozygous or compound heterozygous HFE gene mutations, given the severe hepatic iron overload present, it is possible that the patients in those studies suffered from other forms of genetic iron overload, such as less common HFE gene mutations or mutations in other genes such as hemojuvelin, hepcidin, transferrin receptor 2, or ferroportin [16].

Given that the patients in the prior study by Fenton et al. had severe 4+ hepatic iron deposition at the time of liver transplantation, it is likely that most if not all of those patients had cardiac iron overload prior to liver transplantation as well [8]. Some institutions perform endomyocardial biopsy in the setting of severe hepatic iron deposition as part of the evaluation for liver transplantation. In one series, cardiac iron deposition was identified on endomyocardial biopsy in 9 of 14 liver transplant candidates with 3+ or 4+ hepatic iron deposition [9]. Alternatively, some centers are employing cardiac magnetic resonance imaging in an attempt to identify which liver transplantation candidates have cardiac iron overload [17].

It is important to consider whether the cardiac iron deposition in the patients in our study was already present as that time of liver transplantation or occurred during or following the surgery. While cardiac iron deposition is common in the setting of severe 4+ hepatic iron deposition, none of the patients in this study had this level of hepatic iron deposition. In fact, most had grade 2 or less hepatic iron deposition. In a previous autopsy series, only 1 of 42 patients with cirrhosis and mild to moderate hepatic iron deposition had cardiac iron overload [4]. Thus, it is most likely that most if not all of the patients in our study did not have cardiac iron overload at the time of the liver transplantation procedure. Furthermore, the association of the presence of the cardiac iron overload in our series with the TSAT-uRBC suggests that, in

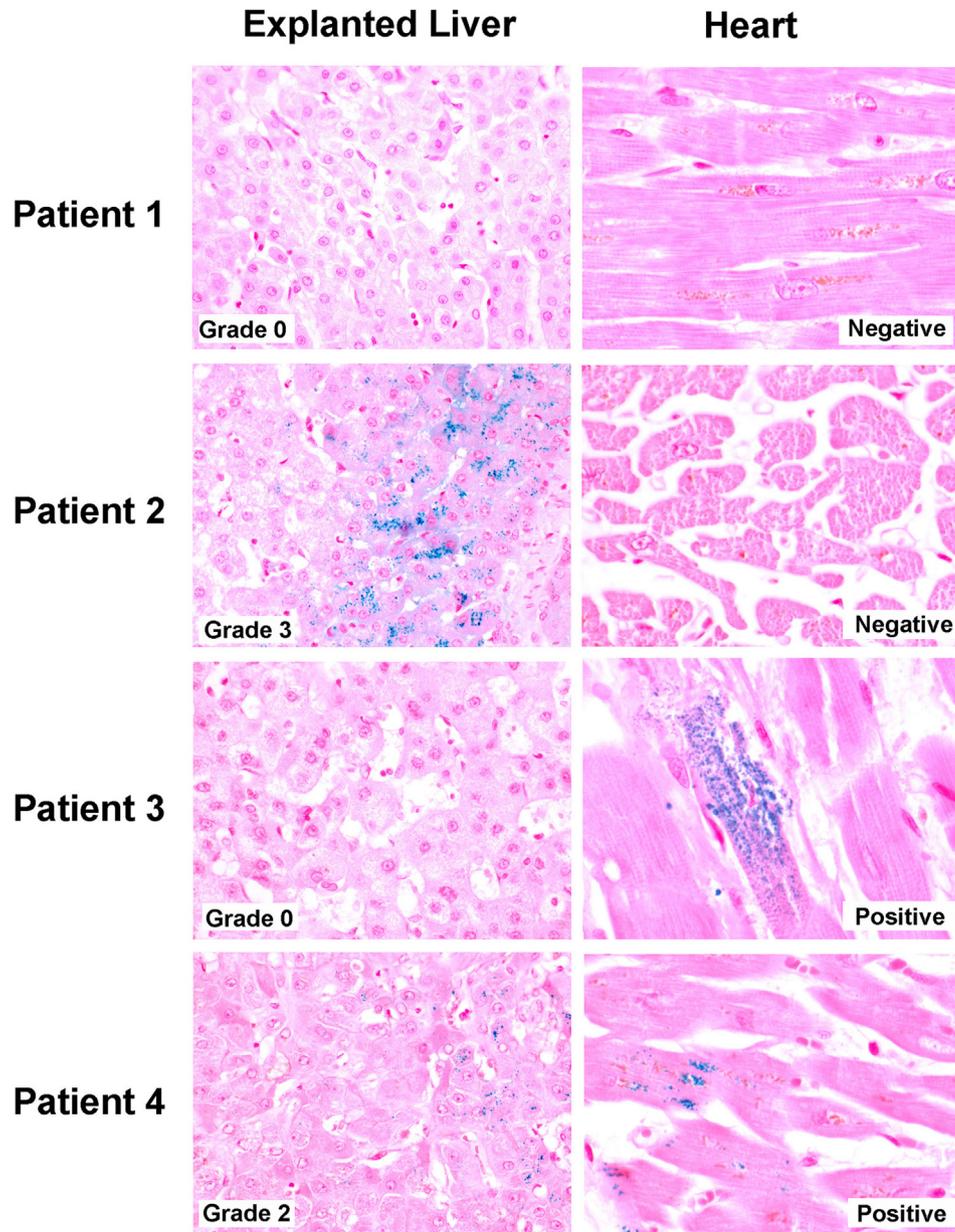


Fig. 2. Comparison of cardiac iron deposition with iron deposition in the resected livers. Depicted are iron stains on the surgically resected livers (left) and corresponding hearts (right) for four patients. Myocardial iron deposition was not related to the degree of preexisting hepatic iron deposition.

these patients, the cardiac iron overload is occurring after the liver transplantation.

A TSAT-uRBC cutoff of 3000 was relatively sensitive and specific in predicting cardiac iron overload following liver transplantation in these patients who did not have preexisting severe hepatic iron deposition. This suggests that patients with a TSAT of 100% will start accumulating cardiac iron after 30 U of RBCs in this setting. Likewise, patients with a TSAT of 20% may be able to tolerate up to 150 U of RBCs before accumulating cardiac iron in this setting. By comparison, patients undergoing chronic transfusions for β -thalassemia major are thought to experience cardiac iron overload only after receiving a total of at least 175 U of RBCs [18]. The TSAT-uRBC cutoff identified here is unlikely to have equally robust test characteristics in patients with preexisting severe hepatic iron deposition, many of whom will have cardiac iron deposition before receiving any transfusions [4]. Also it is not clear if the TSAT-uRBC cutoff identified here will be applicable to other, non-liver-transplant, patient populations.

New-onset heart failure occurs in 3%–10% of patients following liver transplantation [19–22]. It is often clinically attributed to myocarditis, drug toxicity, or preexisting heart disease, such as alcohol-related cardiomyopathy, in the setting of liver-transplant-related hemodynamic alterations. In our series of patients, reduced left ventricular ejection fraction following liver transplantation was only seen in the context of cardiac iron overload, suggesting that this may be a common mechanism for heart failure in this setting.

This study has several limitations. The number of patients studied was relatively small, and not every variable assessed was available for each patient (Tables 1–2). For example, the TSAT-uRBC was available for 16 of the 19 patients in the study. Also, this study focused on patients who either died or required cardiac transplantation within 1 year of liver transplantation and, thus, may have selected for a population that is not entirely representative of the liver transplantation population as a whole. Additional studies will be required to determine if these

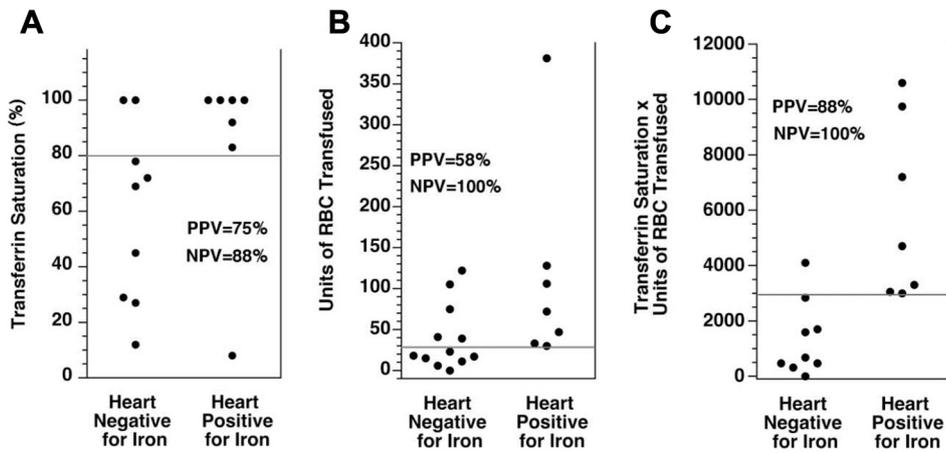


Fig. 3. Test characteristics for predicting cardiac iron overload following liver transplantation in patients without preexisting severe hepatic iron overload. Shown are dot plots for the TSAT (A), uRBC (B), and the product of the TSAT and uRBC (TSTA-uRBC) (C). Horizontal bars indicate optimized cutoff values of 80% TSAT (A), 30 uRBC (B), and a TSAT-uRBC of 3000 (C). PPV, positive predictive value; NPV, negative predictive value.

results are applicable to additional liver transplant and non-liver-transplant patient populations.

In conclusion, in this patient series, cardiac iron overload following liver transplantation without preexisting severe hepatic iron deposition was related to the product of the TSAT and the uRBC, with a TSAT-uRBC cutoff of 3000 having robust positive and negative predictive values. Furthermore, cardiac iron overload in this patient series was frequently associated with new-onset heart failure.

There are no conflicts of interest to report.

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