Establishment of a thalassaemia major quality improvement collaborative in Pakistan

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ABSTRACT

Objectives The aim of this study was to establish multidisciplinary care for patients with transfusion-dependent thalassaemia (TDT) by creating a TDT quality improvement (QI) collaborative in a resource-constrained setting. This study presents our initial experience of creating this collaborative, the baseline characteristics of the participants, the proposed QI interventions and the outcome metrics of the collaborative.

Design and setting TDT QI collaborative is a database comprising patients with TDT from four centres in Karachi, Pakistan. Study variables included symptoms of cardiac or endocrine dysfunction, physical examination including anthropometry and Tanner staging, chelation therapy, results of echocardiography, T2* cardiac MRI (CMR) and serum ferritin. The main outcome of this collaborative was improvement in TDT-related morbidity and mortality. Interventions addressing the key drivers of outcome were designed and implemented.

Results At the time of reporting, the total number of patients in this database was 295. Most patients reported cardiac symptoms corresponding to New York Heart Association class 2. Approximately half (52%, n=153) of the patients demonstrated severe myocardial iron overload (T2* <10 ms). Majority of the patients (58%, n=175) were not on adequate chelation therapy. There was no difference in echocardiographic measures of systolic and diastolic left ventricle among the different spectrums of iron overloaded myocardium.

Conclusion Using T2* CMR and endocrine testing, we have identified significant burden of iron siderosis in our patients with TDT. Lack of adequate iron load assessment and standardised management was observed. Interventions designed to target these key drivers of outcome are the unique part of this QI-based TDT registry.

What is already known on this topic?

- Transfusion-dependent thalassaemia (TDT) is associated with cardiac and endocrine complications, thus leading to increased morbidity and mortality.
- T2* cardiac MRI (CMR) is established as the gold standard technique for assessment of cardiac overload.
- Low-resource settings such as Pakistan have high burden of disease but lack standardised assessment and management protocols.

What this study adds?

- Majority of the patients at the collaborating centres had severe cardiac disease based on T2* CMR.
- Using the key driver diagram, standardised cardiac assessment and chelation protocols were established at all participating centres.
- Over the years, data from this collaborative will help standardise management guidelines among patients with TDT in our region.

INTRODUCTION

Transfusion-dependent thalassaemia (TDT), characterised by inadequate haematopoiesis,[1] is the most common inherited haemoglobinopathy in Pakistan. With a known carrier frequency of 5%–8%, at least 9000 children are born every year with TDT.[2] Although grossly underestimated, approximately 40 000 TDT cases that require chronic blood transfusions are presently registered in Pakistan.[2] It is hence important to recognise myocardial siderosis secondary to recurrent transfusions as the most common known cause of major morbidity and mortality in TDT.[3] Iron overload also puts them at risk of developing frequent endocrine complications,[4 5] impaired quality of life and decreased productivity.[6 7] Myocardial siderosis is the main cause of mortality in patients with TDT[8]; hence, timely assessment of myocardial iron overload and adequate chelation can be paramount in improving prognosis and survival in TDT.[9] However, majority[10] of children with TDT are born in low-income and middle-income countries (LMICs)[11] with limited access to advanced assessment and management protocols.[12] In Pakistan, we first initiated cardiac iron status assessment through a standardised T2* cardiac MRI (CMR) in 2014. Our preliminary data echoed available literature from the region and demonstrated over 50% of the patients in our population to have severe myocardial iron overload,[13] with at least half of these patients on inadequate chelation therapy.

The impact of iron overload-related complications on patients with TDT emphasises the need for standardised diagnostic and management protocols. We therefore created a T2* CMR-based TDT quality improvement (TDT QI) collaborative in 2016 to establish multidisciplinary care for patients with TDT across participating centres. The aim of

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this collaborative was to improve overall morbidity and mortality in patients with TDT via timely management of myocardial iron overload and endocrine complications. This study presents our initial experience of creating a TDT QI registry, description of baseline patient characteristics, key drivers of morbidity and mortality in these patients, intervention being employed to modify these key drivers, and the outcome metrics used to assess the effectiveness of interventions and eventual goal of the collaborative, that is, to decrease morbidity and morality related to iron overload in TDT.

MATERIALS AND METHODS

Characteristics of participating centres

TDT QI registry is a multicentre, collaborative database created in April 2014. It includes four centres in Karachi, Pakistan: Aga Khan University Hospital (AKUH), Fatimid Foundation (FF), Afzaal Memorial Thalassemia Foundation (AMTF) and Kashif Iqbal Thalassemia Care Center (KITCC). AKUH, the parent institute, is a tertiary-care hospital with a T2* CMR facility. It serves as the primary centre for detailed cardiac and endocrine assessment, testing and specialist appointments. FF, AMTF and KITCC are the peripheral centres where follow-up and subsequent management are done. FF has 700 registered patients with TDT, with 40% being over the age of 10 years (n=280). KITC has 560 registered cases, with 32% of cases over the age of 10 years (n=180), while AMTF has 340 registered patients, with 44% being over the age of 10 years (n=150). All our participating centres primarily cater to resource-restricted communities and provide subsidised care. Data on patients included in the registry from April 2014 to December 2016 (n=305) are presented in this manuscript.

Key driver diagram

Only those patients with TDT undergoing a T2* CMR were included. A key driver diagram (figure 1) (similar to those used in Congenital Cardiac Catheterization Project on Outcomes and the International Quality Improvement Collaborative) was constructed to develop the roadmap of the drivers and interventions that would help achieve the purpose of this collaborative.[14 15] The main aim of this collaborative was to improve morbidity and mortality of patients with TDT. The patient flow diagram has been added as figure 2. The key drivers of these outcomes and the interventions designed to modify these drivers fell into the following three main categories:

Optimising patient assessment

- Echocardiographic technique.
  - Echocardiographic assessment—Conventional and tissue Doppler echocardiographic imaging data were recorded as per standard guidelines.[12] At AKUH, Philips iE33 (Andover, Massachusetts, USA) or GE E9 (GE Healthcare, Milwaukee, Wisconsin) machine with a 5–12 MHz phased array transducer was used. GE S6 (GE Healthcare) was used at KITCC and Toshiba (SSH-lOA, Toshiba Medical Systems, Tustin, California) was used at AMTF. Systolic function was obtained from apical four-chamber and short-axis views using 5/6 × area × length method, while diastolic function was assessed using mitral E and A waves, E:A ratio, septal E' and E:E' ratios. Offline analysis with Xcelera R3.2L1 (Koninklijke Philips Electronics NV 2011) or EchoPAC PC software (GE Vingmed Ultrasound, USA) was done. Strain analysis using automated functional imaging was performed on echocardiograms (echo) done at AKUH only.[16]
  - Echocardiographic sonographers—The sonographer selected at these centres were the ones who had some basic knowledge of adult echo and had at least 6 months of experience performing independent echo. Once inducted, they rotated at the AKUH paediatric echo lab for 4 weeks to get hands-on training in performing paediatric and adult echo. Once their studies were deemed appropriate, they were allowed to scan at the peripheral centre. Quality checks were performed on these by sharing 10% of the scans on WhatsApp and during the monthly multidisciplinary clinic visit
- T2* CMR assessment—T2* CMR was only available at AKUH either free of cost or at an affordable price of US$100. All patients who were referred from the three peripheral centres were evaluated and clinically examined by physicians at the parent centre (AKUH), before they were referred for T2* CMR. Detailed T2* CMR was performed as described by Shakoor *et al*.[17 18] Myocardial iron deposition severity was categorised as T2* CMR >20 ms (normal), T2* CMR=10–20 ms (mild to moderate) and T2* CMR <10 ms (severe).[11 13]
- Anthropometric and endocrine assessment—Relevant endocrine biochemical laboratory tests were performed according to the guidelines from the International Network on Endocrine Complications in Thalassemia (I-CET) and included calcium, phosphorus, alkaline phosphatase, luteinizing hormone (LH), follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), free T4 and so on.[4] Management of each endocrine dysfunction (hypothyroidism, hypogonadism, diabetes and so on) was done as per the I-CET guidelines.[4] Anthropometry was performed for all patients using standardised calibrated weighing machines and stadiometers. Tanner staging of external genitalia, breasts (for females) and pubic hair (for males and females) was also noted, for females >13 years and males >14 years of age.[16 17]

Optimising standard management protocols

- Multidisciplinary clinics—These included haematology, cardiology and endocrinology clinics which were organised for patients with TDT at each centre on a monthly rotating basis.
- Continuing Medical Education courses—These were held monthly to disseminate knowledge of T2* CMR, endocrine disorders and evidence-based management of TDT and its complications.
- Patients with cardiac dysfunction, arrhythmias or cardiac-related symptoms were managed by a paediatric cardiologist (BSH) in close collaboration with the peripheral centres. Patients requiring intensive care management were shifted to AKUH.
- A paediatric endocrinologist (SK) also saw these patients as referral at the parent centre. Once the management plan for these patients was formalised, they were referred back to the peripheral centre and continued to be managed in consultation with SK.

Optimising standardised documentation

- Chelation therapy—Three chelation agents, namely deferoxamine (DFO), deferiprone (DFP) and deferasirox (DFX), were primarily used. Adequate chelation was defined according to the Thalassaemia International Federation

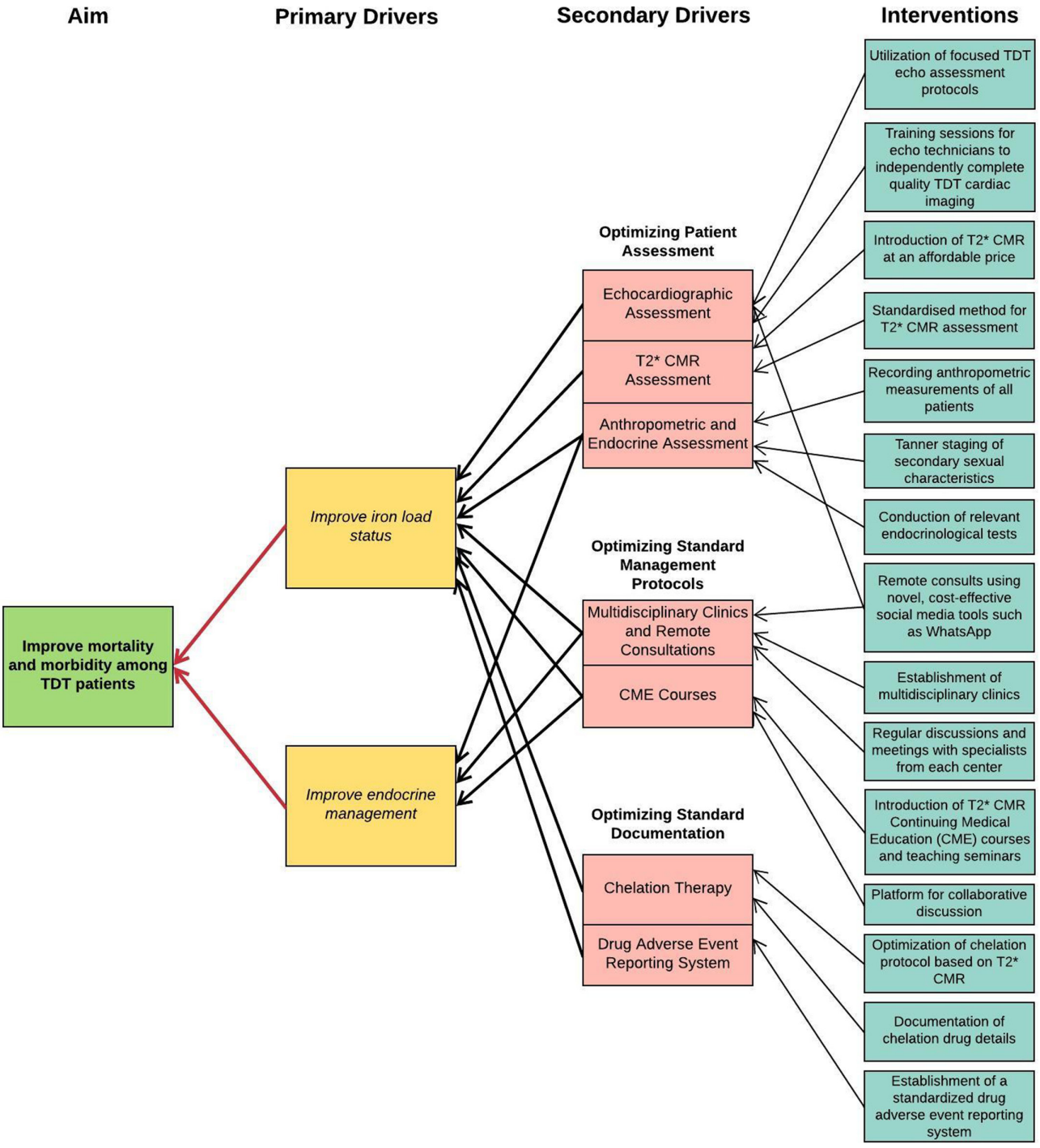

Figure 1 Key driver diagram. Echo, echocardiogram; T2* CMR, T2* cardiac MRI; TDT, transfusion-dependent thalassaemia.

(TIF) guidelines.[5] The type of chelation drug, frequency and dosage were recorded in a standardised manner across the sites.

- A standardised drug adverse event reporting system was established to track such events and share knowledge regarding its management.

Data were added to the TDT QI registry retrospectively from the patient's medical records. Study variables included anthropometry, history of medication use and blood transfusions, psychosocial history, signs and symptoms of cardiac dysfunction (including palpitations, orthopnoea, dyspnoea, syncope) or endocrine dysfunction (weight loss, cold/heat intolerance, bone pain and so on), chelation therapy, and results of echocardiography, T2* CMR, serum ferritin and biochemical endocrine laboratory tests. In order to ensure data quality, an assigned researcher performed quality checks on 10% of all forms from each centre fortnightly. Errors were identified and detailed reports were sent to each centre. Details of the interventions and process evaluation of these interventions are shown in table 1.

Data analysis

Data were analysed using SPSS V.23.0. Normality of data was assessed using histograms. Categorical variables were expressed as percentages and continuous variables were expressed as mean±SD. Differences between the three iron overload groups

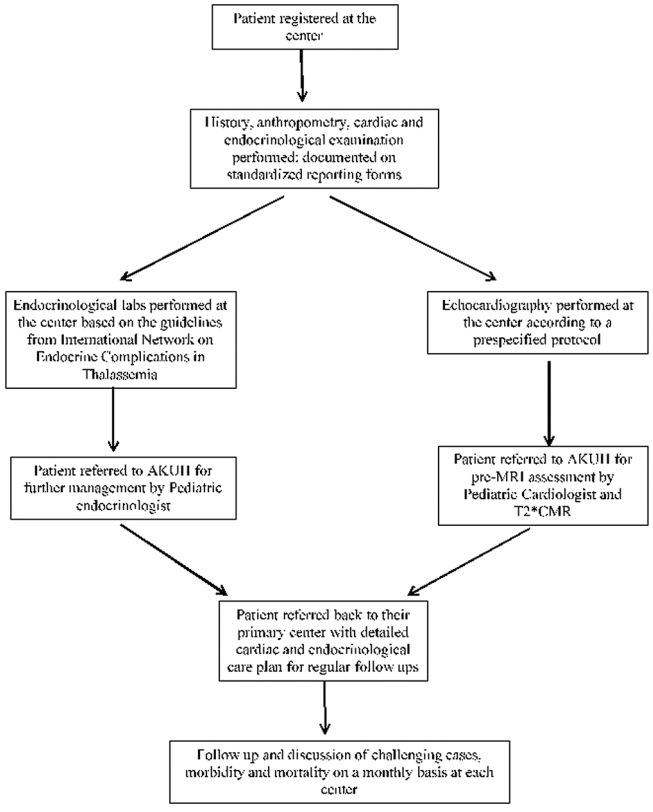

Figure 2 Patient flow diagram. AKUH, Aga Khan University Hospital; T2* CMR, T2* cardiac MRI.

(ie, normal, mild-moderate and severe) were tested using χ^2 test or Fisher's exact test for categorical variables and one-way analysis of variance for continuous variables. A p value of <0.05 was considered to be statistically significant.

RESULTS

Data from 295 patients were included in this registry during the specified time period (as mentioned above). Approximately 58% (n=172) of the patients were male. Majority of them (54.5%, n=161) were receiving treatment at AKUH, 21% (n=64) were at AMTF, 17.8% (n=53) were at FF and 8.8% (n=26) were at KITCC. Majority of the patients at each of these centres were labelled to have severe disease based on the T2* CMR (figure 3).

The main demographic and clinical characteristics of these patients are reported in table 2. The mean age of children was significantly different across the groups, with the severe T2* group being significantly older (18.6±5.8 years) than those with mild myocardial siderosis (p=0.01). Height and weight were also significantly different (p=0.04 and p=0.02, respectively) across the groups; however, body mass index did not show a significant association (p=0.07). Sixty-two per cent of the participants had stunting (n=183). Across the spectrum of the disease, most patients (21%, n=65) were in New York Heart Association (NYHA) functional class 2. Seventeen per cent of the patients (n=53) were on cardiac medications. The most commonly reported cardiac medicines in this group were a long-acting specific β1-blocker (bisoprolol) (n=35, 66%), loop diuretic (furosemide) (n=14, 26%) and amlodipine (n=5, 14%). A higher trend of hepatomegaly and splenomegaly in those with severe disease (29%, n=25, and 36%, n=55, respectively) was noted. Transfusion-related infections such as hepatitis C, hepatitis B and HIV (confirmed by serological testing) were reported to be highest in the group with severe disease. Details of the endocrine complications noted in this collaborative have been previously reported by Ehsan *et al*.[19]

At initial presentation, the mean T2* CMR was 14.8±12.1 ms. More than half of the patients (51.8%, n=153) demonstrated severe myocardial iron overload (T2* <10 ms), while mild to moderate iron overload (T2* CMR of 10–20 ms) was reported in 18.6% (n=55). Serum ferritin was reported to be statistically significant and highest in the severe disease group (6721±4839 μg/L). None of the echocardiographic parameters that assessed systolic (ie, ejection fraction) or diastolic (mitral E:A ratio or E:E' ratio) function were significantly different across the groups (refer to table 2).

The most common chelation drug used for monotherapy across all groups was DFO (48%, n=142), while a DFO and DFP combination regimen was used in 44% (n=130) of patients. Based on the TIF guidelines, approximately 40% (n=123) of patients were being adequately chelated at baseline. Although rare, the most common adverse events reported with DFP were skin rashes and itching, while diarrhoea and mouth ulcers were reported with DFP and DFX combination (2%, n=6).

DISCUSSION

This study sought to provide a detailed overview of the establishment of the TDT QI-based collaborative in a resource-limited setting. Allen *et al*[20] have recognised the difficulties in establishing reliable clinical and laboratory services for thalassaemia in resource-limited countries and have recommended QI approaches as a solution to improve care of those suffering with this disease. Further, quality initiative collaborative like ours are useful for monitoring assessment, management and clinical outcomes across different centres.[14 21]

A key driver-based approach was used to develop a conceptual roadmap of standardising patient care across the participating centres. The approach of our collaborative is similar to that of Balachandran *et al*,[15] where key drivers that impact morbidity and mortality in patients with TDT were addressed through standardising cardiac and endocrine management protocols, arranging regular educational sessions for all concerned healthcare providers, and periodic feedback to ensure compliance to assessment and management protocols. Being a low-resource setting, remote telemedicine consultation between the peripheral centre and AKUH (the tertiary-care facility) was shared free of cost, deploying user-friendly applications such as WhatsApp, which has been shown to play a critical role in revolutionising healthcare.[22] This application has been considered to be a valuable tool in enhancing learning across centres and improve patient care.[23]

The current number of cases reported in this study is considerably lower than the actual burden of patients with TDT at all participating centres. This is because we only included those patients who had T2* CMR, which has been established as the standard of care for iron overload management.[24–26] However, due to ease of availability and reduced cost, serum ferritin is often used to monitor iron overload in LMICs.[13] Using an endowment fund, the project team was able to introduce T2* CMR either free of cost or at a reduced price (US$100) at AKUH. Financial endowment has been used to address the prevention and management of HIV/AIDS epidemic globally by ensuring smooth flow of finances, hence supporting financially sustainable, long-term health interventions.[27] This reduction in cost encouraged the use of T2* CMR as the gold standard imaging modality across all participating centres.

Table 1 Process evaluation measures based on the key driver diagram

Key driver	Intervention	Process measure
Primary drivers		
Improve iron load status Improve endocrine management	► Optimising patient assessment. ► Optimising standard management protocols. ► Optimising standardised documentation.	As listed below.
Secondary drivers		
Optimising patient assessment	► Standardise echocardiographic assessment protocols. ► Training sessions for echo technicians. ► Introduction of T2* CMR. ► Anthropometric measurement. ► Performing Tanner staging. ► Conduct relevant endocrinological tests. ► Counselling.	► The echocardiographic protocol has been described. This would be performed yearly if normal function; 6 monthly if dysfunction (EF <50%); the frequency may be altered if the patient was sick or undergoing emergent chelation due to severe symptoms or progression of cardiac symptoms (as determined by cardiologist BSH). ► Monthly visit by a paediatric cardiologist at each centre to observe imaging. ► 10% of images remotely monitored using WhatApp. ► T2* CMR initiated at an affordable price at AKUH; every 2 years if T2* >20 ms and the patient is compliant; annually if T2* <20 ms or if the patient is not compliant. ► Staff at all centres were trained by the paediatric endocrinologist using standardised calibrated machines. Quality check was done during the monthly visit on 10% of the measurements. ► Tanner staging was also taught by the paediatric endocrinologist to the staff at the peripheral centres. Quality check was performed on 10% of participants during the monthly visit. ► These were decided based on the I-CET guidelines in consultation with the paediatric endocrinologist. ► Lifestyle modification education focusing especially around chelation compliance, healthy diet and exercise as tolerated was provided at each peripheral centre. This was reinforced through CME performed by AKUH at these centres.
Optimising standard management protocols	► CME courses. ► Multidisciplinary clinics and remote consultations.	► Monthly meeting to disseminate knowledge of T2* CMR and evidence-based TDT management. ► Haematology, cardiology and endocrinology multidisciplinary clinic every month. Consultation and management of complicated patients at AKUH.
Optimising standardised documentation	► Standardisation of chelation protocol. ► Standardised adverse event reporting.	► Adequate chelation was defined according to the Thalassaemia International Federation guidelines. ► Standardised documentation for reporting of adverse events. ► Quality check on complete documentation was done on 10% of the study participants fortnightly.

AKUH, Aga Khan University Hospital; CME, Continuing Medical Education; echo, echocardiogram; I-CET, International Network on Endocrine Complications in Thalassemia; T2* CMR, T2* cardiac MRI; TDT, transfusion-dependent thalassaemia.

More than 50% of our patient population demonstrated severe myocardial iron overload, which was similar to our previous work.[13] Adequate chelation can potentially reduce iron accumulation-related complications, including cardiac and endocrine.[28] The adequacy of chelation was higher in our study (42.6%) as compared with WHO reports which suggested that only up to 19.6% of individuals on regular transfusion receive adequate chelation in our region.[11] However, the preregistry protocols were based on the preference of the physicians rather than myocardial iron overload-based chelation. The collaborative would help in ensuring adequacy of chelation and assessing compliance of patients to the prescribed therapy. If iron overload persists despite compliance to adequate chelation therapy, genetic causes of lack of therapy response will need to be explored in our population.

Iron accumulation secondary to blood transfusions can lead to cardiac and endocrine complications. Most of our patients showed evidence of cardiovascular disease based on the NYHA

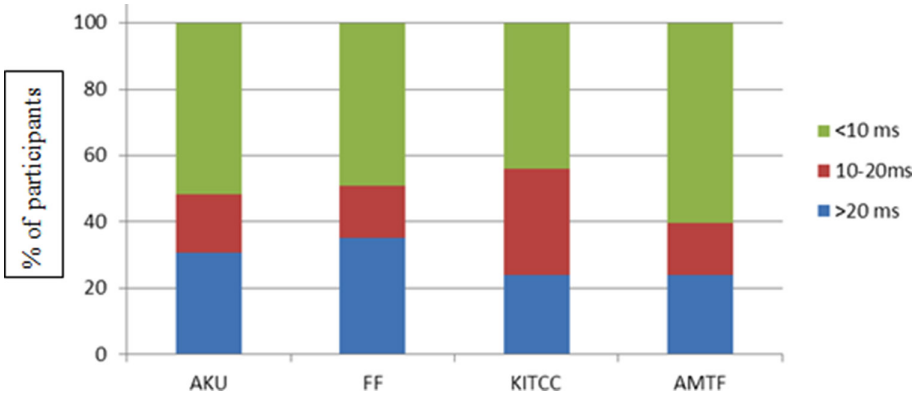

Figure 3 Burden of transfusion-dependent thalassaemia at each of the participating centre based on T2* cardiac MRI. AKU, Aga Khan University; AMTF, Afzaal Memorial Thalassemia Foundation; FF, Fatimid Foundation; KITCC, Kashif Iqbal Thalassemia Care Center.

Table 2 Demographic and clinical characteristics of patients with thalassaemia categorised based on T2* CMR

Variables	Normal T2* CMR (>20 ms) n=87, mean±SD	Mild to moderate T2* CMR (10–20 ms) n=55, mean±SD	Severe T2* CMR (<10 ms) n=153, mean±SD	P value
Age (years)	16.6±5.8	16.6±5.8	18.6±5.8	0.01
Height (cm)	147.4±19.9	138.9±12.7	142.7±18.2	0.04
Weight (kg)	39.8±15.1	33.3±10	38.1±12.6	0.02
BMI (kg/m^2)	18.1±3.3	16.5±3.4	18.1±3.8	0.07
NYHA class*				0.18
Class 1	14 (16)	7 (12)	13 (8.5)	
Class 2	19 (22)	11 (20)	34 (22)	
Class 3	0 (0)	0 (0)	5 (3)	
Class 4	0 (0)	0 (0)	3 (2)	
Hepatomegaly*	13 (15)	12 (22)	45 (29)	0.06
Splenomegaly*	23 (26)	18 (33)	55 (36)	0.35
Presence of infections*				
HBV	1 (0.01)	1 (0.02)	0 (0)	–
HCV	1 (0.01)	1 (0.02)	5 (3.2)	
HIV	2 (0.02)	2 (0.04)	1 (0.6)	
Seizures*	0 (0)	0 (0)	1 (0.7)	–
Laboratory parameters				
Ferritin (ng/mL)	4880±4982	5110±3597	6721±4839	0.02
Pretransfusion haemoglobin (g/dL)	9.2±0.7	8.9±0.6	9.4±0.7	0.33
Echocardiographic parameters				
Ejection fraction (%)	61.5±4.4	60.7±9.1	61.3±7.4	0.85
E:E′	8.6±2.4	8.1±2.0	9.1±2.2	0.07
Mitral E:A ratio	1.7±1.02	1.7±0.4	1.7±0.6	0.91
Transfusion (years)	13.07±5.9	12.2±3.4	15.8±5.8	0.01
Transfusion frequency (per month)	1.62±7.6	2.2±1.8	1.9±0.7	0.005
Chelation drugs*				0.13
DFO	31 (36)	16 (29)	73 (48)	
DFX	25 (29)	19 (34.5)	38 (25)	
DFP	8 (9)	7 (12.7)	11 (7)	

*Reported as n (%).
BMI, body mass index; DFO, deferoxamine; DFP, deferiprone DFX, deferasirox; HBV, hepatitis B virus; HCV, hepatitis C virus; NYHA, New York Heart Association; T2* CMR, T2* cardiac MRI.

classification. These findings are worrisome since cardiac failure is the leading cause of mortality among patients with TDT.[29 30] Apart from cardiac complications, little work has been done in the Pakistani TDT population with regard to endocrine complications.[31] As the presence of hypogonadism and stunting showed high sensitivity (90% and 80%, respectively) in predicting severe iron overload in our population, Tanner staging and basic anthropometry can be used as a cheap yet reliable alternative to predict severity of iron overload in resource-limited settings.[19] The documentation of signs, symptoms, laboratory parameters and medications noted in this collaborative will provide us with the ability to make meaningful interpretations regarding surrogate indicators of management of patients with TDT in our population.

While establishing a multi-institutional collaborative may have its benefits, limitations certainly exist. Participating sites often have difficulty maintaining institutional support in order to fulfil commitments regarding data collection or keep the group updated with the progress. Regular feedback using social media tools such as WhatsApp did help us address this issue to a substantial extent. Currently the number of patients getting MRI from the population at each centre is low and may not be a true representative of the centre, although we are actively recruiting more patients. The collaborative thus will keep on growing and outcome data will be shared when at least 50% of the eligible patients from each centre have had an MRI and from whom data have been collected.

TDT remains one of the leading haemoglobinopathies in our region with significant complications due to iron overload, leading to morbidity and mortality. Using the key driver diagram, the TDT QI collaborative was developed, which aims to focus on improving the quality of techniques for assessment and evaluation of iron overload secondary to blood transfusions, cardiac complications, standardisation of documentation and management, hence improving the quality of care of patients in a low-resource setting.

Contributors LE, NA, ON, AQ, SH, EH, SA, SK and BSH were involved in the initial concept and design of this study. ZH, LE, NA, FS, AA, ON, AQ, SH and EH were involved in data collection. ZH, NA, FS, AA, SA, SK and BSH were involved in quality checks for the data. ZH, NA and LE were involved in data analysis and interpretation. All authors contributed to the development and review of the final draft of the manuscript.

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