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Prevalence and predictors of cardiac and liver iron overload in patients with thalassemia: A multicenter study based on real-world data

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ABSTRACT

Prevalence of cardiac and liver iron overload in patients with thalassemia in real-world practice may vary among different regions especially in the era of widely-used iron chelation therapy. The aim of this study was to determine the prevalence of cardiac and liver iron overload in and the management patterns of patients with thalassemia in real-world practice in Thailand. We established a multicenter registry for patients with thalassemia who underwent magnetic resonance imaging (MRI) as part of their clinical evaluation. All enrolled patients underwent cardiac and liver MRI for assessment of iron overload. There were a total of 405 patients enrolled in this study. The mean age of patients was 18.8 ± 12.5 years and 46.7% were male. Two hundred ninety-six (73.1%) of patients received regular blood transfusion. Prevalence of cardiac iron overload (CIO) and liver iron overload (LIO) was 5.2% and 56.8%, respectively. Independent predictors for iron overload from laboratory information were serum ferritin and transaminase for both CIO and LIO. Serum ferritin can be used as a screening tool to rule-out CIO and to diagnose LIO. Iron chelation therapy was given in 74.6%; 15.3% as a combination therapy.

1. Introduction

Thalassemia is the most common cause of iron overload in many countries. In Thailand, the prevalence of thalassemia is approximately 1% or 500,000 cases [1]. Ineffective erythropoiesis, which results in abnormal iron metabolism, and blood transfusion together lead to iron accumulation in several organs, resulting in organ dysfunction and serious complications like liver dysfunction, heart failure and endocrine abnormality - especially in patients with regular blood transfusion [2,3]. Iron overload of the heart is the leading cause of death in patients with thalassemia [4]. Estimation of iron accumulation within the body and an understanding of iron kinetics is essential in the management of thalassemia patients [2,5]. Iron overload in the liver is more common than cardiac iron overload and liver overload begins earlier in the course of the disease [6]. Serum ferritin is commonly used to reflect total body iron stores, is easy to use, and is inexpensive. However, there are some disadvantages, including increased serum ferritin with inflammation, decrease serum ferritin with ascorbate deficiency, and a

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variable or nonlinear relationship between serum ferritin level and iron overload [7].

Magnetic resonance imaging (MRI) has been proposed as a better method for assessing body iron overload especially in the liver and the heart [8–10]. MRI has been incorporated into many standard practice guidelines for management of patients with thalassemia [7,11]. MRI can also be used as a guide for adjusting iron chelation therapy regimen [12–14]. Survival of patients with thalassemia is significantly improved with iron chelation treatment [15]. Since the development and introduction of iron chelation therapy, most patients with thalassemia were now treated early in the course of their disease, which has helped to prevent complications associated with iron overload [16,17]. Diagnosis of liver and cardiac iron overload in Southeast Asia is has previously been based on patient clinical information plus serum ferritin level. Although MRI has been used in clinical trials, this may not accurately reflect real-world prevalence or outcomes. As such, information regarding the prevalence of iron overload in clinical practice in Southeast Asia is limited. As such, the aim of this study was to determine the prevalence and predictors of hepatic and cardiac iron overload and the management patterns of patients with thalassemia in real-world practice in Thailand.

2. Materials and methods

2.1. Study patients

We studied thalassemia patients aged 8 years or older who were referred for liver and cardiac MRI for assessment of iron overload. A total of 8 hospitals located across Thailand participated in this study. Five out of 8 participating hospitals had MRI systems. The 3 remaining sites without MRI referred cases to a research site which is one of the participating hospitals with an MRI system. This study was approved by the institutional review boards of all participating centers and written informed consent was obtained from all participants prior to their enrollment in this study. MRI scans were performed during the 2011 to 2015 study period. Patients were excluded if they were 1) unable or unwilling to provide informed consent; 2) unable to have MRI assessment of heart and liver iron accumulation; 3) unwilling to share clinical data; or 4) pregnant.

2.2. Clinical information and laboratory data

The following clinical information were collected and recorded: 1) demographic information; 2) height and weight; 3) medical history; 4) transfusion history; 5) medications; and, 6) chelation treatment. The following laboratory data (within 6 months) were collected and recorded: 1) hematocrit and blood cell count including differential; 2) blood chemistry, including fasting plasma glucose, creatinine, and liver function test; and, 3) serum ferritin.

2.3. MRI protocol

The main center at Siriraj Hospital in Bangkok and 3 of the other 4 participating sites used a 1.5 T Philips Achieva XR Quasar Dual Gradient System (Philips Medical Systems, Best, The Netherlands). The fifth participating site used 1.5 T Siemens Aera System (Siemens AG, Munich, Germany).

The image acquisition started with cardiac exam, followed by liver exam. For examination of heart anatomy, the conventional black blood or inversion recovery pulse sequence was performed. Cine images were then obtained to study cardiac function. For iron study of the heart, the patient was scanned with the black-blood technique [18] which uses cardiac-gated multi-echo fast gradient sequence to acquire images within a single breath-hold time. An additional double inversion recovery pre-pulse was used to null the blood signal in the cardiac chamber. Images were acquired during diastole in a single mid-ventricular short-axis slice with a slice thickness of 10 mm. Imaging parameters were a TR of 19 msec, 8 echo times from 2.6 to 16.7 msec with 2.0 msec steps, a matrix of 128 × 256, and field of view of 40 cm, which generated a voxel size of 3.1 × 1.6 × 10 mm^3. Inversion time (TI) was set to suppress the blood signal.

MRI scan of the liver was performed at the mid-hepatic slice with a multi-echo fast gradient-recalled echo sequence, which was acquired within a single breath-hold. Imaging parameters were repetition time (TR) of 80 msec, 20 echo times (1.1–16.3 msec with 0.8 msec increments), slice thickness of 10 mm, flip angle of 20 degrees, and field-of-view (FOV) of 40 cm, which yielded a voxel size of 3.1 × 1.6 × 10 mm^3. Due to a limitation associated with MRI acquisition, the maximum measurable R2* was approximately 1308 Hz, which is the reciprocal of the minimum TE used divided by 1.4, corresponding to a liver iron concentration of 33.4 mg/g dry weight [19].

2.4. Analysis of MRI

T2* images was analyzed by software developed from MATLAB software tool (The MathWorks, Inc., Natick, MA, USA) [18]. All myocardial T2* data were fit to a monoexponential curve without truncation or offset correction. Regions of interest (ROI) were defined manually from the interventricular septal region using a previously reported method [18]. Analysis was performed by MRI technologists with high experience in cardiac MRI. T2* results were reported using the median values of T2* which has been shown to be more precise than a mean value [18].

Liver iron overload was analyzed by an R2* which was measured by manually defining an ROI from the whole area of liver after excluding the major vessels. The liver data were offset corrected. A median value of R2* was reported. Liver iron concentration (LIC) was calculated using the formula described in an earlier report [20].

We have shown that intra- and inter-observer variability had a bias of 0.01 and 0.04 msec and a coefficient of variation of 1.5% and 2.4%, respectively [18]. Comparing data within site and inter-site measurement had a good reliability [21,22].

Cardiac iron status was divided into 3 groups according to T2*:, > 20 msec = no or minimal iron overload; > 10–20 msec = mild to moderate iron overload; and ≤ 10 msec = severe iron overload [6]. Liver iron status was divided into 4 groups, as follows: ≤ 3 = no iron overload; more than 3–7 mg/g dw = minimal iron overload; more than 7–15 mg/g dw = mild to moderate iron overload; and > 15 mg/g dw = severe iron overload [23]. For dichotomous comparisons, Iron overload of heart was defined as T2* ≤ 20 msec and iron overload of the liver was defined as LIC > 7 mg/g dw [6,24,25]. Patients were also classified into transfusion-dependent thalassemia (TDT) for patients who received regular transfusion and non-transfusion-dependent thalassemia (NTDT) for those who did not require regular transfusion.

2.5. Statistical analysis

Continuous data were compared by the Student's *t*-test for unpaired variables and are presented as mean ± standard deviation. Categorical data were compared by chi-square test or Fisher's exact test and are shown as number and percentages. Univariate and multivariate logistic regression analysis was performed to identify predictors for iron overload. A *p*-value of < 0.05 was regarded as being statistically significant.

3. Results

3.1. Prevalence of iron overload

A total of 405 patients were enrolled in this study. The mean age of patients was 18.8 ± 12.5 years and 46.7% were male. Overall, 21 patients (5.2%) had cardiac iron overload and 230 patients (56.8%) had

Table 1
Baseline characteristics in relation to cardiac and liver iron overload status.

Variables	All	Cardiac iron overload (n = 21)	No cardiac iron overload (n = 384)	P value	Liver iron overload (n = 230)	No liver iron overload (n = 175)	P value
Age (year)	18.8 ± 12.5	21.7 ± 6.1	18.6 ± 12.7	0.274	18.6 ± 11.0	19.1 ± 14.2	0.683
Male gender	189 (46.7)	8 (38.1)	181 (47.1)	0.419	116 (50.4)	73 (41.7)	0.081
Height (centimeter)	149.6 ± 14.8	158.9 ± 8.6	149.1 ± 14.9	< 0.001	149.8 ± 14.9	149.4 ± 14.8	0.758
Weight (kilogram)	42.6 ± 12.9	48.3 ± 7.9	42.3 ± 13.0	0.003	42.1 ± 12.0	43.2 ± 13.9	0.402
Clinical diagnosis				0.007			0.003
β – thalassemia major	35 (8.6)	6 (28.6)	29 (7.6)		22 (9.6)	13 (7.4)	
β – thalassemia HbE	296 (73.1)	11 (52.4)	285 (74.2)		179 (77.8)	117 (66.9)	
Others	74 (18.3)	4 (19.0)	70 (18.2)		29 (12.6)	45 (25.7)	
Age at diagnosis (year)	5.4 ± 11.7	1.3 ± 0.9	5.7 ± 12.0	< 0.001	4.0 ± 9.3	7.3 ± 14.1	0.008
Age at 1st transfusion (year)	3.9 ± 5.3	1.7 ± 1.2	4.1 ± 5.4	< 0.001	3.6 ± 5.2	4.4 ± 5.4	0.136
Type of blood transfusion				0.212			< 0.001
None	48 (11.9)	0	48 (12.5)		12 (5.2)	36 (20.6)	
Occasional	61 (15.1)	3 (14.3)	58 (15.1)		33 (14.3)	28 (16.0)	
Regular	296 (73.1)	18 (85.7)	278 (72.4)		185 (80.4)	111 (63.4)	
Total transfusion in 1 year (milliliter/kg)	156.0 ± 78.0	188.4 ± 68.0	153.7 ± 78.2	0.054	148.0 ± 83.2	169.6 ± 66.0	0.013
Average pre-transfusion Hb level (gram%)	8.5 ± 1.1	8.4 ± 1.6	8.5 ± 1.1	0.865	8.2 ± 1.2	8.8 ± 0.8	< 0.001
History of heart failure	9 (2.2)	0	9 (2.3)	1.0	5 (2.2)	4 (2.3)	1.0
History of cardiac dysfunction	12 (3.0)	0	12 (3.1)	1.0	5 (2.2)	7 (4.0)	0.283
History of elevated ALT more than twice upper limit	38 (9.4)	3 (14.3)	35 (9.1)	0.433	32 (13.9)	6 (3.4)	< 0.001
History of splenectomy	80 (19.8)	9 (42.9)	71 (18.5)	0.011	60 (26.1)	20 (11.4)	< 0.001

Values are expressed as mean ± SD or number (%).
ALT = alanine aminotransferase, Hb = hemoglobin.

liver iron overload. The proportion in each cardiac iron status were as follows: cardiac T2* > 20, 10–20 and ≤ 10 msec in 384 (94.8%), 11 (2.7%) and 10 (2.5%), respectively. LIC ≤ 3, 3–7, 7–15, and > 15 mg/g dw were detected in 76 (18.8%), 99 (24.4%), 109 (26.9%) and 121 (29.9%), respectively. Ten patients (2.5%) were classified as having severe cardiac iron overload or T2* less than 10 msec and 121 patients (29.9%) were classified as having severe liver iron overload or LIC more than 15 mg/g dw. All patients with cardiac iron overload also had liver iron overload.

Baseline characteristics of the whole study population and patients with and without cardiac and liver iron overload are shown in Table 1. Patients with cardiac iron overload (CIO) had a higher height and weight; greater proportion of beta-thalassemia major; earlier age of diagnosis; earlier age of first transfusion; greater proportion of splenectomy; and tended to have more blood transfusion – all as compared to those without CIO. Patients with liver iron overload (LIO) had a greater proportion of beta-thalassemia major; earlier age of diagnosis; more regular transfusion, but less amount of blood transfusion; lower pre-transfusion Hb level; greater proportion of splenectomy, and greater amount of alanine aminotransferase (ALT) elevation – all as compared to those without LIO.

Among patients who were enrolled, 35 (8.6%) were β thalassemia major, 296 (73.1%) were Eβ thalassemia, 6 (1.5%) were β thalassemia intermedia, 35 (8.6%) were HbH disease, and 33 (8.2%) were other subtypes. Prevalence of CIO was 17.1% for β thalassemia major, 3.7%, for Eβ thalassemia, 4.9% for β thalassemia intermedia and HbH disease, and 6.1% for other subtypes whereas prevalence of LIO was 62.9% for β thalassemia major, 60.5%, for Eβ thalassemia, 36.6% for β thalassemia intermedia and HbH disease, and 42.4% for other subtypes. Patients were classified as TDT in 296 patients (73.1% and NTDT in 109 patients (26.9%). Prevalence of CIO was 6.1% and 2.8% for TDT and NTDT respectively. For LIO, the prevalence was 62.5% and 41.3% for TDT and NTDT.

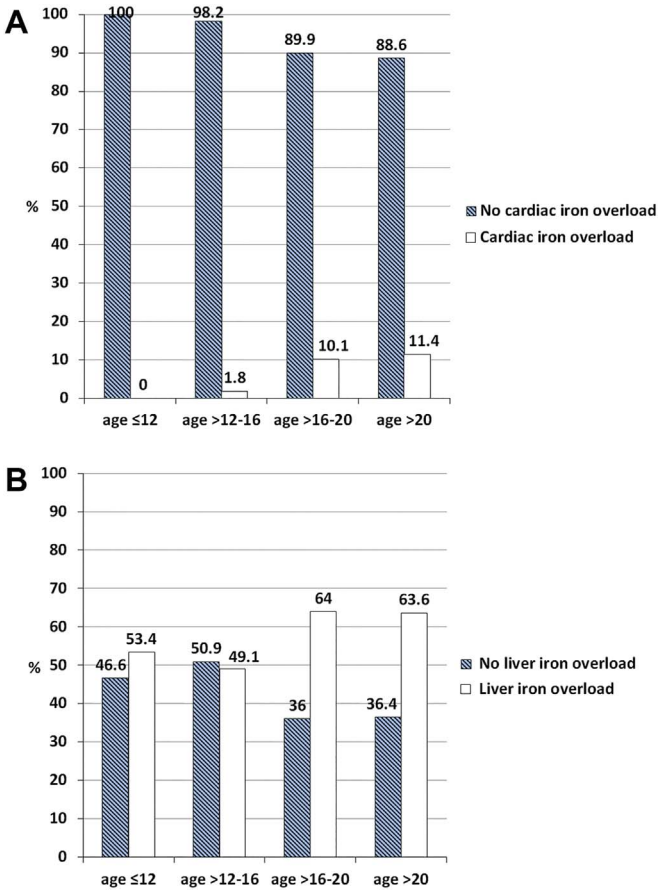

Fig. 1. Prevalence of cardiac (A) and liver (B) iron overload stratified by age group.

3.2. Predictors of iron overload

Prevalence of CIO significantly increased with age (p < 0.001) as shown in Fig. 1A. An age-related trend was also identified for LIO (p = 0.078) but the association did not achieve statistical significance (Fig. 1B). Fig. 2 displays the probability of CIO as a function of age in our study population compared to a historical reference [26]. The Odds ratio was 1.25. The earliest age of the detection of CIO in our study was 13 years. No-gender-related association was observed for either cardiac

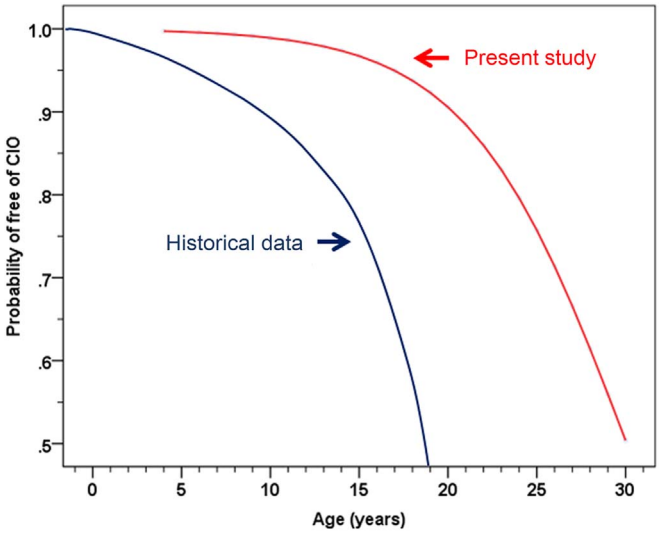

Fig. 2. Probability of free from cardiac iron overload as a function of age of the present study compared to historical data [26].

or liver iron overload. For CIO, there was a trend toward a greater prevalence in the TDT group than the NTDT group. The failure to achieve statistical significance ($p = 0.180$) was likely due to the low prevalence of CIO. Prevalence of LIO in the TDT group was significantly greater than in the NTDT group ($p < 0.001$).

Laboratory results are shown in Table 2. Baseline serum ferritin and hematocrit were 2318 ± 2376 (mcg/L) and 27.2 ± 4.5% respectively. Patients with CIO and LIO had a higher level of serum ferritin transaminase, as compared to those without CIO and LIO. Iron chelation treatments and regimen are shown in Table 3. A greater proportion of patients with CIO and LIO received iron chelation treatment compared to those without CIO and LIO. Additional analysis was performed on the association of the use of the 3 available iron chelation therapy, deferoxamine (DFO), deferasirox (DFX), and deferiprone (DFP) and CIO and LIO. Use of DFO is associated with an increased risk of CIO (10.2% vs 4.5%, OR 2.37 95%CI 0.95–5.91, $p = 0.057$) and LIO (72.7% vs 56.2%, OR 2.07 95%CI 1.27–3.37, $p = 0.003$). Use of DFX is associated with an increased risk of CIO (13.0% vs 5.1%, OR 2.79 95%CI 1.12–6.93, $p = 0.022$) but a lower risk of LIO (36.2% vs 71.1%, OR 0.23 95%CI 0.13–0.41, $p < 0.001$). Use of DFP is associated with a lower risk of CIO (2.6% vs 11.2%, OR 0.22 95%CI 0.07–0.65, $p = 0.003$) but no effect on LIO (66.4% vs 59.9%, OR 1.33 95%CI 0.83–2.12, $p = 0.234$).

Serum ferritin significantly correlated with cardiac T2* ($r = 0.461$, $p < 0.001$) and LIC ($r = 0.612$, $p < 0.001$) but the correlation with LIC is better than cardiac T2*. The correlation of serum ferritin level and cardiac T2* in patients with TDT ($r = 0.479$, $p < 0.001$) is better than NTDT ($r = 0.375$, $p < 0.001$) but the correlation of serum ferritin and LIC is at a similar level between TDT ($r = 0.596$, $p < 0.001$) and NTDT ($r = 0.615$, $p < 0.001$). Data from our study indicate that serum ferritin is a good screening tool to rule out CIO and to rule in (or diagnose) LIO. The serum ferritin level less than 2500 mcg/l in TDT and 3000 mcg/l in NTDT can be used to rule out CIO and level of 2000 mcg/l in TDT and 850 mcg/l in NTDT can be used to diagnose LIO. It is not good for the diagnosis of CIO.

Results of multivariate analysis for independent factors associated with CIO and LIO based on clinical information and laboratory results are shown in Table 4. Using only clinical information, history of splenectomy was the strongest predictor for CIO and LIO. Amount of blood transfusion and height were also the predicting factor for CIO. If we add laboratory results, serum ferritin was the strongest predictor for CIO and LIO. Transaminase was also the predictor for CIO and LIO. When multivariate analysis was performed separately for TDT and NTDT, the results were similar but splenectomy remained in the final equation both for clinical information and when combined with laboratory data for TDT but splenectomy was not in the final equation anymore for NTDT.

4. Discussion

This study found prevalence rates of cardiac and liver iron overload in real-world practice of 5.2% and 56.8%, respectively. Factors that were strongly associated with CIO and LIO were history of splenectomy from a clinical history and serum ferritin from laboratory investigation.

The prevalence of CIO in our study was lower than data from previous reports. Carpenter et al. reported a prevalence of CIO among 3095 thalassemia patients from many centers in Europe, North America, South America, the Middle East, North Africa and Asia. They reported prevalence of CIO of 53% in Southeast Asia, 47% in Europe and 30% in North America from an international survey during 2001–2008 in 2915 patients worldwide [27]. Data from Italian registry showed a prevalence of CIO of 21.4% from data collection 2006–2007 [28]. Investigators of CORDELIA study reported a prevalence of CIO of 40.9% and 45.9% among 203 Far East and 259 Western population with the data collection from 2008 to 2012 [29].

However, these studies are quite difficult to compare. For example, the screening cohort from CORDELIA study was heavily biased toward patients with expected liver iron, thus their average liver iron was nearly double the value in our study. Patients in the Italian registry were well matched to our study population with respect to LIC and

Table 2
Laboratory results of thalassemia patients within 6 months prior to MRI[a].

Variables	n	All	Cardiac iron overload ($n = 21$)	No cardiac iron overload ($n = 384$)	*P* value	Liver iron overload ($n = 230$)	No liver iron overload ($n = 175$)	*P* value
Serum ferritin (ng/ml)	390	2318.4 ± 2376.0	6388.0 ± 3921.2	2086.8 ± 2032.9	< 0.001	3096.6 ± 2732.2	1300.8 ± 1207	< 0.001
Hematocrit (%)	398	27.2 ± 4.5	27.0 ± 4.3	27.2 ± 4.5	0.792	26.2 ± 4.4	28.6 ± 4.3	< 0.001
Hemoglobin (g/dl)	397	8.7 ± 1.5	8.7 ± 1.7	8.7 ± 1.5	0.977	8.4 ± 1.5	9.1 ± 1.5	< 0.001
WBC ($\times 10^3/\mu l$)	396	11.1 ± 12.9	12.6 ± 9.4	11.0 ± 13.1	0.600	12.8 ± 16.3	8.9 ± 5.5	0.001
Platelet count ($\times 10^3/\mu l$)	397	354.0 ± 195.7	372.7 ± 203.3	353.0 ± 195.4	0.653	342.3 ± 200.7	369.2 ± 188.4	0.174
FPG (mg/dl)	117	94.9 ± 25.9	124.2 ± 63.1	92.7 ± 19.9	0.202	97.2 ± 29.1	91.9 ± 20.8	0.275
BUN (mg/dl)	262	13.3 ± 7.1	16.1 ± 11.8	13.2 ± 6.8	0.435	13.9 ± 9.0	12.7 ± 3.8	0.146
Creatinine (mg/dl)	275	0.6 ± 0.7	0.7 ± 0.5	0.6 ± 0.7	0.756	0.7 ± 0.9	0.6 ± 0.2	0.404
AST (U/L)	372	33.9 ± 23.4	53.8 ± 35.0	32.8 ± 22.2	0.015	40.7 ± 26.6	25.6 ± 15.2	< 0.001
ALT (U/L)	373	33.1 ± 37.6	59.2 ± 34.3	31.7 ± 37.2	0.001	43.8 ± 44.5	20.0 ± 20.1	< 0.001
Total bilirubin (mg/dl)	358	2.4 ± 1.6	1.5 ± 0.9	2.4 ± 1.6	0.015	2.4 ± 1.5	2.4 ± 1.6	0.985
Direct bilirubin (mg/dl)	358	0.6 ± 0.6	0.4 ± 0.3	0.6 ± 0.7	0.18	0.6 ± 0.6	0.5 ± 0.7	0.424

n = number of patients with available laboratory data.
WBC = white blood cell count, FPG = fasting plasma glucose, BUN = blood urea nitrogen, AST = aspartate aminotransferase, ALT = alanine aminotransferase.
[a] Based on the last laboratory results within the past 6 months.

Table 3
Medications and chelation therapy prescribed for thalassemia patients.

Variables	All	Cardiac iron overload (n = 21)	No cardiac iron overload (n = 384)	P value	Liver iron overload (n = 230)	No liver iron overload (n = 175)	P value
Cardiac	40 (9.9)	3 (14.3)	37 (9.6)	0.450	26 (11.3)	14 (8.0)	0.270
Endocrine	29 (7.2)	4 (19.0)	25 (6.5)	0.054	18 (7.8)	11 (6.3)	0.551
Vitamin and others	227 (56.0)	7 (33.3)	220 (57.3)	0.031	137 (59.6)	90 (51.4)	0.019
Iron chelation therapy	302 (74.6)	20 (95.2)	282 (73.4)	0.025	190 (82.6)	112 (64.0)	< 0.001
DFO	128 (31.6)	13 (61.9)	115 (40.6)	0.057	93 (48.4)	35 (31.3)	0.003
DFX	70 (17.3)	9 (42.9)	61 (21.6)	0.033	25 (13.0)	44 (39.3)	< 0.001
DFP	152 (37.5)	4 (19.0)	148 (52.3)	0.003	101 (52.6)	51 (45.5)	0.234
Combination treatment	62 (15.3)	8 (38.1)	54 (14.1)	0.008	40 (17.4)	22 (12.6)	0.182
Type of combination				< 0.001			0.342
DFO and DFP	54 (13.3)	3 (14.3)	51 (13.3)		34 (14.8)	20 (11.4)	
DFO and DFX	8 (2.0)	5 (23.8)	3 (0.8)		6 (2.6)	2 (1.1)	

DFO = deferoxamine, DFX = deferasirox, DFP = deferiprone.

Table 4
Multivariable logistic regression analysis for predictors of cardiac and liver iron overload.

Variables	Cardiac iron overload		Liver iron overload	
	OR (95% CI)	P value	OR (95% CI)	P value
From baseline clinical information				
Height	1.077 (1.032, 1.124)	0.001		
Total transfusion in 1 year	1.703 (1.153, 2.517)	0.008		
History of splenectomy	4.219 (1.409, 12.636)	0.01	3.188 (1.582, 6.424)	0.001
From clinical information and lab				
Height	1.105 (1.042, 1.173)	0.001	1.028 (1.007, 1.050)	0.008
Serum ferritin group[a]	2.992 (1.281, 6.988)	0.011	2.137 (1.685, 2.755)	< 0.001
AST	1.060 (1.021, 1.102)	0.003	1.080 (1.045, 1.116)	0.001
ALT	0.978 (0.957, 1.000)	0.051		
Total bilirubin	0.217 (0.090, 0.522)	0.001		

OR = Odds ratio, CI = confidence interval, AST = aspartate aminotransferase, ALT = alanine aminotransferase.
[a] Serum ferritin was group according to the quintile level (≤ 762.8, 762.8–1363.8, 1363.8–2053.4, 2053.4–3174.0, and > 3174.0 ng/ml).

serum ferritin, but averaged nearly a decade older than our study cohort. Given the steep relationship observed in Fig. 2, a decade longer of transfusion exposure would be expected to have a profound effect on cardiac risk.

There are many potential explanations of low prevalence of CIO in our population compared with previous reports, including differences in age, total body iron burden, transfusion rates, and differences in thalassemia genotypes. We found that prevalence of iron overload increased with age, similar to previous reports [26]. However, the risk of cardiac iron overload was right-shifted (toward older ages) compared with the data published by Wood et al. [26]. Several studies also report that CIO can develop in the first decade of life [30,31]. However, and in our study, we found no evidence of CIO among patients aged less than 12 years, despite a prevalence of LIO of 53.4% in this age group. The later age of onset could be the result of differences in disease severity, differences in transfusion practices, or improved practice guideline for the detection, prevention, and management of iron overload condition [5,7,11]. β thalassemia major had a high prevalence of CIO than other subtypes whereas prevalence of LIO was similar between β thalassemia major and Eβ thalassemia which are higher than other subtypes. TDT had a higher prevalence of CIO and LIO compared to NTDT.

One notable regional practice difference is that thalassemia patients in Thailand and other Asian countries received less intensive blood transfusion than US or Europe. The pretransfusion Hb levels are 8.5 instead of approximately 9.5 in Western countries [28]. While this practice was initially driven by demands on the blood supply, it is better tolerated because the endogenous marrow activity is more robust in Eβ thalassemia than in β_0 thalassemia. Having a lower pre-transfusion threshold stimulates more effective erythropoiesis, regenerating apotransferrin and lowering NTBI, albeit at a cost of greater ineffective erythropoiesis and iron absorption.

In fact, we propose that differences in the thalassemia genotype are the most likely explanation for the low prevalence of CIO in our study population. CIO only occurred in 11/296 patients with Eβ thalassemia (3.7%), compared with 6/35 (17.4%) in β_0 thalassemia. Since the pathogenesis of CIO is directly related to the levels of NTBI [3], this suggests that the amount or type of circulating NTBI in Eβ thalassemia is less likely to produce cardiac iron deposition. Patients with Eβ thalassemia have a more active bone marrow, which regenerates apotransferrin and should lower circulating NTBI for any given total body iron burden [2,32]. This logic also explains why TI has much lower CIO than TM.

In many ways, our patient's genetics and management of these patients creates a physiology and cardiac risk profile that is more similar to sickle cell disease [2,33] than β_0 thalassemia major patients. Previous report in patients with sickle cell disease showed that they had a low chance of developing CIO even with a high degree of iron overload [2] which correlated with a lower levels of NTBI in patients with sickle cell disease [34]. The only patients who develop cardiac iron are the ones whose liver iron or ferritin is very high and who never take their chelator or are poor compliance to the chelation treatment. Further support for this explanation comes from the following clinical and lab predictors as indicated in Tables 2 and 3 (for the data comparing patients with and without CIO): 1) Age at first transfusion (1.7 and 4.1 years in patients with and without CIO). A patient with really inactive marrow has to start transfusions within the first two years of life. 2) Total transfusion volume (159 and 149 ml/kg) for the same argument 3) Height (159 and 149 cm in patients with and without CIO) and weight (48 and 42 kg in patients with and without CIO), patients with a marrow that is effectively suppressed by transfusions expend less energy through ineffective erythropoeisis and grow better at the price of more circulating NTBI. And 4) Lower total bilirubin (1.5 and 2.4 mg/

dl). Less active marrow leads to lower endogenous RBC and less hemolysis.

The fact that prevalence of liver iron overload was higher in patients with TDT than in patients with NTDT could be attributed to the amount of blood transfusion. Independent predictors for iron overload were history of splenectomy and amount of blood transfusion from clinical information and serum ferritin and elevated transaminase from laboratory results. Elevated transaminase levels may reflect abnormal liver function induced by liver iron accumulation. Splenectomy, which is mainly performed due to the increased transfusion requirement, increased the rate of CIO and LIO probably by the removal of iron storage [2]. In our study the association of splenectomy and iron overload was stronger in patients with TDT reflecting the more iron overload in TDT and the greater need for iron storage organ in TDT to reduce the effect of iron overload in the heart and liver. This finding was supported by the earlier data that demonstrated that spleen is a major storage organ for iron in both normal and iron overload condition. After splenectomy the capacity of iron storage in the body is markedly reduced and prone to the development of cardiac and liver iron overload despite the reduction in blood transfusion [35]. Serum ferritin is an independent factors predicting CIO. However, previous reports showed that the relation of serum and CIO was not good [8] and cannot replace the need for MRI for the assessment of iron overload even in the area with limited resource [30]. Mortality in patients with thalassemia markedly decreased after the introduction of iron assessment by MRI [36]. In fact, DFP which is the most widely used chelation drug in Thailand is associated with less CIO and may explain the benefit of the drug in lowering mortality of patients with thalassemia in clinical trial [37]. The results of our study indicate an association between the use of DFP and the lower prevalence of CIO. The use of DFO is associated with an increased risk of CIO and LIO. However, the results has to be interpreted with caution since we do not have the data on the duration of the treatment prior to participation in the study and the effect of treatment on the clearance of liver iron is more rapid than the effect on the cardiac iron.

Another striking difference is the glucose abnormalities. Mean FPG is higher than normal in CIO group and tend to be higher than non CIO group (124 and 93 mg/dl). If we grouped FPG into 3 groups; < 100, 100–125 and 125 mg/dl, we will see that these 3 groups had the rate of CIO of 4.4%, 11.8% and 20% respectively. The difference was not statistically significant)($p = 0.124$) due to the small number of CIO patients. However, the finding indicates that cardiac and endocrine complication are closely related as we mentioned earlier.

This study had some limitations. First, patients in this registry were referred for cardiac MRI for clinical purposes. Most patients were being treated with iron chelation therapy and the treatment could have effect on the prevalence of iron overload. Therefore, the data may not represent the general thalassemia population. Second, although the data is represented as coming from large secondary or tertiary care centers with MRI capability, some patients in this study were referred from smaller centers with no MRI capability to large centers with MRI capability.

Lastly, it is critical to remember that cardiac disease can occur in thalassemia patients in the absence of MRI detectable iron. Patients with Eβ thalassemia are at risk for biventricular dilation and hypertrophy, pulmonary hypertension, pericarditis, myocardial fibrosis [38]. The cause is undoubtedly multifactorial including circulating labile iron [39], free hemoglobin [40], microparticles [41], and platelet-derived growth factor [42] as well as chronic hypoxia and mechanical stresses from high cardiac output [43]. Recent work in nontransfused sickle cell disease has identified a unique restrictive cardiomyopathy phenotype [44] analogous to heart failure with preserved ejection fraction, or HFPEF [45]. Since thalassemia patients have many vascular stressors, and microvascular damage is central to HFPEF pathophysiology [46], it is crucial to recognize that solving cardiac iron deposition is only one victory in the war against heart disease in thalassemia.

5. Conclusion

Prevalence of CIO was low (5.2%) in real-world practice, while the prevalence of LIO was found to be relatively high (56.8%). This finding reflects a different pattern of organ specific iron overload in the Far East population. We propose the use of serum ferritin level as a screening tool to rule out CIO and to diagnose LIO.

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Competing interests

The authors hereby declare no personal or professional conflicts of interest regarding any aspect of this study.

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