Real-life experience with liver iron concentration R2 MRI measurement in patients with hemoglobinopathies: baseline data from LICNET

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Iron overload remains a concern in patients with hemoglobinopathy. In regularly transfused patients with β-thalassemia major, iron overload has been associated with significant morbidity in the liver, heart, endocrine glands, among other organs; eventually leading to worsened quality of life and diminished survival (1). Iron overload has also been associated with increased risk of hepatic, endocrine, and vascular disease in β-thalassemia intermedia patients including

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those who remain transfusion-independent (2). Patients with sickle cell disease often require regular transfusion therapy for the prevention of vascular disease such as stroke, ultimately leading to an iron overload state which has been linked to increased pain crisis, hospitalization rates, end-organ morbidity, and even mortality (3). These observations indicate the need for meticulous patient follow-up and early diagnosis of iron overload, so that prompt management with iron chelation therapy can be initiated.

The liver plays a central role in iron regulation and remains the primary site of iron storage, with liver iron concentration (LIC) being a strong surrogate of total body iron (4). In iron overload syndromes, the liver becomes overwhelmed with excess iron which leads to hepatic pathology at one end, and the outpouring of toxic iron species in the body that can cause damage to other vital organs such as the heart and endocrine glands (1). LIC measurement has classically been conducted through liver biopsy which is an invasive procedure, with high sampling errors and complications risk (mortality 1 : 10 000; bleeding 1 : 100; bile leak 1 : 1000; any pain 1 : 4; significant pain 1 : 10–20) (5). A role for liver biopsy, however, is still reserved for cases where simultaneous hepatic histology assessment is needed such as in viral infections and suspected malignancy (1). The use of a superconducting quantum interference device (SQUID) has also been reported but the technology is only available in few centers worldwide (1). In the past decade, the use of non-invasive magnetic resonance imaging (MRI) for organ iron assessment has revolutionized care for patients with iron overload. For assessment of LIC, both the R2 and T2* MRI techniques are used as they have been validated against liver biopsy measurements of iron (6, 7). Both R2 and T2* can accurately measure LIC throughout the clinically relevant range with appropriate calibration and MRI acquisition techniques (8, 9). R2 MRI has been well validated across imaging platforms and is robust to liver inflammation and fibrosis (10), and the technique (FerriScan® Resonance Health Limited, Claremont, WA, Australia) is approved by the FDA.

The aim of the current study was to report experience with the use of R2 MRI in a real-life setting using data from a large sample of patients with hemoglobinopathy. Such information should help clarify the picture of current LIC ‘status’ and identify groups with elevated values that require closer attention. We also aimed to explore the relationship between LIC and other iron overload indices (namely serum ferritin level) in a large group of patients with different hemoglobinopathies, to provide further guidance on the use of such measures in areas where LIC assessment by MRI is not available or feasible.

Patients and methods

This was a cross-sectional study of patients with hemoglobinopathies attending 13 Italian centers participating in the LICNET (Liver Iron Cutino NETwork). Underlying diagnosis included β-thalassemia major (regularly transfused), β-thalassemia intermedia (both transfused and non-transfused), and sickle cell disease (both transfused and non-transfused). ‘Transfused’ status was defined as receipt of ≥7 mL/kg/month of packed red blood cells. Included in this analysis were data from the first R2 MRI scans performed as part of the network, for those patients presenting between February 2013 and June 2015. The R2 MRI protocol followed at the center follows that of St Pierre et al. (6) retrieved information included patient demographics (age and sex), type of iron chelation therapy at the time of MRI assessment, and laboratory values at the time of MRI scan including hemoglobin level (pretransfusion in transfused patients), serum ferritin level, alanine aminotransferase (ALT), and hepatitis C status as determined by ribonucleic acid polymerase chain reaction (RNA-PCR).

The LICNET was established by Foundation Franco e Piera Cutino of Palermo and is addressed to diagnostics of liver iron overload by R2 MRI R2 subjects with hemochromatosis. The LICNET protocol was approved on December 4, 2012 by our Ethics Committee.

Statistical analysis

Descriptive analysis is provided as means ± standard deviations, medians, or percentages. LIC risk categories were considered when appropriate with levels 7–15 mg Fe/g dry weight (dw) indicating increased risk of morbidity and levels >15 mg Fe/g dw indicating greatly increased risk (6). Bivariate LIC comparisons were made using the chi-squared and Fisher’s exact tests for categorical variables and the Mann–Whitney U-test or the Kruskal–Wallis test for continuous variables. Correlations between LIC serum ferritin and ALT values were made using Spearman’s correlation coefficient. Receiver operating characteristic (ROC) curve analysis was used to identify serum ferritin levels that best predict LIC thresholds of clinical significance (7 and 15 mg Fe/g dw) by identifying levels with highest sum of sensitivity and specificity. All P-values are two sided with the level of significance set at <0.05.

Results

A total of 363 patients were evaluated in this analysis, with a mean age of 35.6 ± 13.0 yr (range: 6–76) and including 160 (44.1%) men. The underlying diagnosis were regularly transfused β-thalassemia major (n = 204, 56.2%), β-thalassemia intermedia (n = 102, 28.1%), and sickle cell disease (n = 57, 15.7%). Among β-thalassemia intermedia patients, 60 (58.8%) were on transfusion therapy. Similarly, in patients with sickle cell disease, 34 (59.6%) were on transfusion therapy. Patients’ characteristics and laboratory values for all patients combined and in respective subgroups are
summarized in Table 1. The mean LIC in the study population was 7.8 ± 9.6 mg Fe/g dw, and the median was 4.0 mg Fe/g dw (range: undetectable to 43.1). LIC values were similar between men (mean: 7.8 ± 8.8, median: 4.7 mg Fe/g dw) and women (mean: 7.9 ± 10.1, median: 4.0 mg Fe/g dw) \( (P = 0.375) \), and between children (<18 yr, mean: 8.3 ± 11.2, median: 3.7 mg Fe/g dw) and adults (mean: 7.8 ± 9.5, median: 4.2 mg Fe/g dw) \( (P = 0.854) \). Figure 1 illustrates the distribution of LIC risk categories according to age, noting a slightly higher percentage of patients with LIC >15 mg Fe/g dw in children than adults (17.6% vs. 14.9%, \( P = 0.574) \). The following sections further characterize LIC values in relation to different study parameters.

Liver iron concentration across underlying diseases

Across underlying diseases, LIC distribution was as follows: \( \beta \)-thalassemia major (mean: 9.0 ± 10.7, median: 4.9 mg Fe/g dw), transfused \( \beta \)-thalassemia intermedia (mean: 7.1 ± 7.3, median: 5.0 mg Fe/g dw), non-transfused \( \beta \)-thalassemia intermedia (mean: 5.1 ± 6.0, median: 3.2 mg Fe/g dw), transfused sickle cell disease (mean: 8.5 ± 11.0, median: 4.5 mg Fe/g dw), and non-transfused sickle cell disease (mean: 3.1 ± 1.9, median: 2.4 mg Fe/g dw). Figure 2 illustrates the distribution of LIC risk categories according to underlying disease, while Fig. 3 illustrates actual MRI images of patients with high and low iron burden across diseases. In transfused patients, the proportion of patients with high LIC risk categories (>7 mg Fe/g dw) was comparable among the three diagnosis \( (P = 0.627) \). Interestingly, however, that despite none of the non-transfused patients with sickle cell disease having LIC values >7 mg Fe/g dw,

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All patients ( n = 363 )</th>
<th>( \beta )-thalassemia major ( n = 204 )</th>
<th>( \beta )-thalassemia intermedia ( n = 102 )</th>
<th>Sickle cell disease ( n = 57 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, mean ± SD (range)</td>
<td>35.6 ± 13.0 (6–76)</td>
<td>32.1 ± 10.9 (6–67)</td>
<td>43.2 ± 13.2 (19–76)</td>
<td>38.2 ± 15.3 (6–70)</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18 yr</td>
<td>34 (9.4)</td>
<td>23 (11.3)</td>
<td>0 (0.0)</td>
<td>7 (16.7)</td>
</tr>
<tr>
<td>≥18 yr</td>
<td>328 (90.4)</td>
<td>180 (68.7)</td>
<td>60 (100.0)</td>
<td>35 (83.3)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>160 (44.1)</td>
<td>83 (40.7)</td>
<td>24 (40.0)</td>
<td>15 (44.1)</td>
</tr>
<tr>
<td>Iron chelation, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None/Not available</td>
<td>88 (24.2)</td>
<td>18 (8.8)</td>
<td>10 (16.7)</td>
<td>31 (73.8)</td>
</tr>
<tr>
<td>DFO</td>
<td>55 (15.2)</td>
<td>35 (17.1)</td>
<td>10 (16.7)</td>
<td>5 (11.9)</td>
</tr>
<tr>
<td>DFP</td>
<td>56 (15.4)</td>
<td>36 (17.6)</td>
<td>11 (18.3)</td>
<td>2 (4.8)</td>
</tr>
<tr>
<td>DFX</td>
<td>119 (32.8)</td>
<td>75 (46.8)</td>
<td>25 (41.7)</td>
<td>3 (7.1)</td>
</tr>
<tr>
<td>DFO+DFP</td>
<td>34 (9.4)</td>
<td>32 (15.7)</td>
<td>2 (3.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Other combination(^1)</td>
<td>11 (3.0)</td>
<td>8 (3.9)</td>
<td>2 (3.3)</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>HCV positive by RNA-PCR, n (%)</td>
<td>59 (24.8)</td>
<td>38 (27.1)</td>
<td>12 (29.3)</td>
<td>4 (9.5)</td>
</tr>
<tr>
<td>Hemoglobin in g/dL, mean ± SD (range)</td>
<td>9.5 ± 0.9</td>
<td>9.6 ± 0.7</td>
<td>9.3 ± 1.0</td>
<td>9.5 ± 1.3</td>
</tr>
<tr>
<td>Serum ferritin in ng/mL, median (range)</td>
<td>6.5–12.0</td>
<td>6.7–11.2</td>
<td>6.5–12.0</td>
<td>6.5–12.0</td>
</tr>
<tr>
<td>ALT in IU/L, mean ± SD (range)</td>
<td>37.3 ± 28.2</td>
<td>41.0 ± 32.6</td>
<td>35.7 ± 25.4</td>
<td>35.1 ± 19.1</td>
</tr>
</tbody>
</table>

\(^1\)DFO=DFP or DFX+DFP.  
\(^2\)Pretransfusion measurement in transfused patients.
around 20% of patients with non-transfused β-thalassemia intermedia had such high LIC thresholds (13.3% vs. 36.4% in non-chelated vs. chelated patients).

Of note, there was a negative yet non-significant correlation between hemoglobin level (severity of anemia) and LIC in non-transfused patients with β-thalassemia intermedia...
(rs = −0.148, P = 0.362). However, there was a significant and positive correlation between advancing age and LIC in this patient subgroup (rs = 0.374, P = 0.016).

On analysis of medians, LIC values were lower in patients with HCV (mean: 5.8 ± 6.4, median: 3.5 mg Fe/g dw) than those without (mean: 7.4 ± 9.2, median: 4.7 mg Fe/g dw), although this did not reach statistical significance (P = 0.859).

**Liver iron concentration across different chelators**

Among chelated patients, LIC distribution was as follows: deferoxamine (mean: 7.3 ± 8.5, median: 4.7 mg Fe/g dw), deferasiprone (mean: 11.6 ± 11.4, median: 8.4 mg Fe/g dw), deferasirox (mean: 7.8 ± 10.3, median: 3.2 mg Fe/g dw), deferoxamine+deferasiprone (mean: 8.2 ± 10.6, median: 4.5 mg/Fe/g dw), and other combinations (mean: 6.5 ± 4.0, median: 5.1 mg/Fe/g dw), with a statistically significant difference noted between groups (P = 0.009) with the highest median among chelated patients noted in deferasiprone-treated patients and lowest median noted in deferasirox-treated patients. These significant differences were further noted upon analysis of different LIC risk categories (P = 0.023, Fig. 4) and were further observed when the analysis was stratified into children (P = 0.015) and adults (P = 0.012).

**Liver iron concentration vs. serum ferritin level**

Table 2 illustrates correlations between LIC and serum ferritin along with predictor serum ferritin values according to underlying disease. The significant correlation between LIC and serum ferritin was maintained for underlying disease groups, except for non-transfused patients with sickle cell disease. Serum ferritin levels that best predict LIC thresholds of 7 and 15 mg Fe/g dw varied, although patients with β-thalassemia intermedia showed lowest serum ferritin levels to predict these thresholds especially non-transfused patients (Table 2; Figure S1).

**Liver iron concentration vs. alanine aminotransferase**

There was a significant and positive correlation between LIC and ALT (rs = 0.305, P < 0.001; Fig. 5). A significant correlation was only noted in HCV-negative (rs = 0.316, P < 0.001) but not HCV-positive (rs = 0.093, P = 0.487) patients. Moreover, it was only noted in deferasirox (rs = 0.409, P < 0.001)- or deferasiprone (rs = 0.307, P = 0.030)-treated patients but not with other chelation regimens, with a stronger correlation noted for patients on deferasirox.

**Discussion**

Our study demonstrated that around one-third of patients with hemoglobinopathy across a large network in Italy continue to have high LIC thresholds >7 mg Fe/g dw with around 15–20% of patients having very high levels >15 mg Fe/g dw. Our findings were consistent across transfused patients with β-thalassemia (major and intermedia) and sickle cell disease. Although proportions noted in β-thalassemia major are considerably lower than recently published screening data from a clinical trial including 121 β-thalassemia major patients from the west (66.1% with LIC >7 and 44.6% with LIC >15 mg Fe/g dw) (11), they still present a population at risk of adverse clinical outcomes that require further attention. The difference may also be attributed to a more restrictive screening protocol in the study by Aydinok et al. (in the context of a clinical trial) compared to our study (11). LIC values >7 mg Fe/g dw have been associated with increased complications and liver disease in β-thalassemia major while values >15 mg Fe/g dw are associated with progressive liver fibrosis and cardiac mortality (12–14). In regularly transfused sickle cell disease, patient groups with mean LIC values >7 mg Fe/g dw show high proportion of hepatic fibrosis (15, 16) while patients with mean values >15 mg Fe/g dw show evidence of endocrine disease (17).

Interestingly, non-transfused patients with β-thalassemia intermedia also showed a considerable proportion of patients with high LIC (~20%). Despite the absence of transfusion, the globin chain imbalance and ineffective erythropoiesis lead to the secretion of several erythroid regulators from erythroblasts, erythroferrone being the most recently uncovered. These factors lead to hepcidin suppression and iron export to plasma from macrophages (iron recycling) and duodenum (iron absorption) (18). This in turn leads to depletion of macrophage iron, relatively lower levels of serum ferritin, increased LIC and release into the circulation of free iron species that can cause target-organ damage (19). The degree of anemia has been recently associated with iron overload severity (20), as apparent in our study although not reaching...
statistical significance. Iron overload in non-transfused $\beta$-thalassemia intermedia patients is a cumulative process with advancing age (21), as evident in our study, leading to a considerable proportion of patients reaching LIC thresholds of clinical significance (2), with iron-related morbidity appearing beyond 10 yr of age (22). Elevated LIC in non-transfused $\beta$-thalassemia has been associated with several morbidities including hepatic, renal, vascular, endocrine, and bone disease (23–25).

High LIC levels (>7 mg Fe/g dw) were also noted in pediatric patients. In studies of patients with $\beta$-thalassemia major, elevated LIC was documented in patients as young as 2 yr of age. Such early onset of iron overload in transfused patients confirms the need for early assessment and monitoring of patients while applying effective iron chelation therapy to prevent further iron accumulation and the subsequent development of clinical complications (26, 27). This becomes even more essential before patients enter the transition from childhood to adulthood owing to the observed challenges in managing patients in this critical phase (28).

Our study observed a differential distribution of LIC risk categories with different iron chelators. In patients with $\beta$-thalassemia, few prospective studies evaluated iron chelation therapy in patients with low LIC (<7 mg Fe/g dw) at baseline, with favorable results in terms of maintenance of iron balance noticed among all chelators: deferoxamine, deferasirox and its combination with deferoxamine, and deferasirox (29–33). Most prospective clinical trials in patients with high LIC (>7 mg Fe/g dw) at baseline, however, are deferasirox studies (31, 32, 34–37); with very limited randomized clinical trial data for deferiprone or its combination with deferoxamine (38, 39), where the combination was proven to be more effective in reducing LIC than deferiprone monotherapy. Deferasirox was shown to be effective at reducing liver iron in patients with high LIC, for

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$\beta$-thalassemia major</th>
<th>$\beta$-thalassemia intermedia</th>
<th>Sickle cell disease</th>
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<tbody>
<tr>
<td></td>
<td>Transfused: $n=60$</td>
<td>Non-transfused: $n=42$</td>
<td>Transfused: $n=34$</td>
</tr>
<tr>
<td>Spearman’s correlation coefficient</td>
<td>0.705</td>
<td>0.687</td>
<td>0.801</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum ferritin (ng/mL) for LIC &gt;7 mg Fe/g dw</td>
<td>1900</td>
<td>1100</td>
<td>650</td>
</tr>
<tr>
<td>AUC</td>
<td>0.824</td>
<td>0.824</td>
<td>0.905</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Serum ferritin (ng/mL) for LIC &gt;15 mg Fe/g dw</td>
<td>2100</td>
<td>1200</td>
<td>900</td>
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<tr>
<td>AUC</td>
<td>0.882</td>
<td>0.873</td>
<td>0.961</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.001</td>
<td>0.002</td>
<td>0.030</td>
</tr>
</tbody>
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LIC, liver iron concentration; dw, dry weight; AUC, area under the curve; NA, not applicable in the absence of patients with outcome.

1Numbers were rounded to the nearest 50.
LIC in hemoglobinopathies

Vitrano et al.

whom values were almost halved in some studies. Continued reduction of LIC on long-term therapy up to 5 yr was also observed (31, 32, 34–37). Deferasirox has also demonstrated LIC reduction in patients with sickle cell disease (40, 41). Data from the first clinical trial in patients with non-transfusion-dependent thalassemia including β-thalassemia intermedia have also demonstrated significant and considerable reduction in LIC for up to 2 yr of therapy (42, 43). More recently, a randomized clinical trial has shown comparable long-term iron chelation efficacy of deferiprone and deferoxamine for patients with β-thalassemia intermedia, although mainly relying on serum ferritin levels (44). Data from this study, being cross-sectional, should, however, be interpreted with caution, as we could not attribute previous history of chelation nor dose and duration of therapy on each chelator to be able to confirm the ability of certain chelators to reduce LIC better than others.

Our study established a correlation between serum ferritin level and LIC and identified serum ferritin values that can help predict LIC risk thresholds of 7 and 15 mg Fe/g dw across evaluated diseases when such assessment is not available or feasible. In patients with β-thalassemia major, several current treatment decisions are based on the serum ferritin threshold of 2500 ng/mL which signifies high risk, considering its association with morbidity, especially cardiac and endocrine disease (45, 46). Our data suggest a lower value of ~2000 ng/mL can also be highly indicative of future risk due to its association with high LIC levels. In non-transfused patients with β-thalassemia intermedia, values higher than 650–900 ng/mL were predictive of high LIC. Such lower thresholds to predict high LIC compared with β-thalassemia major or even transfused patients with β-thalassemia intermedia are in agreement with several recent observations in this patient population and reflect the aforementioned pathogenesis of iron overload in this patient population (47–50). The values also resonate with a recent study that showed a significant association between serum ferritin levels >800 ng/mL and morbidity risk in non-transfused β-thalassemia intermedia (21). It should be noted that the discriminating range for serum ferritin levels to predict an LIC of >7 or >15 mg Fe/g dw in transfused patients with β-thalassemia is narrow (~200 ng/mL), indicating that if such detailed risk stratification is necessary, LIC assessment may still be required. The correlation between serum ferritin levels and LIC by biopsy in patients with sickle cell disease was previously shown to be nonlinear over the segment of 1500–3000 ng/mL, although values <1500 and >3000 ng/mL were shown to be predictive of low and high risk of hepatic disease, respectively (51). Our values seem in good agreement with these thresholds noting values of <1300 and >2700 ng/mL being predictive of LIC values of <7 and >15, respectively. Although serum ferritin may be the only assessment technique available in some centers, physicians should continue to be aware that the variability of serum ferritin levels remains high and the predictive power for LIC is not perfect. Thus, some patients with low serum ferritin level may continue to have high LIC, and the opposite can also be valid.

Our study also identified a correlation between LIC and ALT, primarily in HCV-negative patients. Progressive iron accumulation in the liver damages tissue on microscopic and macroscopic levels, which may lead to hepatic complications including fibrosis, cirrhosis, and hepatocellular carcinoma (1, 2, 52). Although incidence rates of such complications are not widely available, data from recent large registries indicate a rising trend over the last decade in mortality from hepatic causes in patients with hemoglobinopathies (53). It should be noted, however, that other risk factors can promote liver disease especially in transfused patients. HCV virus infection remains a concern in resource poor countries with suboptimal blood screening programs and can further complicate hepatic health in this patient population if not treated with antiviral therapy (54). Moreover, comorbidities such as endocrine and heart dysfunction, which remain common in heavily iron overloaded patients, can further deteriorate hepatic function (1). Taken together, this stresses the role of ‘holistic’ care and optimal monitoring and management of multiple morbidity in patients with hemoglobinopathies to ensure favorable hepatic outcomes.

Our study illustrated R2 MRI experience across a large group of patients with hemoglobinopathies and identified patient subgroups with low and high-risk LIC values. Such assessments can help guide physicians toward optimal care especially for patients at risk of iron-related morbidity. We also further explored the relationship between LIC and serum ferritin levels and established serum ferritin values that predict high-risk LIC threshold across different diagnoses. These latter observations should remain useful for iron overload management especially in settings where MRI assessment is not possible. Future directions of our network include longitudinal assessment of MRI changes over time, with the aim of identifying clinically meaningful changes and factors that govern them.

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Author contributions

AM involved in study concept design. All authors performed data collection, assembly, critical revision of manuscript for intellectual content, and approved the manuscript
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Conflicts of interest

All authors have no conflicts of interest to disclose.

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**Supporting Information**

Additional Supporting Information may be found in the online version of this article:

**Figure S1.** (A) Receiver operating characteristic curve analysis of serum ferritin level for predicting LIC of >7 mg Fe/g dw β-thalassemia major. (B) Receiver operating characteristic curve analysis of serum ferritin level for predicting LIC of >15 mg Fe/g dw β-thalassemia major. (C) Receiver operating characteristic curve analysis of serum ferritin level for predicting LIC of >7 mg Fe/g dw transfused β-thalassemia intermedia. (D) Receiver operating characteristic curve analysis of serum ferritin level for predicting LIC of >15 mg Fe/g dw transfused β-thalassemia intermedia. (E) Receiver operating characteristic curve analysis of serum ferritin level for predicting LIC of >7 mg Fe/g dw non-transfused β-thalassemia intermedia. (F) Receiver operating characteristic curve analysis of serum ferritin level for predicting LIC of >15 mg Fe/g dw non-transfused β-thalassemia intermedia. (G) Receiver operating characteristic curve analysis of serum ferritin level for predicting LIC of >7 mg Fe/g dw transfused sickle cell disease. (H) Receiver operating characteristic curve analysis of serum ferritin level for predicting LIC of >15 mg Fe/g dw transfused sickle cell disease. LIC, liver iron concentration; dw, dry weight; AUC, area under the curve.