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# Multicentric cross-sectional review of blood transfusion, iron chelation therapy, T2 * MRI, and hematopoietic stem cell transplantation practices in thalassemia major patients in North India

## Abstract

**Purpose**: India has a huge burden of β thalassemia patients with an estimated 100,000 patients. Of the 10,000 to 12,000 thalassaemic babies born each year in India, very few are adequately managed even in urban areas. Aim of the study is to conduct a cross-sectional audit of Thalassemia Major patients from seven centres in North India and collecting information about blood transfusion, iron chelation, T2* MRI, and HSCT practices.

**Methods**: A total of 129 Thalassemia Major patients above 9 years of age from seven centres in North India were included. The study was conducted on 4/5/2019 and 5/5/2019 as part of a study (Fast MR study) conducted in the Cardiac-Radiology Department of AIIMS, Delhi. There were patients from 5 government hospitals (GH-113 patients) and from 2 private hospitals (PH). A pre-set questionnaire was filled.

**Results**: None of the patients at any of the centres had pre-transfusion haemoglobin between 9.5-10.5g/dl. To 15% of the patients, leukodepletion in any form was not available. Free chelation therapy was available to 74 (57.4%). Only GH5 had availability of T2 * MRI scan at their centre HSCT services are available at GH5 & PH1. A total of 57 (44.2 %) were not counselled regarding HSCT. Out of the 48.8 % who were counselled for HSCT, 73.5% HLA matching could not be done.

**Conclusion**: Developing an integrated closed referral system among centres and strict implementation of subsidized rates for tests is crucial to overcome disparities in Thalassemia patient care.

**Keywords:** thalassemia, North India, T2* MRI, HSCT, blood transfusion

Volume 10 Issue 2 - 2022

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**Received:** May 26, 2022 | **Published:** July 18, 2022

## Introduction

Thalassemia's and structural haemoglobin variants are the most common monogenic disorders worldwide. India has a huge burden with an estimated 100,000 patients with beta thalassemia syndrome and around 150,000 patients with sickle cell disease, but few of them are well managed, and allogeneic cell implants are not available in most families. In India, Thalassemia is prevalent across the country, with an average frequency of carriers being 3-4%. A higher frequency has been observed in certain communities, such as Sindhis, Punjabis, Gujaratis, Bengalis, Mahars, Kolis, Saraswats, Lohanas and Gaurs.[1]

There are estimated to be 10,000 to 12,000 babies born with thalassemia major each year in India, very few are adequately managed even in urban areas though the Government of India has included the care and management of thalassemia and sickle cell disease patients in the 12th Five Year Plan. The backbone of management of Thalassemia Major patients comprises of safe blood transfusion practices, affordable and timely initiation of iron chelation therapy, monitoring for iron overload complications (MRI T2*), and early referral and evaluation for hematopoietic stem cell transplant (HSCT). There is heterogeneity in the availability of resources and practises across various centres in North India which provide care for Thalassemia Major patients.

The Guidelines for the management of Transfusion dependent thalassemia (4th Edition - 2021) states that multidisciplinary care (MDC) should be provided with a referral system where necessary and collaboration with in-patient services. Networking with secondary centres as well as with other centres of excellence, nationally or internationally, is of added value. A twinning programme with an academic centre is also an additional advantage.[2]

So, we undertook this cross-sectional audit of patients coming to our centre for a free T2 star MRI test. The T2*MRI rapid sequence was initiated as a thesis protocol and standardized as a service for patients. We evaluated the iron overload status of patients to understand how the T2*MRI could help in management. We collected baseline information about serum ferritin, iron chelation as well as blood transfusion, and hematopoietic stem cell transplantation practices in these Thalassemia Major patients across seven centres in North India.

## Material and methods

This was a Cross-sectional audit of patients with Thalassemia Major above nine years of age from seven centres in North India. The study was conducted between August 2018 and May 2019 at the All India Institute of Medical Sciences, Delhi, after receipt of approval from the local ethical review board. A total number of 129 patients were included in the study. The government hospitals were labelled as GH, and there were patients from 5 government hospitals (GH1, GH2, GH3, GH4, GH5). The private hospitals were labelled as PH, and patients from 2 private hospitals (PH1, PH2) had come for the Fast MR study.

The patients were required to answer a pre-set questionnaire under the following headings.

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### Blood transfusion practices-

Transfusion thresholds and frequency, adverse reactions, alloimmunization, availability of leukodepletion at source, leukodepletion filters-availability & cost, Hepatitis B vaccination status, transfusion-transmitted infections.

### Iron chelation therapy practices-

Age at starting chelation, current chelation therapy, availability and cost, serum ferritin monitoring, monitoring of Iron overload-cardiovascular disease, liver disease, growth abnormalities, endocrine disease, bone disease.

### T2 * MRI practices-

Age at first MRI, availability, cost, frequency of monitoring

### HSCT practices-

HLA advised-yes or no, HLA match present or absent.

### Statistical Analysis

Categorical variables were presented as proportions, while continuous variables were either presented as mean with standard deviation (SD) or median with range. Continuous variables were analysed using independent Student's t-test or Mann – Whitney test for parametric or nonparametric data, respectively. Categorical variables were analysed using Fisher exact test or Pearson's chi-square test between two groups. ANOVA was used for comparing more than two variables for parametric test and Kruskal-Wallis for the nonparametric test. All tests were 2-tailed, P<0.05 was considered significant. SPSS version 25.0 (IBM, Armonk, NY) was used for data analysis.

## Results

A total of 129 thalassemia major patients above nine years of age were included in the study. Of them, 89 (69%) were males. Of 129 patients, 7(5.5%) were above 30 years of age, 54 (41.9%) were underweight, 67.9% of underweight patients were less than 18 years of age. 32(25%) were diagnosed between 2-6 years of age, and 6(4.7%) were diagnosed at more than six years of age. The patients were from seven different centres from north India. The maximum number of patients (113) were from government hospitals (GH), and the rest were being treated at private hospitals (PH). Baseline characteristics are summarized in Table 1.

**Table 1** Baseline characteristics of all thalassemia major patients

| Characteristics | n (%) |
|---|---|
| Male, n (%) | 89 (69.0) |
| **Age, years** | |
| 10-20 | 95 (74.2) |
| 20-30 | 26 (20.3) |
| >30 | 7 (5.5) |
| **BMI** | |
| Underweight | 54 (41.9) |
| Age <18 years | 37 (67.9) |
| Age > 18 years | 17 (32.1) |
| Normal | 74 (57.4) |
| Overweight | 1 (0.8) |
| Age | 30 years |
| **Occupation** | |
| Student | 85 (65.9) |
| Full time | 10 (7.8) |
| Part time | 13 (10.1) |
| Unemployed | 16 (12.4) |
| Left school | 5 (3.9) |
| Median number of missed days from school/work per month | 2 [range 0 - 15] (because PRBC taken at night monthly) |
| **Monthly income/month (Rupees)** | |
| **Parental income** | 106 (82.2) |
| <10,000 | 17 (15.5) |
| 10,000-24,999 | 47 (45.0) |
| 25,000-1,00,000 | 42 (39.5) |
| **Employed** | 23 (17.8) |
| <10,000 | 8 (34.7) |
| 10,000-24,999 | 11 (47.8) |
| 25,000-80,000 | 4 (17.3) |
| **Age at Diagnosis** | |
| <6 months | 17 (13.3) |
| 6 months-2 years | 73 (57.0) |
| 2 - 6 years | 32 (25.0) |
| >6 years | 6 (4.7) |
| **Primary physician** | |
| Paediatrician | 71 (55.0) |
| Medicine | 30 (23.3) |
| Haematologist | 28 (21.7) |
| **Proximity to Transfusion centre** | |
| <50 km | 82 (63.6) |
| 50-200 km | 25 (19.4) |
| Different state | 22 (17.1) |

Table 2, summarizes the blood transfusion practices across the seven hospitals. None of the patients had maintained a consistent pretransfusion haemoglobin between 9.5-10.5 g/dl. Majority of patients (84.5%) had pretransfusion haemoglobin between 7-9 g/dl. The total blood transfused in the last one year was more than 300 ml/kg in 33 patients (25.6%). Majority of patients (47.3%) had received 200-300ml/kg. Alloimmunization was not tested in 49 patients (38%). Leucodepletion at source was not available at GH2, GH3, GH4, PH2, and they were using bedside leukodepletion filters (51.9%) at a cost of 786 ± 124.5 Indian rupees (mean ± SD). PRBC was available free of cost at GH2, GH3, GH4, GH5 and was available at a cost ranging from rupees 670-5000 at GH1, PH1, PH2. Hepatitis C was positive in 24 (18.6%) patients.

Table 3 a summarizes iron chelation therapy practices across the centres. The median age at starting chelation was at 5 years. Chelation therapy was deferasirox in 63(49.2 %), and the second most common was deferasirox and deferiprone in 48 (37.5%). In GH1, deferasirox and deferiprone were used in 26 (54.2%) patients. Chelation therapy was not free in 51(39.5 %) at a cost ranging from 900-7500 rupees. Serum ferritin was more than 2500ng/ml in 61 (47.7) and less than 1000ng/ml in 18 (14.1 %). Complications of iron overload were hypothyroidism in 14 (10.9%), osteoporosis 11 (8.5%), hypogonadism 6 (4.7%), and none of the patients had diabetes mellitus.

Table 3B- Correlation between Serum ferritin values and cost of chelation. 55.7% of patients with serum ferritin values >2500ng/ml had access to free chelation therapy. 65.3% of patients with serum ferritin values between 1000-2500 ng/ml had access to free chelation.

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**Table 2** Blood transfusion practices

| Practice | Patients (n=129) | GHI (n=48) | GH2 (n=30) | GH3 (n=5) | GH4 (n=2) | GH5 (n=28) | PHI (n=14) | PH2 (n=2) |
|---|---|---|---|---|---|---|---|---|
| **Pretransfusion Haemoglobin (g/dl)** | | | | | | | | |
| <7 | 20(15.5) | 2(4.2) | 2(6.7) | 2(40.0) | 0 | 12(42.9) | 2(14.3) | 0 |
| 7-9.0 | 109(84.5) | 46(95.8) | 28(93.3) | 3(60.0) | 2(100) | 16(57.1) | 12(85.7) | 2(100) |
| 9.1-10.5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Frequency of blood transfusion** | | | | | | | | |
| <2 weekly | 11(8.5) | 4(8.3) | 0 | 1(20.0) | 0 | 5(17.9) | 1(7.1) | 0 |
| Every 2-5 weekly | 118(91.5) | 44(91.7) | 30(100) | 4(80.0) | 2(100) | 23(82.1) | 13(92.9) | 2(100) |
| **Blood transfused in last year(ml/kg)** | | | | | | | | |
| 100-200 | 35(27.1) | 14(29.2) | 7(23.3) | 2(40.0) | 0 | 12(42.9) | 0 | 0 |
| 200-300 | 61(47.3) | 22(45.8) | 19(63.3) | 1(20.0) | 2(100) | 11(39.3) | 6(42.9) | 0 |
| >300 | 33(25.6) | 12(25.0) | 4(13.3) | 2(40.0) | 0 | 17.9(28) | 8(57.1) | 2(100) |
| **Alloimm unization** | | | | | | | | |
| Not available | 49(38.0) | 20(41.7) | 2(40.0) | 2(40) | 1(50) | 0 | 0 | 0 |
| Yes | 31(24.0) | 20(66.7) | 1(20.0) | 1(20) | 1(50) | 12(42.9) | 5(35.7) | 1(50) |
| No | 49(38.0) | 21(43.8) | 2(40.0) | 2(40) | 0 | 16(57.1) | 9(64.3) | 1(50) |
| Access **to pre-storage leucodepletion?** | | | | | | | | |
| Yes | 79(61.2) | 40(83.3) | 0 | 0 | 0 | 28(100) | 11(78.6) | 0 |
| No | 50(38.7) | 8(16.7) | 30(100) | 5(100) | 2(100) | 0 | 3(21.4) | 2(100) |
| **If no pre-storage leucodepletion, using Leukodepletion filter?** | | | | | | | | |
| Yes | 26(51.9) | 1(12.5) | 14(46.6) | 4(80.0) | 2(100) | 0 | 3(100) | 2(100) |
| No | 20(40.4) | 7(87.5) | 11(36.6) | 0 | 0 | 0 | 0 | 0 |
| Irregular availability | 4(7.7) | 0 | 3(16.6) | 1(20.0) | 0 | 0 | 0 | 0 |
| **Mean cost (in rupees) of leukodepletion filter** | 785.96 ± 124.5 | 808.7 ± 160.3 | 755.8 ± 58.9 | 750 ± 70.7 | 700 | Not applicable | 772.7 ± 60.7 | 900 |
| **PRBC cost** | | | | | | | | |
| Free | 76(58.9) | 8(16.7) | 30(100) | 5(100) | 2(100) | 28(100) | 3(21.4) | 0 |
| Paid | 53(41.1) | 40(83.3) | 0 | 0 | 0 | 0 | 11(78.6) | 2(100) |
| Ifpaid, cost of PRBC | 1000 [670-5000] | 1000 (Cost for leucodepleted blood only) | | | | | 670 | 5000 |
| **Hepatitis B vaccination status** | | | | | | | | |
| Yes | 91(70.5) | 34(70.8) | 21(70.0) | 5(100) | 1(50) | 17(60.7) | 12(85.7) | 1(50) |
| No | 3(2.3) | 2(4.2) | 1(3.3) | 0 | 0 | 0 | 0 | 0 |
| Does not remember | 35(27.1) | 12(25.0) | 8(26.7) | 0 | 1(50) | 11(39.3) | 2(14.3) | 1(50) |

**Table 3A** Iron chelation practices

| Practices | Patients (n=129) | GHI (n=48) | GH2 (n=30) | GH3 (n=5) | GH4 (n=2) | GH5 (n=28) | PHI (n=14) |
|---|---|---|---|---|---|---|---|
| Median age at starting chelation (years) | 5 [1.5-26] | 4 [2-26] | 6.5 [1.5-21 | 5 [4-7] | 7 [4-10] | 4.5 [2-10] | 4.5 [2-10] |
| **Current Chelation therapy** | | | | | | | |
| No chelation | 3 (2.3) | 1 (2.1) | 0 | 0 | 0 | 2 (7.4) | 0 |

**Citation:** Vijayaran M, Seth T, Ganga KP. et al. Hematology & Transfusion International Journal. *Hematol Transfus Int.* 2022;10(2):49–55. DOI: 10.15406/htij.2022.10.00281

Table Continued...

| Practices | Patients (n=129) | GHI (n=48) | GH2 (n=30) | GH3 (n=5) | GH4 (n=2) | GH5 (n=28) | PHI (n=14) |
|---|---|---|---|---|---|---|---|
| Deferasirox (DFX) | 63 (49.2) | 21 (43.8) | 19(63.3) | 1(16.6) | 1(50) | 12 (44.4) | 7(50) |
| Deferiprone (DFP) | 4 (3.1) | 0 | 1 (3.3) | 0 | 0 | 0 | 3(21.4) |
| Deferoxamine (DFO) | 1 (0.8) | 0 | 1 (3.3) | 0 | 0 | 0 | 0 |
| DFX + DFP | 48 (37.5) | 26 (54.2) | 7(23.3) | 4(66.6) | 0 | 9 (33.3) | 2(14.3) |
| DFX + DFO | 4 (3.1) | 0 | 1(3.3) | 0 | 1(50) | 0 | 2(14.3) |
| DFP + DFO | 5 (3.9) | 0 | 0 | 1(16.6) | 0 | 4 (14.8) | 0 |
| **Availability of Chelation Free** | | | | | | | |
| Paid | 74(57.4) | 40(83.3) | 27(90) | 4(80) | 2(100) | 0 | 1(7.1) |
| Payment required for | 51(39.5) | 8(16.7) | 0 | 0 | 0 | 28(100) | 13(92.9) |
| certain chelators | 4(3.1) | 0 | 3(10) | 1(20) | 0 | 0 | 0 |
| **If paid, cost of Chelation therapy** | 3000 [900-7500] | 2000 [1000-3000] | 2500 [2000-3500] | 4000 | Not applicable, as free | 3000 [900-6000] | 3000 [1200-7500] |
| **Current serum ferritin (ng/ml)** | | | | | | | |
| <1000 | 18(14.1) | 6(12.5) | 2(6.7) | 0 | 0 | 6(22.2) | 4(28.6) |
| 1000-2500 | 49(38.3) | 25(52.1) | 10(33.3) | 2(40) | 1(50) | 7(25.9) | 2(14.3) |
| >2500 | 61(47.7) | 17(35.4) | 18(60.0) | 3(60) | 1(50) | 14(51.9) | 8(57.1) |
| Highest Serum ferritin (ng/ml) | 4000 [1100-16000] | 3000 [1100-9654] | 5776 [2120-10000] | 8900 [6500-12000] | 11500 [7000-16000] | 3625 [1200-14015] | 4000 [1700-9800] |
| **Frequency of monitoring serum ferritin** | | | | | | | |
| 3 monthly | 81(62.8) | 39(81.3) | 22(73.3) | 4(80) | 2(100) | 1(3.6) | 11(78.6) |
| 6-12 monthly | 37(28.9) | 8(16.7) | 8(26.7) | 1(20) | 0 | 17(60.7) | 3(21.4) |
| Irregularly | 11(8.5) | 1(2.1) | 0 | 0 | 0 | 10(35.7) | 0 |
| **Complications of Iron overload** | | | | | | | |
| None | 74(57.4) | 29(60.4) | 18(60) | 5(100) | 1(50) | 12(42.9) | 8(57.1) |
| Hypothyroidism | 14(10.9) | 6(12.5) | 3(10.0) | 0 | 0 | 4(14.3) | 1(7.1) |
| Diabetes Mellitus | nil | Nil | Nil | Nil | Nil | Nil | Nil |
| Hypogonadism | 6(4.7) | 2(4.2) | 1(3.3) | 0 | 0 | 3(10.7) | 0 |
| Osteoporosis | 11(8.5) | 2(4.2) | 1(3.3) | 0 | 1(50) | 4(14.3) | 2(14.3) |
| Hypoparathyroidism | nil | Nil | Nil | nil | Nil | Nil | Nil |
| Osteopenia | 3(2.3) | 1(2.1) | 0 | 0 | 0 | 1(3.6) | 1(7.1) |
| Hepatitis | 21(16.3) | 8(16.7) | 7(23.3) | 0 | 0 | 4(14.3) | 2(14.3) |

**Table 3B** Correlation between Serum ferritin values and cost of chelation

| | | Current Serum ferritin (ng/ml) | | |
|---|---|---|---|---|
| | | <1000 | 1000-2500 | >2500 |
| **Chelation Therapy n(%)** | Free | 8 (44.4%) | 32 (65.3%) | 34 (55.7%) |
| | Paid | 10 (55.6%) | 15 (30.6%) | 25 (41.0%) |
| | Payment required for certain chelator | 0 | 2 (4.1%) | 2 (3.3 %) |

Table 4 summarizes MRI T2* Therapy practices across the centres. The mean age of the first MRI was 14.91± 4.6. MRI T2* was not available at respective hospitals for 102 (79.1%) patients, and the centres were GH1, GH2, GH3, GH4, PH1, PH2. It was available at a mean ± SD cost of 5590 ± 1229.7 rupees. MRI T2* cardiac was <20 msec in 7(5.2%), between 10-20 msec in 20 (15.5%) and >20 msec in 102 (79.1%). MRI R2 * liver was <2.1 ms in 61 (47.3%) and was >17 ms in 2 (1.6%)

Figure 1 show the cardiac iron status in patients receiving deferasirox and oral combination therapy (DFX+DFP). In patients receiving DFX, 87.3% of patients had normal cardiac iron status,7.9% had mild cardiac iron overload, 3.2% had moderate grade overload, and 1.6% had severe cardiac siderosis. In patients receiving DFX with DFP, 72.9% of patients had normal cardiac iron status, 6.3% had mild cardiac iron overload, 14.6 % had moderate cardiac siderosis, and 6.3% had severe cardiac siderosis.

Table 5 summarizes HSCT practices across the centres. The median number of siblings was two (range- 0 to 9). HLA matching was not advised in 57 patients (44.2%) and was advised in 63 patients (48.8%). HLA matching was not advised in GH1 (33,68.8%), GH2(16, 53.3%). HLA match was advised but was not done in 46 (73.5%)

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**Table 4** MRI T2* Practices

| Practices | Patients (n=129) | GHI (n 48) | GH2 (n=30) | GH3 (n=5) | GH4 (n=2) | GH5 (n=28) | PHI (n=14) | PH2 (n=2) |
|---|---|---|---|---|---|---|---|---|
| Mean age at lst MRI | 14.91±4.6 | 14.06±4.3 | 13.5±2.8 | 13.4±3.2 | 16.5±4.9 | 16.1±5.8 | 18.4±5.3 | 18±2.8 |
| Median number of times MRI done before | 1[0-5] | 1.5[0-5] | 1.5[0-4] | 2[0-4] | 4[3-5] | 1[0-3] | 2[1-4] | 3[2-4] |
| **Availability of MRI T2*** | | | | | | | | |
| Yes | 27(20.9) | 0 | 0 | 0 | 0 | 27(96.4) | 0 | 0 |
| No | 102(79.1) | 48(100) | 30(100) | 5(100) | 2(100) | 1(3.6) | 14(100) | 2(100) |
| Mean cost of MRI T2* in rupees | 5590.2 ±1229.7 | 6035.7 ±951.9 | 5233.3 ±1425.1 | 4833.3 ±288.7 | 3250 ±1767.8 | 3000 | 5450 ±1141.4 | 6500 ±707.2 |
| **MRI T2* cardiac (ms)** | | | | | | | | |
| >20 | 102(79.1) | 40(83.3) | 25(83.3) | 4(80) | 2(100) | 19(67.9) | 10(71.4) | 2(100) |
| 15-20 | 8(6.2) | 2(4.2) | 4(13.3) | 1(20) | 0 | 1(3.6) | 0 | 0 |
| 10-15 | 12(9.3) | 4(8.3) | 0 | 0 | 0 | 6(21.4) | 2(14.3) | 0 |
| <10 | 7(5.4) | 2(4.2) | 1(3.3) | 0 | 0 | 2(7.1) | 2(14.3) | 0 |
| **MRI T2* Liver (ms)** | | | | | | | | |
| >17 | 2(1.6) | 2(4.2) | 0 | 0 | 0 | 0 | 0 | 0 |
| 4.5-17 | 34(26.4) | 12(25) | 6(20) | 2(40) | 1(50) | 8(28.6) | 4(28.6) | 1(50) |
| 2.1-4.4 | 32(24.8) | 12(25) | 8(26.7) | 1(20) | 0 | 8(28.6) | 2(14.3) | 1(50) |
| <2.1 | 61(47.3) | 22(45.8) | 16(53.3) | 2(40) | 1(50) | 12(42.9) | 8(57.1) | 0 |

**Table 5** HSCT Practices

| Practices | Patients (n=129) | GHI (n 48) | GH2 (n=30) | GH3 (n=5) | GH4 (n=2) | GH5 (n=28) | PHI (n=14) | PH2 (n=2) |
|---|---|---|---|---|---|---|---|---|
| Median number of siblings | 2[0-9] | 2[1-4] | 2[0-4] | 3[1-4] | 6[3-9] | 2[0-4] | 1[0-3] | 1.5[0-3] |
| **Median number of siblings affected with Thalassemia** | 0[0-4] | 0[0-1] | 0[0-2] | 0[0-1] | 2[0-4] | 0[0-1] | 0[0-1] | 0 |
| **Was HLA matching advised when <10 years of age** | | | | | | | | |
| Not applicable | | | | | | | | |
| Yes | 9(7.0) | 2(4.2) | 2(6.7) | 0 | 0 | 2(7.1) | 1(50) | 1(50) |
| No | 63(48.8) | 13(27.1) | 12(40) | 4(80) | 0 | 24(85.7) | 9(64.3) | 1(50) |
| | 57(44.2) | 33(68.8) | 16(53.3) | 1(20) | 2(100) | 2(7.1) | 3(21.4) | 0 |
| **HLA match** | | | | | | | | |
| Testing not done | 46(73.5) | 9(69.2) | 10(83.4) | 3(75.0) | 0 | 4(16.6) | 5(55.5) | 1(100) |
| Yes | 4(6.2) | 2(15.4) | 1(8.3) | 1(25) | 0 | 3(12.5) | 1(11.1) | 0 |
| No | 13(19.7) | 2(15.4) | 1(8.3) | 0 | 0 | 17(70.8) | 3(33.3) | 0 |

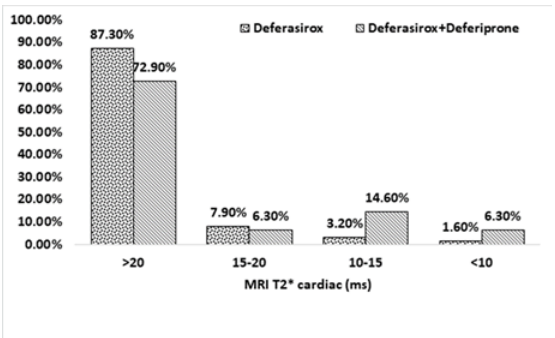


**Figure 1** Show the cardiac iron status in patients receiving deferasirox and oral combination therapy (DFX+DFP).

## Discussion

Our healthcare services are becoming increasingly strained and healthcare authorities worldwide need to invest in integrated care, particularly in the case of chronic, multi-organ diseases such as the haemoglobin disorder.

The variation in resources and practices in thalassemia management across seven centres in North India will be discussed under the following headings.

### Blood transfusion practices

None of the patients at any of the centres had a pre-transfusion haemoglobin between 9.5-10.5g/dl as per the 2021 guidelines for Transfusion Dependent Thalassemia.[2] The possible reasons for this could be irregular visits due to long distance from the transfusion centre

**Citation:** Vijayaran M, Seth T, Ganga KP. et al. Hematology & Transfusion International Journal. *Hematol Transfus Int.* 2022;10(2):49–55.
DOI: 10.15406/htij.2022.10.00281

(26.5% lived >50 km), unavailability of extended phenotypically matched red blood cells (38%), alloimmunization (24%) or lack of awareness by patient or physician.

The extended phenotypically matched red blood cells were available at GH5, PH1, PH2. In our study, 24% of patients presented with alloantibodies. Most common was Kell, followed by c and E. In a study by Ashutosh Lal,[3]it was stated that more than 25% of older children and adults with thalassemia would develop an alloantibody following one or more transfusions when red cell matching is limited to ABO/D only. This is in accordance with our study. Baseline and regular testing for antibodies is important to decrease the amount of blood transfused and henceforth important in preventing complications of iron overload. Antibody testing is the first step in thalassemia care and should be universally available. In cases requiring antibody matched blood, coordination among centres will be beneficial.

Access to leucodepletion at source was available at three centres -GH1, GH5, PH1. At the rest of the centres, leukodepletion filters were used 51 % of the time. 15% (20/129) of the patients did not receive leukodepletion in any form-the likely cause being the cost. Leukodepletion filters were available at a variable cost ranging from rupees 700 to 900. PRBC was available free of cost at GH2, GH3, GH4, GH5. At the rest of the centres, it was available at a variable cost ranging from rupees 670-5000. Hepatitis C antibody was positive in 24 (18.6%) of patients.

## Iron Chelation therapy availability and practices

Free chelation therapy was available to 74 (57.4%) patients and was available at GH1, GH2, GH3, GH4. In some hospitals having facilities for free chelation therapy, occasionally, patients had to purchase certain iron chelators due to intermittent unavailability. 55.7 % of patients with Serum ferritin values more than 2500ng/ml had access to free chelation therapy, and also 65.3% of patients with Serum ferritin values between 1000 to 2500ng/ml were receiving free chelation therapy. Despite having access to free chelation, they had suboptimal ferritin values likely due to compliance issues, side effects of iron chelators, lack of access to alternative medicines, late presentation, delay in starting chelation therapy and errors in weight-based prescription.

The chelation therapy in 63(49.2%) was DFX. DFX with DFP was the most preferred combination chelation therapy in GH1 (54.2%), GH2 (23.3%) and GH5 (33.3%), with respective percentage of patients with serum ferritin >2500ng/ml in GH1 (35.4%), GH2 (60%) and GH5 (51.9%). Multiple studies have evaluated the combination chelation therapy of DFX with DFP.[4–7] In a study conducted in 2021 on twenty-three Thalassemia major patients by Diwakar et al.[5] The combination therapy led to a significant decrease in serum ferritin values over one year. In 2015 Todari et al.[6] in their study, which included twenty-six thalassemia major patients, concluded that the oral combination was found to be safe, efficacious, and a feasible option in patients with suboptimal response to monotherapy. Elalfy *et al*.[7] in 2013, conducted a randomized open-labelled trial comparing DFP with DFO (arm 1) versus DFP with DFX (arm 2). Treatment compliance, satisfaction, improvement in QoL was significantly higher in arm 2 than in arm 1.

Similarly, in our study, DFP with DFX was the preferred combination chelation therapy being used in 37.5% versus DFP with DFO being used in 3.9% of patients. Availability of all three chelators decreases prescription inhibition for a certain chelator if indicated. It was purchased at a cost ranging from rupees 900-7500 for patients at GH5, PH1, PH2.

## Complications from iron overload

Hypothyroidism was present in 14 (10.9%) patients in our study. Eshragi *et al*.[8] studied 130 patients with thalassemia major, from which 14.6% suffered from hypothyroidism. It was 21.6% in Italy as reported by De Sanctis et al., 7% in Shiraz by Karamifar, 16% in Tabriz by Najafpour.[9-11] Hypogonadism was documented in 4.7% of male patients in our study, which is in contrast to earlier studies showing hypogonadism rates ranging from 40-70%[12-14] The possible explanation for underdiagnosing hypogonadism could be due to lack of testing facility and multidisciplinary care (endocrinologist). There is a need for referral to centers with multidisciplinary care. Osteoporosis was present in 11(8.5%) patients in our study, which is in contrast to other studies showing 25-50% suffering from osteoporosis[15-17] The low percentage in our study could be due to regular supplementation of minerals and vitamins, activity, or under reporting.

## T2* MRI availability and practices

GH1, GH2, GH3, GH4, PH1, PH2 did not have availability of T2 * MRI scans at their respective hospitals and were dependent on private diagnostic centres for the same. The charges for T2* MRI was variable, with a mean range costing rupees 5590.2±1229.7 across various diagnostic centres. There is a need for central regulation for the pricing of T2 * MRI scan costs. As per the 2021-TDT guidelines, T2* MRI cardiac and liver should be done every 1-2 years depending upon the previous cardiac T2* values. 102 (79.1%) had normal cardiac T2* MRI with values more than 20 ms, 27(20.9%) had cardiac T2* values less than 20 ms. In a study by Daar et al. (2009-2017),[18] out of ninety-nine Thalassemia major patients, 53% had cardiac T2* MRI values less than 20 ms. The median age in their study was 18 years. In 2010 Merchant et al.[19] studied sixty Thalassemia major patients, 50% had no cardiac siderosis; 33.3% had mild to moderate and while 16.7% had severe cardiac siderosis. The chelation therapy in 41 patients was single-agent deferiprone.

The lower incidence of cardiac siderosis (20.8%) could be due to the younger age group in our study and the greater use of dual anti chelation (46.5%). There were 12.6 % patients on single agent deferasirox who had cardiac siderosis. In this category of patients, a change in chelation therapy should be coupled with MRI T2* scans every 6-12 months to monitor chelation therapy adequacy, and hence affordable access to MRI T2* scan is required. Liver T2* MRI was normal in 2 patients (1.6%) while moderate to severe iron loading (<4.5 ms) was present in 82.1 %. The values are comparable to the study by Merchant et al. with 81% of patients showing moderate to severe liver iron overload.

## Hematopoietic stem cell transplantation (HSCT) availability and practices

HSCT services are not available at GH1, GH2, GH3, GH4, PH2. A total of 57 (44.2 %) were not counselled regarding HSCT. Out of the 48.8 % who were counselled for HSCT, HLA matching could not be done in 73.5 % of the patients. The most common reason for not getting HLA matching done was the cost, varying from rupees 12,000 in government centres to rupees 5,000/sibling in private labs. There is a need for implementing subsidized HLA testing at centres or easy shipping of samples to referral centres for the same, as already directed in the Ministry of health and family welfare (MOHFW), India 2018 policy for prevention and control of hemoglobinopathies.[20] In 4 (6.2%) patients, an HLA match sibling donor was present, but the patient was not transplanted.

There are many shortcomings of this study. The shortcomings of the study are a small representative number of patients from individual centres, and a questionnaire-based study would be associated with some degree of recall bias.

An easy, coordinated referral system and strict implementation of subsidized rates for tests for Thalassemia Major patients would significantly improve their outcome. This is the first study in India evaluating the lacunae in the referral system in Thalassemia Major patients. Integrated care would provide higher quality care while at the same time containing the costs.

## Conclusion

Serum Ferritin monitoring was appropriately done, and this reflects the good knowledge among doctors and patients about the need for iron chelation. Across centres, deferasirox with deferiprone was the preferred combination chelation therapy in patients with suboptimal response to monotherapy and patients with cardiac siderosis. Patients from all the seven centres had a pre-transfusion haemoglobin below the recommended cut-off of 9-10.5g/dl. The unavailability of extended phenotypically matched red blood cells at many of the centres is a major concern. There is a need for subsidizing rates and uniform pricing for leukodepletion filters, T2* MRI scan, and HLA testing in the private centres. There is an underdiagnosis of complications secondary to iron overload, especially endocrine and bone diseases. The availability of T2*MRI at government centres or alternate methods to improve access to this are required. Delayed referral to transplant centres for evaluation for HSCT was also seen. Developing integrated care, closed referral system among centres is crucial to overcome disparities in Thalassemia patient care.

## Acknowledgments

None

## Conflicts of interest

None.

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