Use of Rapid Cardiac Magnetic Resonance Imaging (rCMR) to guide chelation therapy in patients with transfusion-dependent thalassemia in India
UMIMI Study

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Introduction

In India there are over 100,000 thalassaemia patients and 17,000 homozygous births annually (1). Thalassaemia care has been designated to be of national strategic importance in India, but there are still many areas of concern, including access to diagnostics and appropriate use of chelation therapy (2). Transfusion allows survival (3), but it leads to iron accumulation and without effective chelation treatment there is a high risk of iron toxicity. (4) Transfusions in India have been available in an organized fashion for over 20 years (5) (6) and all three chelators (deferoxamine, DFO; deferiprone, DFP and deferasirox DFX) are available (7). Successful chelation can be difficult to achieve in practice and effective clinical care requires targeting therapy to those individuals most at risk (8, 9). Current practice in India relies on serum ferritin (SF) concentrations to identify iron loading; however, the correlation of SF with myocardial iron is variable (10) and over-reliance on SF is sub-optimal (9). Cardiac Magnetic Resonance (CMR) is the accepted standard for detection and management of iron loading (11),(12), but training and standardisation are needed (13). When therapy is guided by CMR T2*, a >70% reduction in mortality has been reported (14) and this CMR guided approach is routinely available in high income countries (HICs) (3), but has been underused in Low-Middle Income Countries (LMICs), including India, despite MRI scanners being widely available (15). Obstacles to uptake include lengthy scan times, high costs, a lack of training and standardisation, as well as poor integration of results into care pathways due to a lack of appreciation of the potential to reduce mortality (16).

Thalassemia ‘‘medical camps’’, where patients from local and distant centres gather over a number of days for a concentrated effort of clinical assessment, often with experts gathered together from abroad, have been employed in India, for many

years (6) and the UK investigators (JMW, EA, AA-G and JKW) have been contributors to these camps, some for more than two decades. However, this is the first time CMR scanning has been integrated into the assessments, driven by an appreciation of the historical inadequacy of clinical data available for decision making for attendees at the camps. Previously it has been demonstrated the feasibility of rapid CMR (rCMR) in LMICs using existing equipment, by undertaking up to 50 CMR scans per day (17-19). Here we exploit that experience in a study that brought together local patient advocates (the patient and family charity, Thalassemics India (TI); https://www.thalassemicsindia.org) and local Haematology leadership, supported by expertise from the UK, at 2 sites over 2 days. We assessed a care model adapted to local circumstances, which would be applicable to many LMICs. This incorporated rCMR, immediate reporting and a clinical review, with treatment recommendations based on published international guidelines.

We tested success by evidence of reduced cardiac iron, a process likely to be associated with improved outcomes, and changes in reported chelation usage.

Methods:

Ethics:

Ethical approval was obtained in 3 sites: United Kingdom - University College London - UCL REC Project ID/Title: 11255/001 and in India - Institutional Ethics Committee – Clinical Studies, New Delhi: Reg. ECR/5/Inst/DL/2013/RR-16 and in Jaipur: N – IEC/2019/01. All subjects had been referred for a clinical CMR by their haematologists. A team of six from the UK traveled to India for each visit to train/partner with local personnel, help undertake assessments and support Cardiac

Magnetic Resonance scanning which was also assisted by staff from All India Institute of Medical Science (AIIMs) New Delhi.

Patients:

Thalassaemic patients, aged over 16 and known to TI through their regular program of patient medical camps (6), were invited to attend an assessment, which was to include a MRI scan. They were sent a patient information leaflet, translated from an original approved by the ethical committees. The sample size was pragmatic, based on our previous experience and availability of local MRI scanner time (1 working day per centre: 25 patients per ½ day session). The follow-up visit was 13 months later, in January 2020.

Study Implementation:

All participants provided written consent to participation in the study (See Supplement Figure S1). Patients were requested to bring their medical records to the camp.

Demographic data, previous clinical care and medical assessments were undertaken by the local haematologists with the support of the UK visiting doctors (JMW and EA) and detailed clinical data in 6 domains was recorded using a browser-based software (REDCap – Research Electronic Data Capture) (20). The transfusion regimes for patients were assessed by history, and an estimate of the Iron loading Rate was calculated on the reported number and frequency of transfusions assuming a uniform red blood cell content (RBC) of the transfused units, ([units of blood per year]*200)/[weight]/365) (21).

All patients underwent an ECG (CardioSecur-Pro, Personal MedSystems GmbH, 60329 Frankfurt am Main, Germany) and an abbreviated CMR scan. The cardiac and liver T2* values, as well as cardiac function (LVEF) were available for the clinical

review. All patients received a written record of their results and the recommendations for treatment. Three chelation therapy options (Deferasirox (DFX), Deferipone (DFP), Desferrioxamine (DFO)), were recommended to patients, following internationally agreed standards of care (9): **Treatment option one** *1) Ejection Fraction > 60%, cardiac T2* > 20ms (no cardiac iron): No change in treatment; 2)* **Treatment option two**: *Ejection Fraction > 60%, T2*: 10 - 20ms (moderate/ mild cardiac iron overload): Increase doses of current drug or change chelator(s) to improve adherence; 3)* **Treatment option three:** *Ejection Fraction < 60% or T2* <10ms (severe cardiac iron overload); or liver T2*<2.0ms (severe liver iron overload): Recommend combination therapy at guideline recommended doses; the precise combinations to be determined by the patient's Haematologist.* See Figure 1.

All patients who attended the first clinic were invited to attend for review, where assessments were repeated. Non-attenders were contacted by telephone. Each attendee received an updated report. See Figure 1.

Abbreviated CMR protocol (rCMR): See Supplement Figure S2

The protocol (cardiac volumes, function, and cardiac/liver iron assessment) was imported and archived in each 1.5T MRI scanner under the supervision of the physicist (RB): centre 1: GE Healthcare Signa HDxt; centre 2: Siemens Avanto Syngo MR B17. The protocol included:

A. A pilot three-place localizer.
B. Pilots: 2 chamber, five slices short-axis stack.
C. Anatomy: A transverse bright blood single-shot fast spin-echo stack for anatomic evaluation (optional ungated).
D. Volume and cardiac structure assessment: four, two, three chambers and SAX cine acquisitions. Short-axis cine stack (7 mm slice thickness, 3-mm inter-slice gap.

E. Iron Assessment: Cardiac (T2*) - 1 mid SAX slice, Liver (T2*) - 1 single slice (11).

- T2*: Heart – Single breathold, gradient-echo, multi-echo scan with a series of eight echo times equally ranging from 3 to 18 ms—1.5 T (with each echo iteratively spaced by 1.5 to 2ms) (11, 22).
- T2* liver – A non-ECG-gated image was acquired in the axial orientation through the mid portion of the liver (a gradient-echo, multi-echo scan starting at 0.8–1.3 ms up to 12ms, with each echo iteratively spaced by 0.8 to 1ms).

An expert radiographer (LM) oversaw scanning, supported by local radiographers, who were trained to acquire images. Scan time was defined from the timestamp of the first image to the last image acquired.

rCMR Analysis: See Supplement Figure S2

Images were analyzed using CVI42 (Version 5·11·4 - 1559, Circle Cardiovascular Imaging Inc, Calgary, Canada).

-Cardiac function and volume: End diastolic (ED) and end systolic (ES) phases were defined as the largest and smallest long-axis ventricular volumes visually at mid ventricular level. Contiguous short-axis slices were segmented using a semi-automated thresholding technique in ED (endocardium first then epicardium) and ES (endocardium) to derive left ventricle (LV) end diastolic volume (EDV), end systolic volume (ESV), stroke volume (SV), ejection fraction (EF) and LV mass, with allometric scaling using body surface area. To address basal slice variability, blood volume was included if there was over 50% of LV myocardium surrounding blood-pool, and a long-axis atrioventricular plane correction was used. The left ventricular

outflow tract was included in the blood volume and LV papillary muscles were included as part of LV mass and excluded from the volume (11).

-T2* CMR Post-procession analysis: The post-processing CMR analysis was restricted to the septum, drawing a full-thickness ROI by limiting the epicardial and endocardial border. Liver T2* analysis was restricted to a liver parenchymal area, drawing a full-thickness ROI and avoiding the inclusion of blood vessels. A truncation method was applied to calculate iron values and discard the late “plateau” points and fit each curve to a monoexponential equation (23). Anonymized scans were reported immediately after acquisition, with reports completed by two level 3 CMR EACVI – ESC trained doctors with at least 4 years of experience in reporting CMR (K.M.M, J.B.A). Reports were made blind to the patient’s clinical status. The imaging reports were translated appropriately and incorporated into the medical records, by study administrators (TS, JKW).

Statistical Analysis:

Data were analyzed using SPSS (version 24·0, Statistical Package for the Social Sciences, International Business Machines, Inc., Armonk, New York, United States). Continuous data were expressed in mean with standard deviation and categorical data are presented as absolute numbers and percentages. Normal distribution was formally tested using Shapiro-Wilk test. Comparison of baseline and follow-up cardiac function and iron parameters were only analysed in the participants who completed the study, for this cohort, continuous data were compared using two-sided Student's t-tests and categorical variables were compared using Chi Square test or Fisher’s exact test as appropriate. Statistical significance was defined as a two-sided p value < 0·05.

Results:

1) Characterization of the study population:

One hundred three patients attended the baseline assessment, 53 at centre 1 and 50 at centre 2, (table 1). The average age was 25 years (15 – 46 years), 52% being male; 28% of patients had had a splenectomy. The prevalence of reported diabetes was 8% and thyroid disease in 13%. The average blood pressure was 116 ± 11.7 / 79 ± 9.5 mmHg, heart rate 88 ± 12.7 bpm, with normal ECGs in 60%, borderline changes of uncertain clinical significance in 33% and abnormalities in 5 patients (4.8%); these abnormalities were QTc interval >440ms in three male patients, nodal rhythm in one patient and RBBB with QRSd > 120ms in one patient; no patients were in atrial fibrillation. 9.7% of participants reported history of heart failure and other cardiac morbidity in 6.7%. 76% of patients reported having had a previous MRI scan (87% centre 1 vs 60% centre 2; p=0.002), however, scan results were available for only seven participants (7%), despite 95% having their detailed medical records at the review. The median baseline ferritin level was 1750 mcg/L (IQR 1859 mcg/l). All patients were receiving chelation therapy and average doses being taken are shown in table 1. The proportion of patients taking DFX monotherapy was higher in the centre 1 cohort (45% vs 12%, p=0.001). Combination therapy, using two chelators was similar in both centres (DFO + DFP: 6% vs 10%, p=NS; DFO + DFX: 19% vs 18%, p=NS; DFP + DFX: 19% vs 23% p=NS). Iron loading Rate was within the internationally recommended average being: 0.3 - 0.5mg/kg/day: 0.43 ± 0.1 in centre 1 vs 0.34 ± 0.1 mg/kg/g in centre 2.

2) Cardiac Magnetic Resonance Results:

All attendees were scanned without complication at both sites and both visits.

The average scanning time was 11.3 minutes ± 2.5 at the baseline and 9.8 minutes ± 2.4 (p<0·001) at follow-up. Extra-cardiac findings were common (29%) and included: small pericardial effusions in 10% of participants. Within the group of patients with a spleen, 77% had splenomegaly. Extramedullary hematopoiesis (e.g. paravertebral, retrosternal, and rib expansion location) was found in 13% of the patients. Other incidental findings were cirrhotic fibrotic liver in 1 patient (already known), remnant spleen in 2 patients, kidney cysts in 2 patients.

Baseline T2* CMR analysis was completed in 103 patients; overall cardiac T2* value was 29.2ms ± 11.9, with a mean LVEF of 64.5% ± 5.7. At the first visit, 30 patients (29%) had cardiac T2* < 20ms; 13 patients (6%) had severe cardiac iron (T2*<10ms) and 12 patients (12%) had an LVEF<60%. Seven patients (6%) had cardiac T2*<20ms plus an LVEF <60%. Between the two participant centres, the prevalence of cardiac T2* values <20ms was 21 (40%) in centre 1 vs. 9 (18%) in centre 2, p<0.02. Data is summarized in Table 2.

The mean liver T2* was 4.8ms ± 4.2; 48% had severe liver iron overload (T2*<2.2ms) and only three patients had no liver iron (T2*>17ms), with no differences between centres. Twelve healthy volunteers were scanned (six in each participant centre): overall cardiac T2* was 37.5ms ± 3.5 (37.4ms ± 3.2 for centre 1 vs 38ms ± 4.6 for centre 2, p=0.7) and LVEF of 66.6% ± 5.9 (66.4% ± 4.5 for centre 1 vs 66.9% ± 5.8 for centre 2, p= 0.1).

3) *Follow-up results:*

At 13-month follow-up visit, 86 (83%) attended; 10 patients could not attend on either of the two days offered, but were successfully contacted and clinical data obtained; none had suffered any adverse events. Six patients were lost to follow-up and one died in the follow up period; this individual had presented at the baseline exam in

overt cardiac failure attributed to iron overload and had failed to respond to intensive in-patient therapy.

The dominant change between the first and second visits was the reduction in the use of monotherapy [47(55%) vs. 39(45%), p=0.032] and increase in the use of combined oral chelators [48(43%) vs. 39(55%), p=0.002]. Figure 2 and Supplement Table S3.

The average doses used changed little: DFO (-11mg/kg/day ± 14.9, p=0.01) DFP (+2.8 mg/kg/day ± 23, p=NS) DFX (+2.5 mg/kg/day ± 9.5, p = 0.03).

For the whole group, overall average cardiac T2* and LVEF did not change significantly (cardiac T2* at 29.1ms ± 11.8 at baseline vs. 30.2ms ± 11.7 at follow-up (p=0.12) and LVEF 65.1% ± 5·3 at baseline vs. 66% ± 4.8 at follow-up (p=0.06).

The liver T2* did not change (4.8ms ± 4.2 vs. 4.9ms ± 4.5, p=0.61), (Table 3).

Twenty-one participants with clinically significant iron loading (T2*<20ms), completed both visits. Cardiac T2* increased significantly from 10.9ms ± 5.9 at baseline to 13.5ms ± 8.7 at the follow-up visit (p=0.005). Given the linearity of R2* (1/T2*) to iron concentration, this represents a 23% reduction in cardiac iron. Of the entire cohort, who completed the follow-up, cardiac T2* became normal (T2* >20ms) in seven (8%) patients and three participants (2%) with no cardiac iron overload at the first visit, became abnormal (T2*<20ms) at the second visit.

DISCUSSION:

In India ineffective transfusion, infections, and lack of appropriate chelation continue to be significant risk factors for mortality in Beta Thalassaemia (24). Cardiac MRI T2* is a key test for diagnosis, guiding therapy, and its adoption is associated with improved outcomes (5) (9). The implementation of CMR has been difficult in

countries such as India (1, 2, 16, 18, 25) impeding the delivery of optimal care. There are several barriers that block CMR delivery, including the perception by healthcare providers that it is a time consuming, expensive and intricate technique.

We did four things to make CMR more accessible and relevant to the local conditions:

1. We embedded our project in a locally organised thalassaemic medical camp.
2. We used an agreed, structured clinical evaluation, which included an MRI scan to guide therapy.
3. We implemented an average 10 minute - rCMR protocol.
4. We trained the local care providers to enable them to undertake the rCMR scans.

The UMIMI project was undertaken in two centres in India on regularly transfused TDT patients, referred for cardiac iron and clinical assessment by their local haematologists. The selection of patients was controlled by the local advocate charity Thalassemics India and was thus not a random selection within the region. All the components for the patients' clinical and imaging assessment were completed at the visit and recommendations for management were based on the result of the rCMR and discussed with the patient, with a written record for their haematologist, (Supplement Figure S4 and S5). At the follow-up visit those patients with clinically significant cardiac iron loading (T2* <20ms at baseline) had improved and the prevalence of cardiac T2*<20ms fell from 24% to 16%. No changes in LVEF were seen in this young population, which was not unexpected; it would be unusual to see changes in cardiac function in this age group (26), despite cardiac iron overload. There was only one patient in cardiac failure at the baseline visit and, despite intensive therapy, this individual did not survive to the follow up.

In this study, we embedded CMR scanning in a familiar patient medical camp scenario and found that a third of participants had cardiac iron overload and 97% of patients had liver iron. We have previously shown that CMR to assess cardiac and liver iron could be performed rapidly and less expensively in Thailand (17), India (18). However, the impact of such rapid CMR protocols on patients' therapy and tissue iron loading, has not previously been investigated. For our study, the average time of scanning was only 10 minutes with the overall time improved progressively once local radiographers gained experience (e.g., our second visit, the average scan time was 9 minutes vs. 11 minutes for the first visit).

This study represents a collaboration between the UK team, the local haematologists and the patient advocate charity (Thalassemics India) and it was felt to be unethical to include a comparable non-intervention group in this study. Patients attended the TI organized medical camp specifically to have a cardiovascular assessment. This group of TDT patients and their advocates were aware of the importance placed on CMR scans in management guidelines, and keen to avail themselves of the opportunity to access this investigation. Thus, they might represent a more motivated group than other less supported patients in India. We formally incorporated in a one-stop clinic format, the results of the CMR scans in the treatment recommendation given to each patient and made available to the local haematologists, some of whom were part of the patient camp medical team. We have not assessed whether adoption of the recommendations depended on the presence of the haematologist at the camp, or whether it was taken up equally for those patients from more remote centres.

Although note was taken of liver iron loading, the main emphasis of this study and clinical assessment was biased towards the heart. Patients with very severe liver iron loading (T2*<2.0ms) were advised to increase their chelation intensity. The lack improvement in liver iron assessed by T2* in this group may be due to the very severe nature of the liver iron loading and changes within the liver iron content being difficult to be reliably detected by our methods.

The UMIMI intervention was associated with an increase in the intensity of chelator therapy with more patients receiving combination treatment with the two oral chelators. It is highly likely that improved chelation was responsible for the improvement in cardiac T2* over a relatively short time. Subgroup analysis to establish which chelation regime provided the best response was not pre-specified and not attempted in this small group studied over such a short interval. The adoption of regular MRI scanning for T2* measurement and intensified chelation, has previously been credited with improving mortality in TDT, via improved cardiac iron loading (3) (27, 28), so that it is not unreasonable to suggest that this result in India is consistent with previous experience. Demonstrating a practical method to incorporate rCMR scanning into the routine care of thalassaemic patients in India has been achieved. The next steps require that this methodology is adopted more widely and determining if the benefit can be sustained and clinical outcomes improved.

Conclusion:

This data demonstrates that a faster and simpler CMR protocol can be successfully embedded into patients' care within the thalassaemic medical camp model in a LMIC

and that improvements in cardiac iron loading follow. In those countries where cardiac iron has been improved, there has been a demonstrable improvement in survival for TDT patients and it would be reasonable to predict similar outcomes could be achievable in India by wider adoption of this approach.

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Contributors

JMW conceptualised the study, acquired funding, collected, analysed and interpreted the data, co-wrote the article. KM collected, analysed and interpreted the data, co-wrote the article. AA-G and EA collected & analysed data. KG, VO, SP, AR and SP supported acquisition of data. RB, LMcG and NM guided the study method and acquired data. VK, AM, RB, HM and VM provided resources and supported acquisition of data. JW and ST acquired data and undertook project administration.

JM guided the study method and supported interpretation of data. All co-authors were involved in reviewing and editing the final article.

Conflict of Interest: All authors declare that there is no conflict of interest.

Data availability: Data used for the current study are all anonymized and are available to other researchers upon reasonable request and approval of the collaborative groups.

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Figure 1: UMIMI Study – Workflow and Design of the study

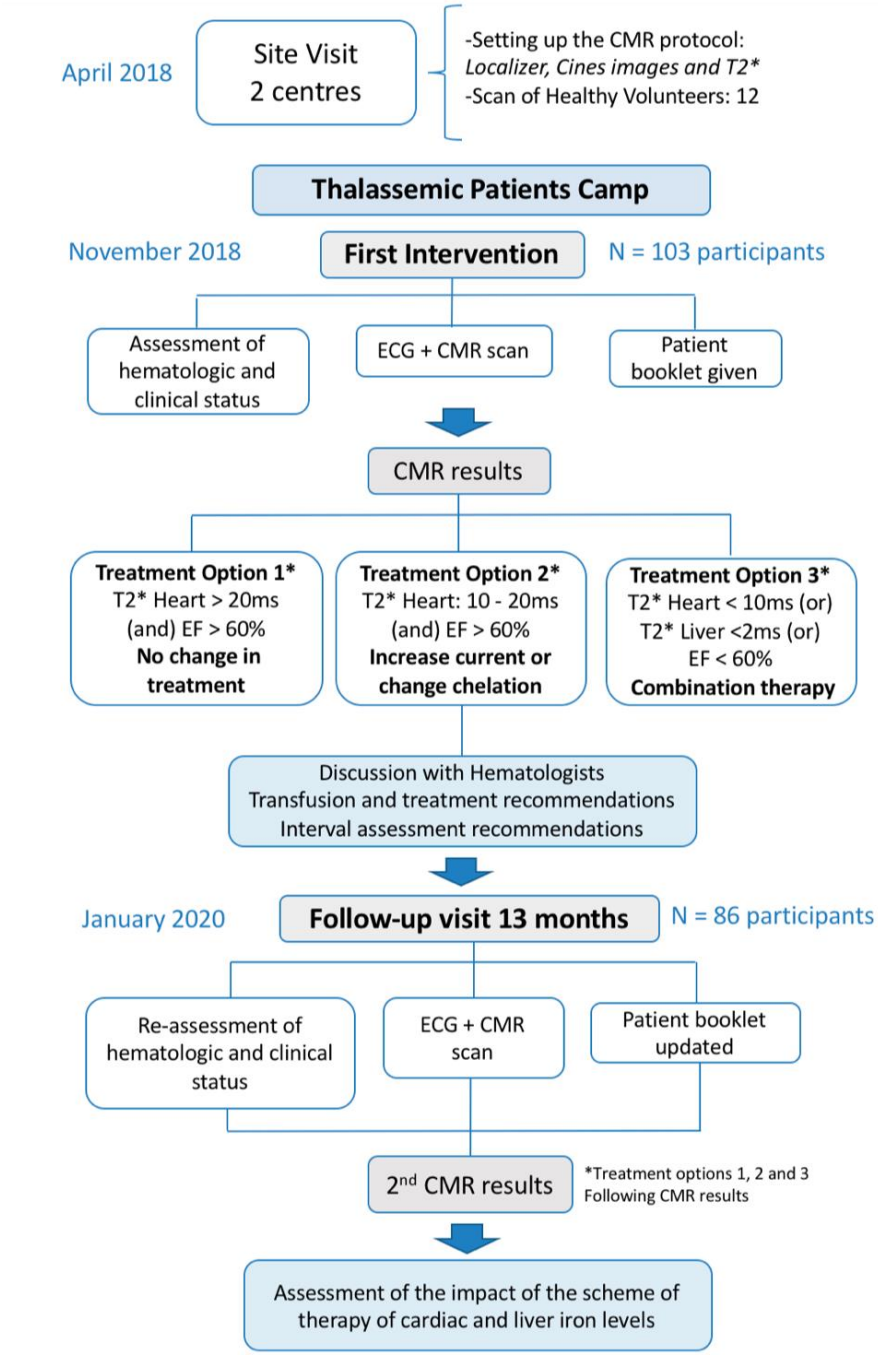

Figure 2: UMIMI Study – a) Change in Monotherapy and Dual Chelation Therapy between Baseline and Follow-up intervention (N= 86 patients) and overall changes in

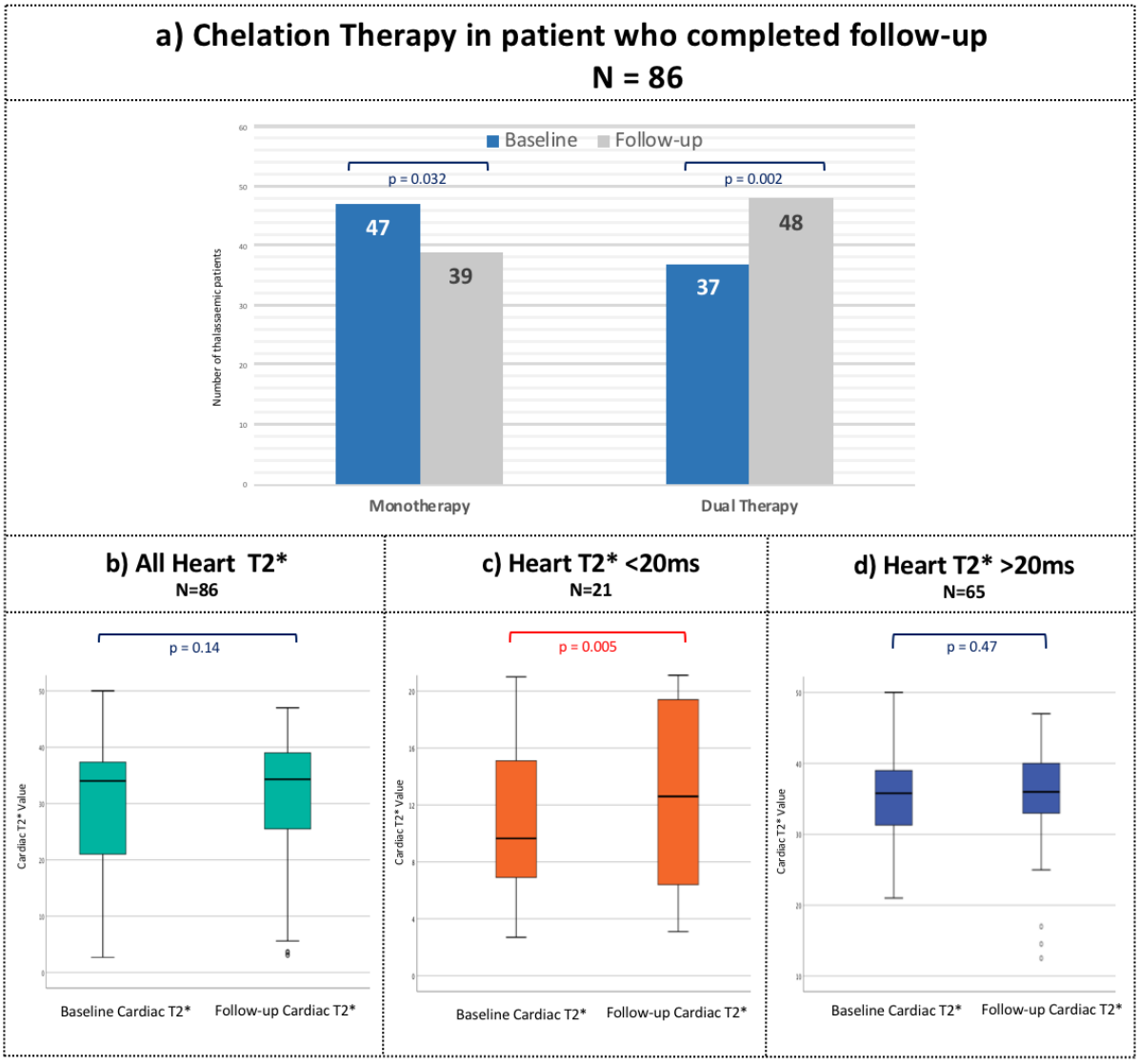

Table 1: Demographic, clinical, and CMR data – UMIMI study Baseline first visit data. SD: Standard Deviation, ECG: Electrocardiogram, MRI: Magnetic Resonance Imaging. [+]Iron Loading Rate Estimate: (([units of blood per year]*200)/[weight]/365))

Clinical Data	**Total**	**Centre 1**	**Centre 2**	**P value**
Demographic				
Total (%)	103 (100%)	53 (52%)	50 (48%)	
Age (mean ± SD)	25 ± 7	26.7 ± 6.7	23.2 ± 7	0.013
Gender male (%)	54 (52%)	30 (57%)	24 (48%)	NS
BSA (m^2) (mean ± SD)	1.49 ± 0.2	1.55 ± 0.21	1.42 ± 0.2	0.0006
Thalassemic details				
Ferritin level (ng/dl) median ± IQR	1750 ± 1859	1846 ± 2431	1700 ± 2241	NS
Diabetes, n (%)	8 (8%)	7 (13%)	1 (2%)	0.034
Thyroid, n (%)	13 (13%)	11 (20%)	2 (4%)	0.01
Normal ECG (%)	62 (60%)	33 (62%)	29 (58%)	NS
Previous Cardiac MRI (%)		6 (11%)	1 (2%)	0.001
Iron loading Rate mg/kg/day (mean ± SD)[+]	0.38 ± 0.1	0.43 ±0.1	0.34 ±0.1	0.0002
Chelation Therapy				
Desferrioxamine (DFO) n (%) *Mean dose (*32 ± 13 *mg/kg/day)*	3 (3%)	1 (2%)	2 (4%)	NS
Deferipone (DFP) n (%) *Mean dose (70* ± 25*mg/kg/day)*	22 (21%)	6 (10%)	16 (33%)	0.001
Deferasirox (DFX) n (%) *Mean dose (33* ± 9.5*mg/kg/day)*	30 (29%)	24 (45%)	6 (12%)	0.001
Combined (DFO + DFP) n (%)	8 (8%)	3 (6%)	5 (10%)	NS
Combined (DFO+ DFX) n (%)	19 (19%)	10 (19%)	9 (18%)	NS
Combined (DFP+DFX) n (%)	21 (21%)	10 (19%)	11 (23%)	NS

Table 2: Baseline Cardiac Iron and Cardiac Structure and Function Results. SD: Standard deviation, LVEF: Left Ventricle Ejection Fraction, RVEF: Right Ventricular Ejection Fraction.

CMR variable	All patients	Centre 1	Centre 2	P value
Total (%)	103 (100%)	53 (52%)	50 (48%)	
Time of scanning (min) (mean ± SD)	11.3 ± 2.5	13.2 ± 4.2	10.6 ± 2.4	<0.052
Heart T2* (ms) (mean ± SD)	29.1 ± 11.9	29.5 ± 12.1	30.8 ± 11.6	0.12
Heart T2* <20ms N (%)	30 (29%)	21 (40%)	9 (18%)	<0.02
Heart T2* <10ms N (%)	13 (6%)	8 (15%)	5 (10%)	<0.019
Liver T2* (ms) (mean ± SD)	4.8 ± 4.2	4.9 ± 4.2	4.7 ± 5.5	0.84
LVEF (%) (mean ± SD)	65 ± 4.8	65.9 ± 5	66.9 ± 4.9	0.23
RVEF (%) (mean ± SD)	67.1 ± 6.1	66.7 ± 6.9	67.6 ± 5.8	0.051

Table 3: CMR Iron Status and Left Ventricle systolic function data – comparison between basal and 13 months follow-up – UMIMI study. SD: Standard Deviation, LVEF: Left Ventricle Ejection Fraction

	Baseline	Follow-up	p value
All participants who completed follow-up N = 86			
Heart T2* (ms) (mean ± SD)	29.2 ± 11.8	30.2 ± 11.7	0.14
Heart T2* <20ms, N (%)	21 (24%)	14 (16%)	<0.001
Severe heart iron (<10ms), N (%)	10 (12%)	6 (7%)	<0.001
Liver T2* (ms) (mean ± SD)	4.8 ± 4.2	4.9 ± 4.5	0.61
LVEF (%) (mean ± SD)	65 ± 5.3	66 ± 4.8	0.06
Cardiac T2* <20ms N = 21			
Heart T2* <20ms (mean ± SD)	10.9 ± 5.9	13.5 ± 8.7	0.005
LVEF (%) (mean ± SD)	65 ± 8.1	66 ± 7.3	0.61
Cardiac T2* >20ms N = 65			
Heart T2* >20 (ms) (mean ± SD)	34.7 ± 6.4	35.4 ± 6.9	0.47
LVEF (%) (mean ± SD)	66 ± 4.2	66 ± 3.8	0.06