6. GLOBAL REVIEW OF MRI SERVICES FOR THALASSAEMIA TIF'S PERSPECTIVE

AUTHORS: Angastiniotis M., Eleftheriou A., & Farmakis D.

INTRODUCTION

Measuring Iron Load In Vital Organs – The Role of Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) has been widely adopted for iron quantification in vital organs, mainly the heart and the liver. In addition to assessing the distribution and grading of iron overload, this method offers the possibility to monitor treatment response and thus guide effectively iron chelation therapy. It was soon recognised as superior to biochemical methods of measuring iron overload and mainly serum ferritin, since these can be influenced by factors such as inflammation and infection and cannot be used a surrogates of cardiac iron content.

The measurement of iron in the heart by MRI was the first to be implemented. This was in response to the high mortality caused by iron overload cardiomyopathy, which results in heart failure and arrhythmias. This was the cause of both long-term morbidity and death, even in centres which offered 'adequate' iron chelation, and was identified as the cause of death in over 70% [1,2,3] of thalassaemia patients. It was also recognised that this form of cardiomyopathy is reversible when intensive iron chelation was initiated early [4]. This led to the need for early detection of iron accumulation in the heart, before heart failure is established. Direct measurement of myocardial iron was required, and the MRI technology was developed and rapidly adopted [5]. The impact on survival of early intervention by intensification of iron chelation, was soon evident [6,7] in centres where this measurement was implemented, and TIF Guidelines included the recommendation that periodic testing should be routine.

Likewise, measuring liver iron became important. The liver is the main iron storage organ (in hepatocytes and Kupffer cells) and the first to show iron overload. Importantly, it also has a linear relationship with total body iron [11]. Biopsy of liver was used by many centres, but sampling variability, small size of specimens, and the invasiveness of biopsy led to its replacement by non-invasive MRI methods [8, 9, 10]. Early detection of iron overload in the liver is important since it may lead to liver fibrosis, organ failure, cirrhosis and hepatocellular carcinoma. This imaging technique, beyond just measurements of iron load, also provides the imaging of liver pathology such as detecting liver nodules and fibrotic changes. Overall, MRI imaging and measuring iron load provides the opportunity for timely interventions, such as iron chelation intensification and follow-up of chelation therapy thus allowing for treatment fine tuning.

Practical implementation in clinical practice has demonstrated that the quality of images, and the accuracy and reproducibility of measurements varies considerably, and experts have recommended a number of steps to ensure accurate assessment of measurements, especially where hepatic iron is concerned (Figure 1).

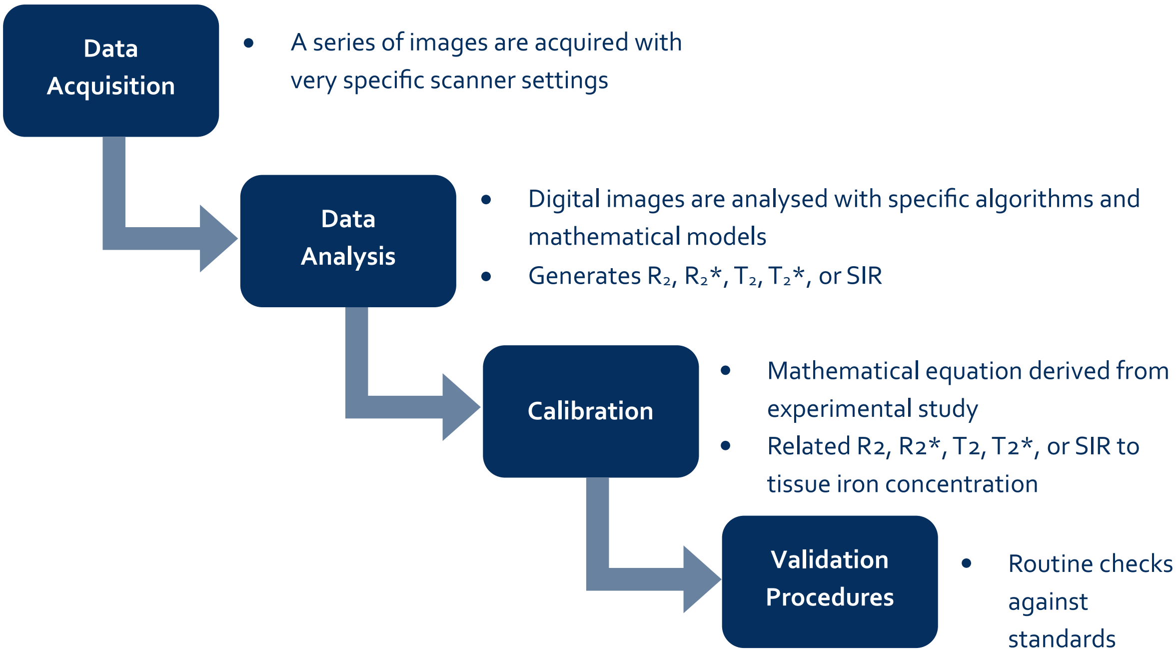

Figure 1. Four key steps for a MRI-based liver iron concentration measurement method. Borrowed from Quinn CT, St Pierre TG. Pediatr Blood Cancer 2016; 63:773–780 [21]

It is essential that data acquisition, data analysis, and validation procedures match exactly to those used in the calibration study. Even small deviations from protocols will cause calibration shifts and hence inaccurate measurements. The importance of image quality is emphasised in a study from Sweden, in which it is concluded that assessing iron overload can be performed in a non-dedicated centre with sufficient image quality [12]; the study recognised that T2* assessment needs to be repeatable, and the normal range of myocardial and liver T2*-values needs to be known in relation to the limits used in monitoring the chelation therapy, especially, since non-specialized centres may perform only a few clinical iron overload MRI each year. The study evaluated the image quality of T2* parametric maps of the heart and liver

Liver MRI

Several MR imaging techniques have been developed for liver iron quantification, each with advantages and limitations [13, 14]:

- **R2 RELAXOMETRY**: R2 relaxometry [10] is validated but is prone to respiratory motion artefacts due to a long acquisition time. This is the validated method marketed by Resonance Health as Ferriscan®, now with a new version called FeriSmart®, which uses artificial intelligence (AI) to replace the first version that required direct communication with the company and cost and time to report results. The AI version has been through trials and has gained FDA approval. It is now cheaper since it saves on staff time and is easier to use. FerriSmart®, according to a recent company statement, "provides an accurate, validated and standardised MRI-based measurement of liver iron concentration (LIC). FerriSmart delivers fast, accurate results, unaffected by inflammation, fibrosis and cirrhosis, and returns standardized results directly to clinicians and radiologists in seconds. The FerriSmart neural network was trained using Resonance Health's proprietary FerriScan technology and delivers state of the art liver iron concentration quantification".

- **R2* TECHNIQUE**: The R2* technique has fast acquisition time, using single or multiple breath holds and allows a wide range of liver iron content, but requires additional post-processing software which must be purchased, while some centres are using their own 'house made' sequence. R2* allows 3D imaging. For liver iron, T2* calibrations have been developed by J Wood et al [15] and Gabrowski MW et al [16]. During the discussions held during the International Conference on Thalassaemia in Thessaloniki in 2017, it was acknowledged that using T2* for liver iron, when well done and in well controlled conditions, is an "excellent tool".
- **SIGNAL INTENSITY RATIO (SIR):** SIR is the simplest method, measuring the ratio of signal intensity between the liver and skeletal muscles. The method is accessible since it can be used on any machine and with different magnetic strengths. It is not accurate in severe iron load since upper limit is 21mg Fe/g dry weight. However, SIR is being used in clinical settings and recently a study showed that the method is feasible also using 3T scanners [17].

The R2 technique is used mainly by Resonance Health, which is the only FDA/EMA approved and commercially available method. It is calibrated and validated for standard liver iron measurements on many scanners. At present, however, the R2* technique is the one used in most centres across the world. An example of the usefulness of measuring LIC is to follow progress over time and the effect of iron chelation regimes. One such study from Plovdiv, Bulgaria, indicated that patients who had normal liver MRI T2*, increased from 2011 to 1014, due to appropriate iron chelation [18].

Imaging and biochemical markers of liver iron toxicity should be used together with MRI for a complete clinical assessment. For example, Transient Liver Elastography, used to measure liver fibrosis is a non-invasive method and correlates well with the degree of fibrosis. In a study from Indonesia, based on MRI T2* examination of the liver, all subjects experienced liver toxicity; 48.9% of the subjects, receiving blood transfusions on a regular basis and aged over 18 years (42% 18-30 years), experienced severe liver haemosiderosis with liver fibrosis [19]. Such examples demonstrate the usefulness of MRI as a monitoring tool for the liver and iron overload in general.

Heart MRI

T2* techniques and validated software have been developed independently by various groups for iron measurement of the heart. These include CMR Tools (originally from the Brompton Hospital [5]), HIPPO MIOT IFC-CNR [20] and later Circle CVi42 cardiac MRI package [21]. These products are software packages for reading and analysing digital images and offer complete MRI readings. Access to such quantification software is limited often by cost. There are, however, open-source online software packages that many centres in poor resourced countries have resorted to [22].

MRI measurements of cardiac iron overload have been adopted as standard practice in most thalassaemia treatment centres where have the technology is available. The good results of treatment adjustments according to measurements were identified early [6] and recognised as a major contribution to reduced morbidity and mortality. It is important to note that cardiac MRI serves not only to measure iron load but also to assess heart function using parameters such as LV function, diastolic dysfunction and Global longitudinal strain (GLS). Myocardial iron overload in thalassemia major may cause subclinical left ventricular (LV) dysfunction which manifests with abnormal strain parameters before a decrease in ejection fraction (EF). Early detection of MIO using cardiovascular magnetic resonance (CMR)-T2* is vital and will provide the possibility of timely prevention of worsening heart function by intensifying iron chelation [23,24, 25]

The unavailability of MRI to study both myocardial iron and heart function, has led many centres to study the correlation between any echocardiographic parameters, which would correlate with MRI findings and so make such findings an alternative way to timely predict the danger of heart failure; such echocardiographic parameters include left ventricular ejection fraction, diastolic dysfunction and global longitudinal strain. A study from Oman on 84 TDT patients found no correlation between any of the echo findings and the MRI T2*. [23]. A similar study from Greece estimated global longitudinal strain (GLS) analysis of the LV performed by speckle-tracking imaging, which is an echocardiographic imaging technique aiming to detect LV subclinical dysfunction. The findings suggest that TM patients with high iron cardiac load had low left ventricular longitudinal deformation, although LVEF values were normal [26]. Similar results are reported form other centres, emphasising the need for parallel echocardiographic studies [27].

Pancreatic MRI

Pancreatic magnetic resonance imaging (MRI) using multi-echo gradient-echo sequences is not a routine investigation at this time. Pancreatic iron overload has been found to be predictive of cardiac iron overload in TM patients, and responsive to iron chelation [28, 29]. Also, pancreatic iron accumulation measured by gradient-echo imaging is associated with fasting glucose, and is an effective way to discriminate between patients with impaired glucose function and normoglycemia [30].

GLOBAL ACCESSIBILITY TO MRI IRON MEASUREMENTS

Member organisations of TIF have for many years reported that patients in many locations are not benefitting from MRI imaging techniques. Difficulties include:

- Limited MRI scanners in country or region
- Competition with other community needs for scanning (e.g. cancer), thus limiting the time available for iron measurements
- Technical limitations such as having a scanner which does not support the application for iron measurement, not including a cardiac module on the scanner etc.

Limited affordability by patients where there is no benefit from health insurance coverage.

Pituitary Volume by MRI

Pituitary volume and iron load may require 3T MRI to predict the risk of hypogonadism in beta Thalassemia [32].

Various approaches have been put forward to address these difficulties. One example is the 'ultrafast TIC-TOC method', which is a technique developed using T1 for heart and liver iron content [20]. The purpose is to reduce magnet time and complex analysis, thus reducing costs in high-prevalence and low-resource settings. A clinical study found that it was possible to scan six subjects per hour and detect liver and heart iron in 99%. This approach has not been universally adopted, and for many countries, accessibility and affordability remain the main reasons why the majority of multi-transfused patients do not benefit.

TIF has investigated the availability of MRI globally in an effort to identify the main areas of unmet need.

The first step was to investigate whether scanners were available globally. The source for such information was WHO, which produces a global atlas of medical devices [22]. The corresponding pieces of evidence are summarised in Table 1.

Table 1. MRI density and possibility of iron measurement per million population (WHO data)

COUNTRY	WORLD BANK INCOME GROUP	HUMAN DEVELOPMENT INDEX	ESTIMATED NUMBER OF PATIENTS	MRI DENSITY PER 1 MILLION POPULATION	POSSIBILITY OF IRON MEASUREMENT
Quatar	High	0.855	163	9.22	High
Saudi Arabia	High	0.875	8919	9.7	High
Austria	High	0.914	60	25.35	High
Cyprus	High	0.873	659	14.021	High
France	High	0.891	666	16.26	High
Greece	High	0.872	3241	33.56	High
Malta	High	0.885	21	9.324	High
Netherlands	High	0.933	350	14.9	High
Spain	High	0.893	100	20.4	High
Singapore	High	0.939	258	7.761	High
Oman	High	0.834	591	4.405	Medium
Canada	High	0.922	450	10.1	High
Italy	High	0.883	7044	31.24	High
UK	High	0.920	942	8.6	High
USA	High	0.920	1046	34.66	High
Bulgaria	High	0.795	270	11.5	High
Albania	Upper Middle	0.791	356	1.576	Low
Brazil	Upper Middle	0.770	662	6.79	High
Azerbaijan	Upper Middle	0.754	3300	0.53	Low
Iraq	Upper Middle	0.689	17000	1.629	Low
Iran	Upper Middle	0.774	20777	3.8	Medium
Lebanon	Upper Middle	0.757	375	8.295	High
Jordan	Upper Middle	0.723	1300	2.062	Low
Malaysia	Upper Middle	0.804	5980	2.984	Low
Maldives	Upper Middle	0.747	670	2.898	Low
Mauritius	Upper Middle	0.790	200	4.822	Medium
Tunisia	Upper Middle	0.739	742	2.001	Low
Turkey	Upper Middle	0.806	5500	11.26	High
Romania	Upper Middle	0.816	300	12.9	High
Lao	Lower Middle	0.607	275	0	None
Morocco	Lower Middle	0.683	500	0.4	Low
Pakistan	Lower Middle	0.560	50000	0.220	Very Low
Philippines	Lower Middle	0.712	600	0.305	Very Low
Sri Lanka	Lower Middle	0.782	3500	0.423	Very Low
Egypt	Lower Middle	0.731	10000	2.0	Medium
Afghanistan	Low	0.496	15000	0.1	Very Low
Cambodia	Low	0.593	160000	0.066	Very Low
Myanmar	Low	0.584	4080	0.0745	Very Low
India	Lower Middle	0.633	150000	0.3	Very Low

According to Table 1 (which does not include all affected countries due to lack of data), it appears that around 10% of the thalassaemia patient population live in countries that have high or medium possibility of MRI iron measurements, based on the MRI density. In fact, 89.6% live in countries with low, very low or no MRI machines/ million population making the measurement of iron an impossibility with the exception of an occasional academic centre serving a negligible number of patients. Countries with even a medium MRI density will have less chance to provide MRI time for thalassaemia patients when compared to the other needs for imaging in the general population.

According to information gathered by TIF delegation visits, it seems that some patients benefit from MRI iron measurements even in countries where the service is not generally available; services are either offered in the private sector or in a neighbouring country, thus benefitting those who can afford to pay, representing usually a small minority of patients (e.g. Azerbaijan patients go to Turkey). In addition, MRI services are often available in academic or other centres of expertise, where they are used as tools for research, benefitting a minority of patients but not reaching the total of the country's patient population. One example of this phenomenon is **Pakistan** [34]. As in many LMICs, MRI has a limited availability in **Bangladesh** (R2 scan/ Ferriscan/ Ferrismart is available in Bangladesh since 2008 in collaboration with Resonance Health at a cost of 95$, Cardiac T2* MRI is available since 2018 at a cost of 70$). Availability is only at the Thalassemia Foundation Hospital in Dakka and with limited uptake since patients have to pay the cost (Information from the local Association). In **Indonesia**, an upper middle-income country, MRI T2* examination is only available in four centres, Aceh, Jakarta, Bandung and Surabaya (three of them in the Java Island). MRI is not available in the central and eastern region of Indonesia. This has led the clinical services to assess other surrogate markers of iron overload such as serum transferrin saturation and ferritin and echocardiography. 61,8% of subjects of this study have normal T2* value yet a weak correlation between serum ferritin and left ventricular ejection fraction. Cardiac magnetic resonance imaging remains as the recommended modality for timely detecting iron toxicity [35]. Access to T2* MRI should be provided in areas with high prevalence of TDT [36]. In **Sri Lanka** the first reported patients benefitting from Cardiac MRI from a centre in the capital Colombo was in 2022 and 42.5% of patients were found to have iron overload in the heart at a young age (median age 10 years) [37]. In **Iran**, even though there is wide availability of MRI tools, there is lack of insurance support for the test. The proportion of the patients who have received this service seems to be about 60%, as stated in a recent communication with TIF. The real figure may be less since out-of-pocket payment may out of reach for many families.

The low availability of MRI for 90% of the thalassaemia population reflects the poor quality of clinical services offered for a chronic disease like thalassaemia. This is mostly related to the economic and developmental aspects of each nation and its willingness or ability to cope with complex health issues.

In order to estimate the real availability and clinical use of MRI services across the world, TIF has attempted to reach two additional sources of information, the patients view of services and their vision of unmet needs, and the view of healthcare providers. To tap these sources of information, separate questionnaires were distributed and, in addition, published literature was examined.

TIF MRI SURVEY – PART 1: THE PATIENT'S VIEW

A total of 522 patient participants from 55 countries equally distributed across the 6 WHO regions participated in this questionnaire-based survey performed in October 2019. About 400 of the responders answered the questionnaire online, through the SurveyMonkey platform, while about 100 answered on paper during a TIF patient conference held in Hamburg, Germany.

Among the 522 responders, 80% reported having thalassaemia major, 14% thalassaemia intermedia, 1% HbH disease and 5% other hereditary anaemias. A number of graphs that follow depict the main characteristics of survey responders (Figure 2, 3 and 4).

The main findings of this survey can be summarised as follows:

- Existence of accredited MRI centre: yes, 40%; no, 37%; do not know, 23%
- Frequency of measuring T2*: annually, 36%; biannually, 14%; rarely, 9%; never, 41%.
- Use of MRI for LIC estimation: 57%
- MRI methodology for measuring LIC: T2*, 83%; R2, 17%.
- Latest T2* level: >20 ms, 27%; 10–20 ms, 15%; 6–10 ms, 28%; <6 ms, 30%

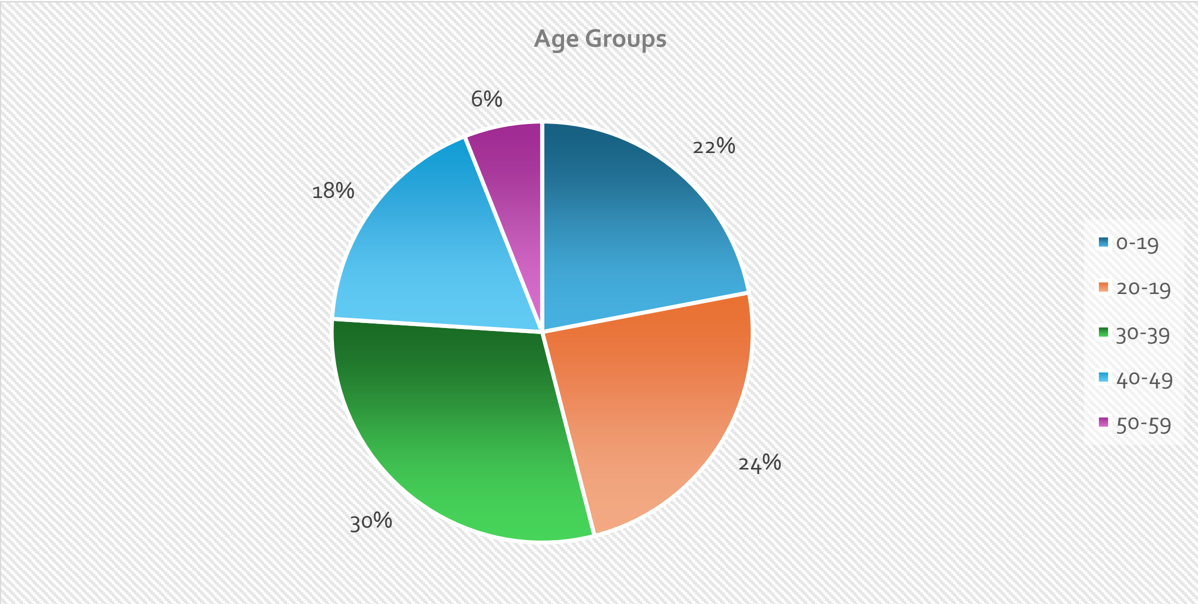

Figure 2. TIF MRI patient survey: patients' age distribution

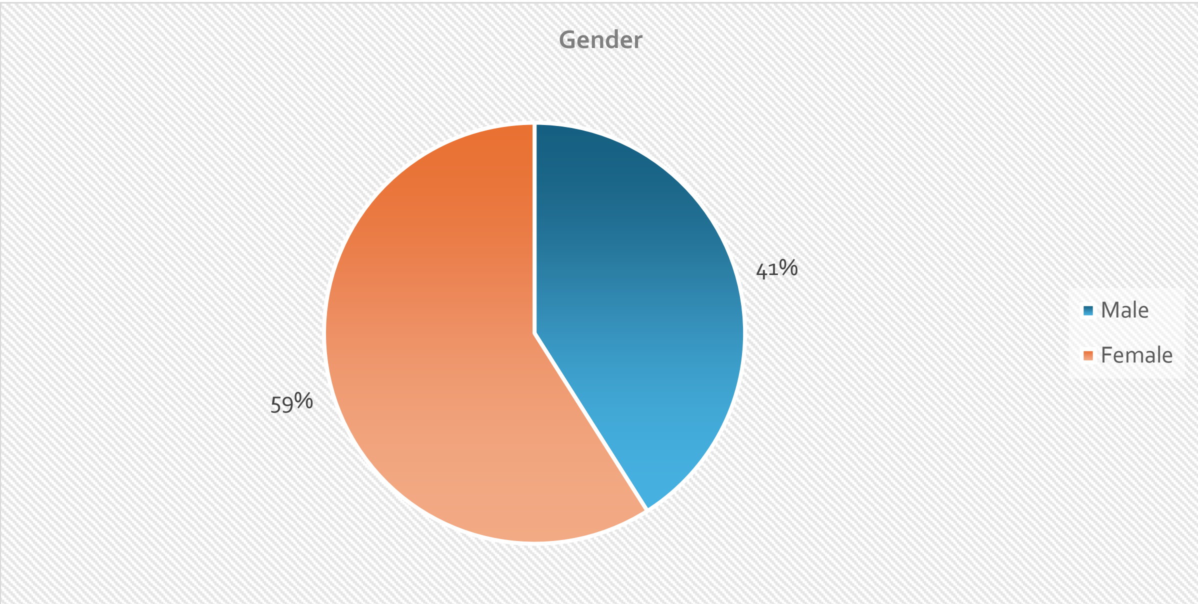

Figure 3. TIF MRI patient survey: patients' gender

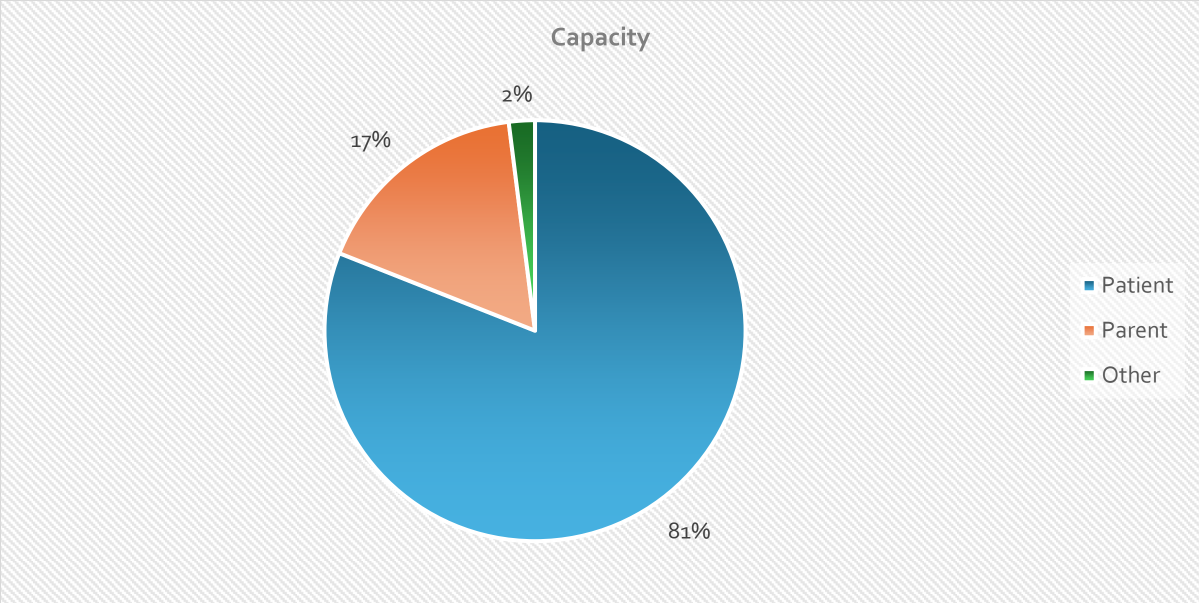

Figure 4. TIF MRI patient survey: responders' capacity

Regarding the level of education of participants, of 522 responders, 300 (57.5%) benefitted from tertiary education, 186 (35.6%) had secondary education, 22 (4.2%) stated "other" (including some infants and 14 (2.7%) did not answer this question.

Overall, the level of education of the responders was generally high and 78% were adults (>20 years) and able in their majority to respond electronically; this means that this group of patients is not representative of the global thalassaemia population. The majority of patients, around 80%, live in developing countries and are often children or adolescents (<20 years). For this reason, responses from such countries are from a selected group of survivors, assumed to be beneficiaries of better than average care and so responses are skewed towards a better care than that of patients in the developing world. However, these patients were able to observe and comment on the services that they receive and their reports are indicative of what is available.

The questionnaire tested their knowledge and awareness of MRI services. The responses are not analysed by country but by groups of countries that share some common characteristics. For example, in Europe, countries that have traditionally developed services due to high prevalence were separated from those that host patients from migration and have low prevalence in the indigenous population.

Europe

A total of 82 responders live in the WHO European Region. European countries are divided into 3 groups:

1. The high-prevalence countries that have developed policies of control from the 1970s (Italy, Greece, Cyprus, United Kingdom, and France) - 41 responders
2. Low- prevalence countries where thalassaemia has been introduced more recently through migrations and services are developed locally and not through a national strategy (Germany, Austria, Belgium, Netherlands, Norway, Sweden, Switzerland) - 24 responders
3. Countries where the indigenous population is affected but services are not part of a national strategy aiming at ensuring optimal care for all (Romania, Bulgaria, Albania, Azerbaijan, North Macedonia, Malta, Spain, Turkey) - 17 responders

✓ Patients' knowledge of whether the MRI centre serving them is accredited or not

From the distribution of responses to this question (Figure 5), it is concluded that patients from Group 1countries either know or have confidence that the MRI centres that serve them have accreditation and are presumed to be accurate in their results. Likewise, patients from Group 2 countries, which are countries with strong health service infrastructure, are less confident but also are most likely to state ignorance if the MRI centres are accredited. Patients who live in Group 3 countries have the least confidence in the MRI services.

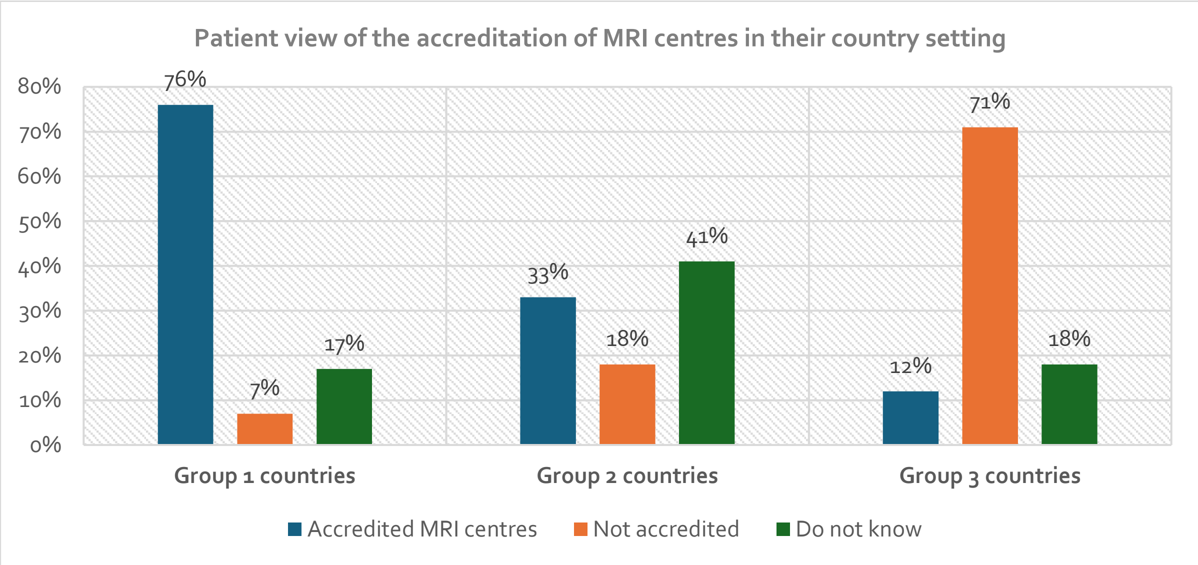

Figure 5. Knowledge of whether the MRI centre serving the patient is accredited or not (Europe)

✓Patients' knowledge of the method used to measure liver iron

The distribution of responses to this question (Figure 6) indicates that patients from group 1 countries are aware (by 78%) that T2* is the most commonly used method while patients in the other country groups are uncertain by around 60%.

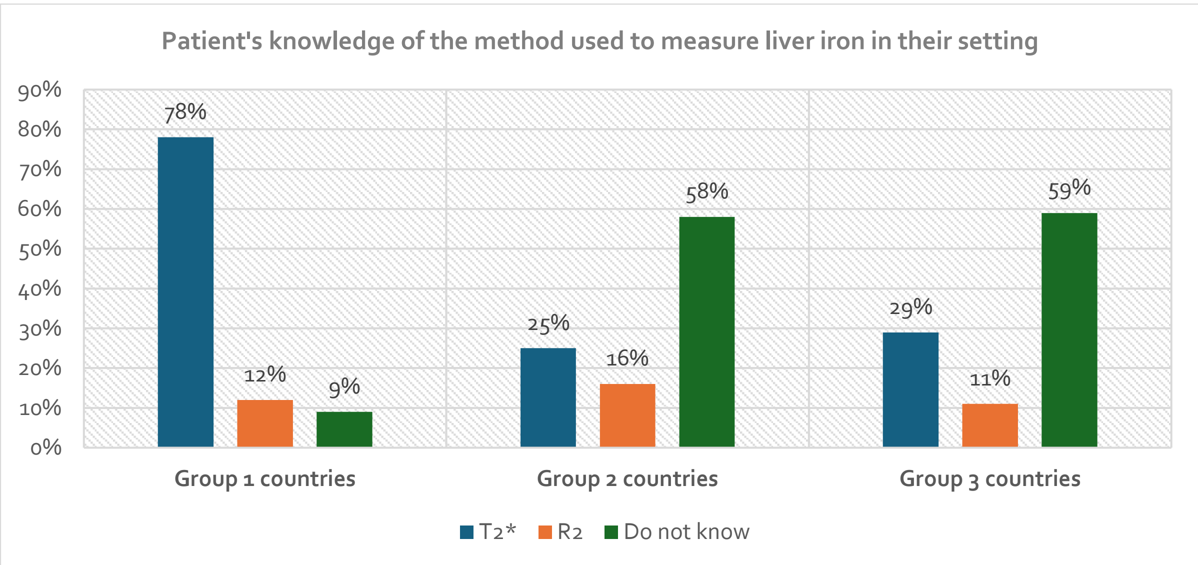

Figure 6. Knowledge of the method used to measure liver iron (Europe)

✓Patients' knowledge of their liver iron level

Poor knowledge of their own liver iron (Figure 7) is evident in most patients, in all three country groups, even though this is much worse in groups 2 and 3. Overall, 42.7% of all European patients were able to state a level of liver iron but only 28% stated levels below 7mg/g dry weight; 57.3% were not told or did not search or had no measurement at all.

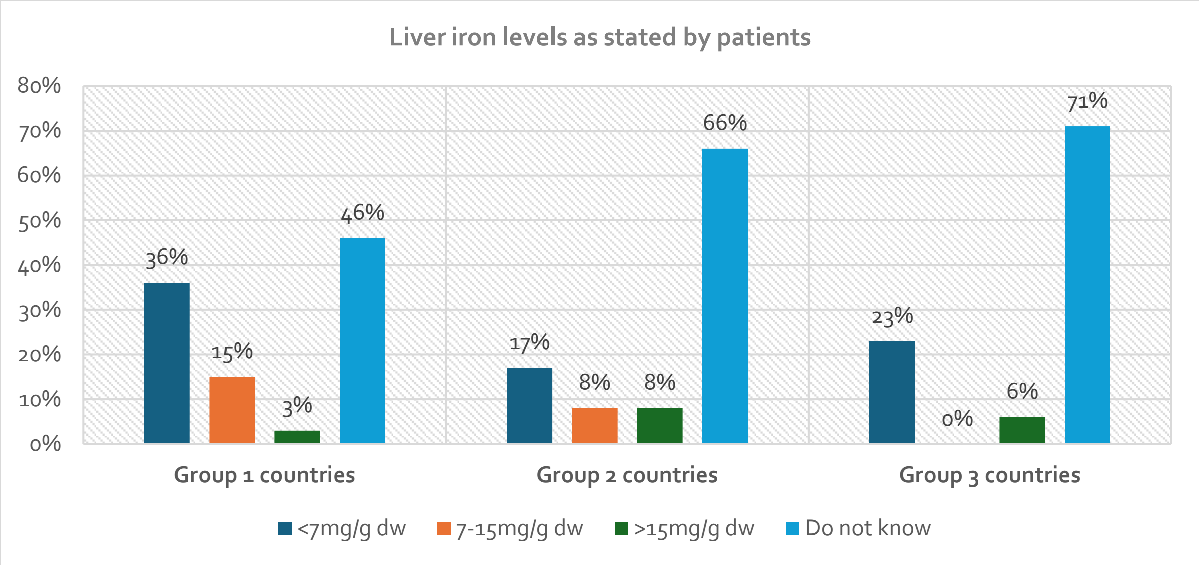

Figure 7. Patients' knowledge of their liver iron level (Europe)

✓Patients' knowledge of their cardiac iron measurements

Similar to knowledge of liver iron, knowledge of cardiac iron (Figure 8) was evident but with more profound differences. Group 1 countries had very few patients who did not know their results and many more with normal T2* value. Where services are long standing and organised patients have better results as well as being more aware of their clinical status.

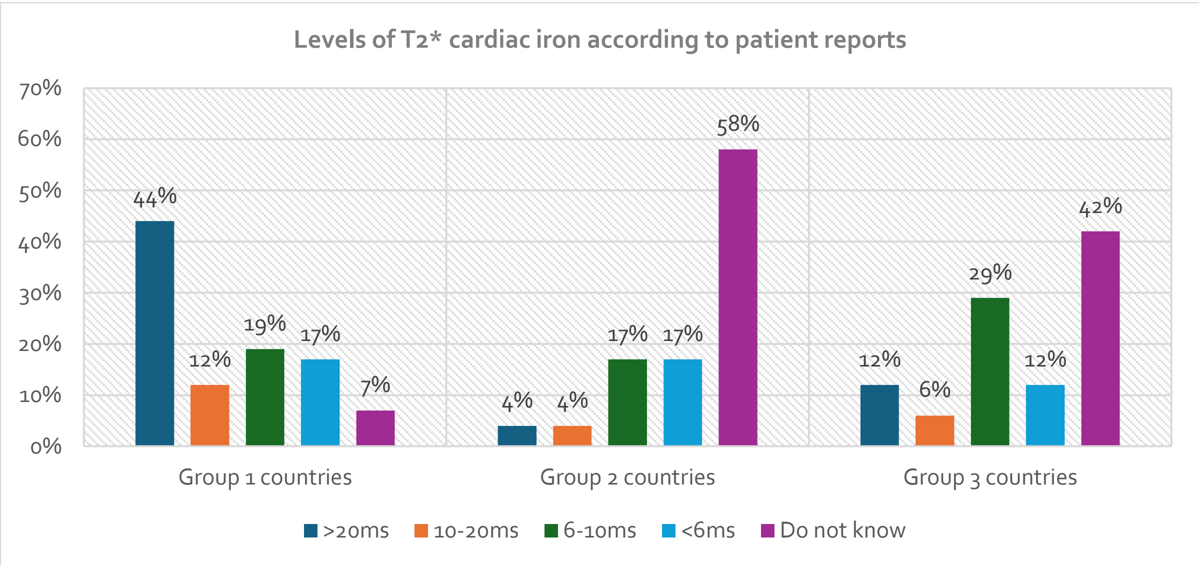

Figure 8. Patients' knowledge of cardiac iron measurements (Europe)

The Americas and Australia

The countries of the American continent host haemoglobin disorders from immigrant populations. However, these are migrations dated a long time ago and several generations of migrants from southern Europe, the Middle East, Asia and Africa must currently be regarded as an indigenous group. Patients who have responded to our questionnaire are from the USA, Canada, Argentina, Trinidad & Tobago. We have included Australia in this group since there are many common characteristics in terms of population structure but also health infrastructure. A total of 113 patients have responded, most from USA and Australia.

✓Patients' knowledge of whether the MRI centre serving them is accredited or not

Overall, 66 patients (58.4%) reported that they believed that their MRI centre had accreditation, 25 patients (22.1%) that their centres were not accredited and 22 patients (19.5%) that they did not know. These results are close to those of patient experience in Western Europe which included 65 patients (country groups 1 and 2; Figure 9).

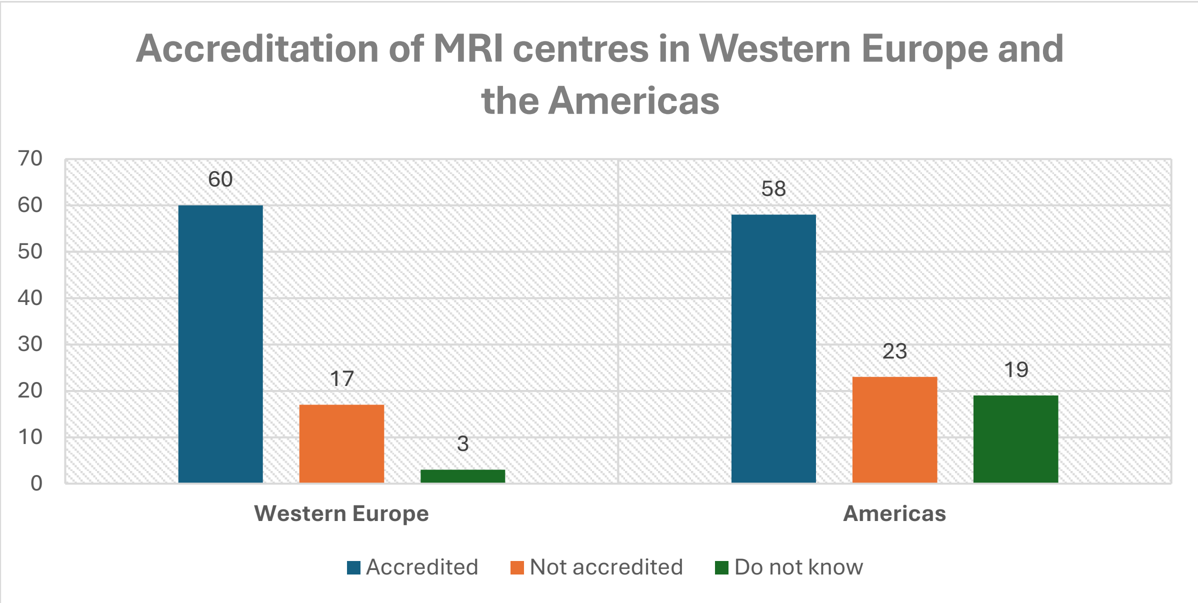

Figure 9. Patients' knowledge of whether the MRI centre serving them is accredited or not (Americas and Western Europe)

✓Patients' knowledge of the method used to measure liver iron

In this question, also patients living in the Americas gave answers comparable to those given by patients living in Western Europe (country groups 1 and 2; Figure 10).

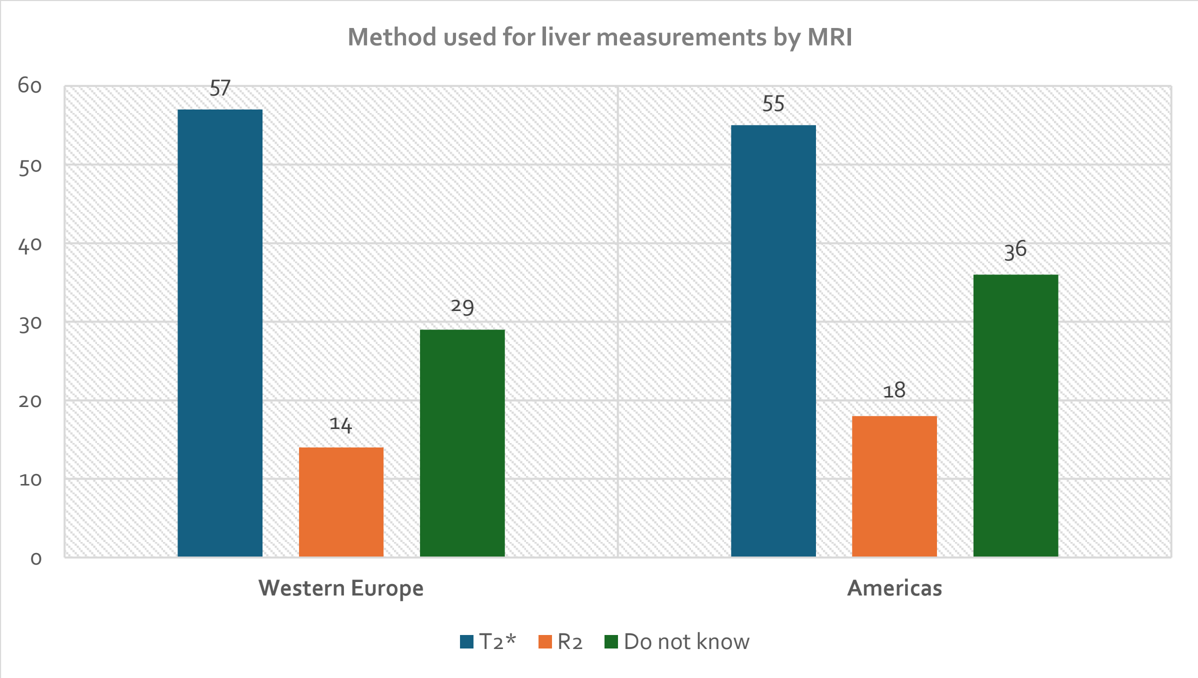

Figure 10. Patients' knowledge of the method used to measure liver iron (Americas and Western Europe)

✓Patients' knowledge of their liver iron level

From this question, Trinidad and Tobago have been excluded since the patients stated that no liver iron measurements were made by MRI. Although results between the Americas and Europe are quite close the proportion of patients who reported <7mg/g dry weight is 7% higher in European patients (Figure 11).

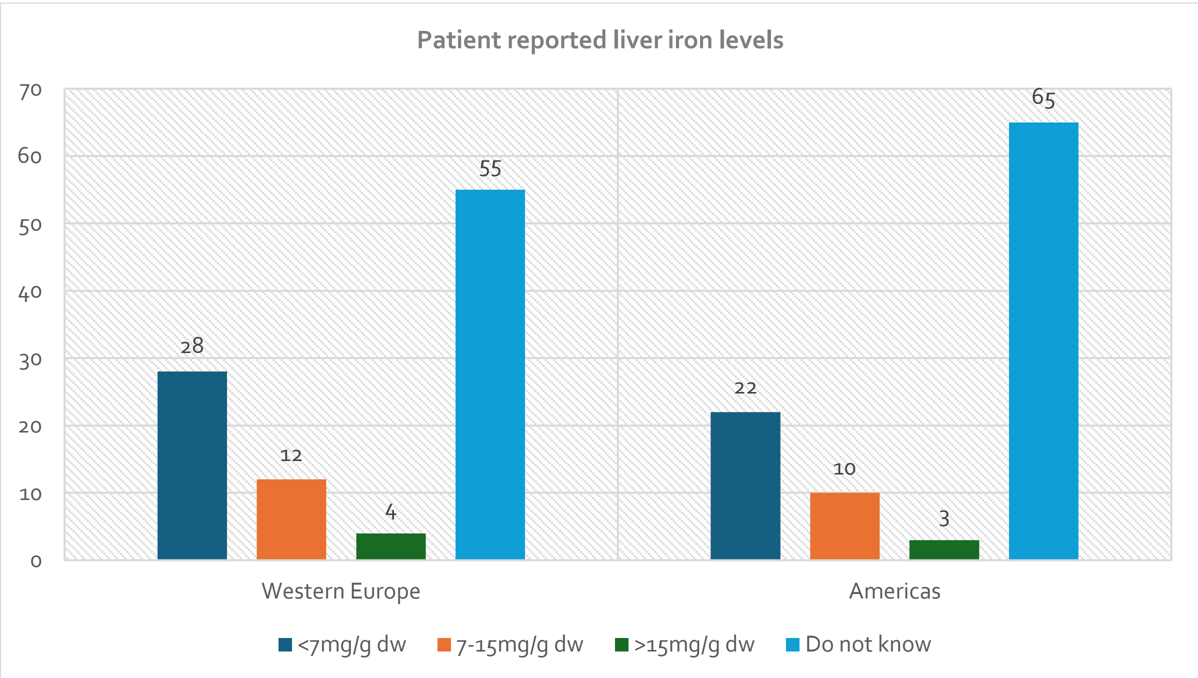

Figure 11. Patients' knowledge of their liver iron level (Americas and Western Europe)

✓Patients' knowledge of their cardiac iron level

In the reported results of cardiac iron, the range of results is again similar (Figure 12).

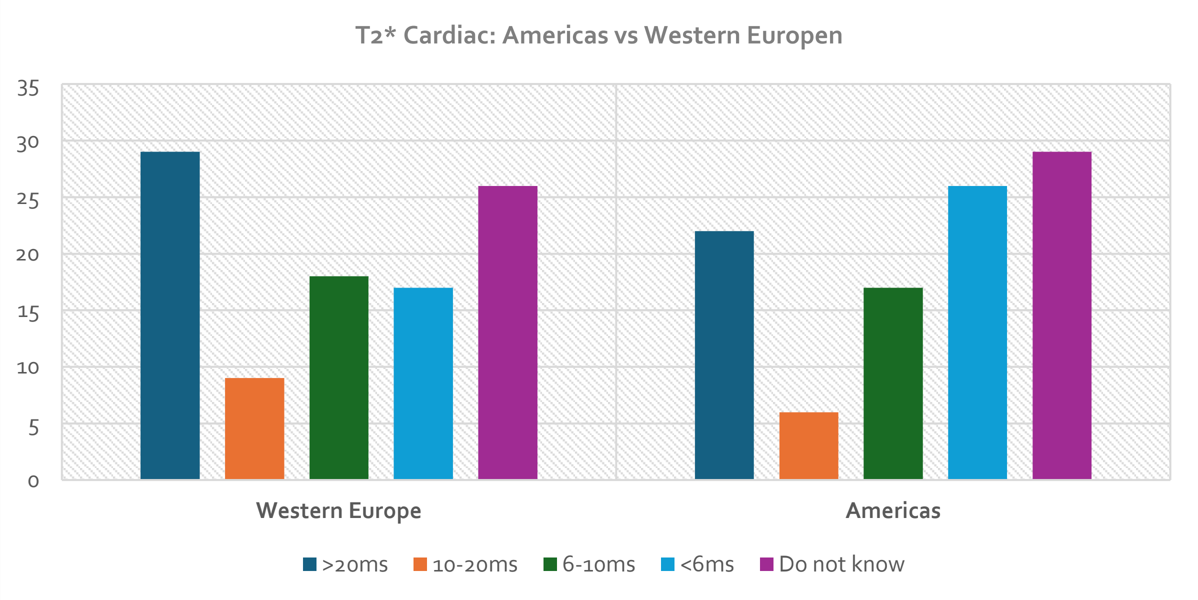

Figure 12. Patients' knowledge of their cardiac iron level (Americas and Western Europe)

For the purpose of further comparisons among groups of countries, the European (Mediterranean + Western Europe) and American groups and other groups (such as Middle East and Asia), Europe and America will be considered as a single group under the title West.

The Arab World (Middle East and North Africa Countries)

The Arab countries / territories were divided into 2 groups:

1. Those of relatively low income - Algeria, Egypt, Iraq, Jordan, Morocco and Palestine. From these countries / territories, there were 45 responses.
2. Those of high income - Kuwait, Saudi Arabia, United Arab Emirates and Oman or, in the case of Lebanon, those that have developed thalassaemia services. In this group, there were only 11 responses, and only the United Arab Emirates stand out with positive outcomes.

Despite the diversities between these 2 country groups, the observed differences were not obvious, possibly due to the small sample from the group 2.

✓Patients' knowledge of whether the MRI centre serving them is accredited or not

Most patients stated that the MRI centres had not gone through an accreditation process (Figure 13); only 9 out of 56 patients (16%) thought that their centres were accredited and of them, 6 patients originated from the high-income group (United Arab Emirates).

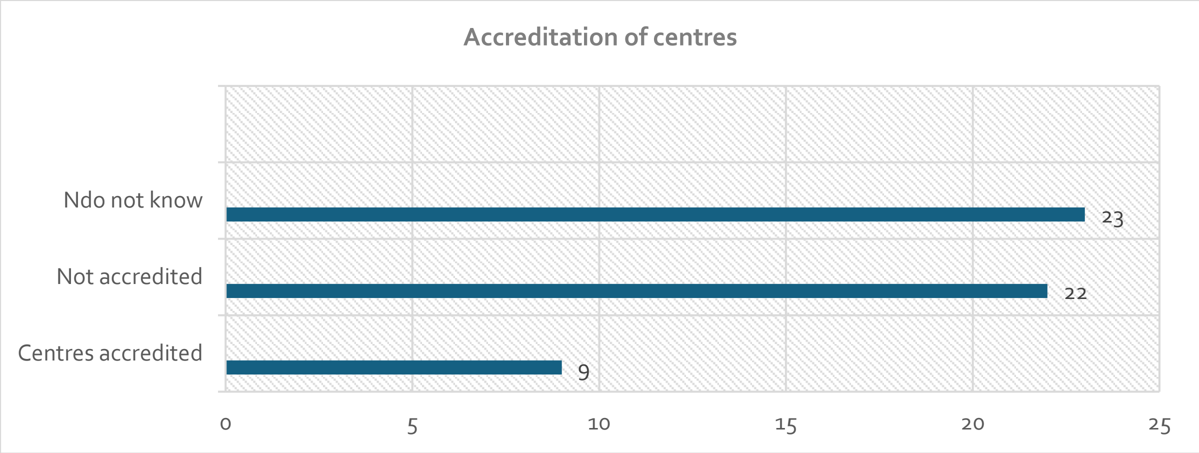

Figure 13. Patients' knowledge of whether the MRI centre serving them is accredited or not (Arab World)

✓Patients' knowledge of the method used to measure liver iron

In the answers provided herein (Figure 14), a new response emerged as a major concern, the response that LIC is not measured at all; almost 70% of patients gave this answer, mostly from Iraq. Still, patients from Palestine, Morocco, Lebanon and Saudi Arabia gave the same response.

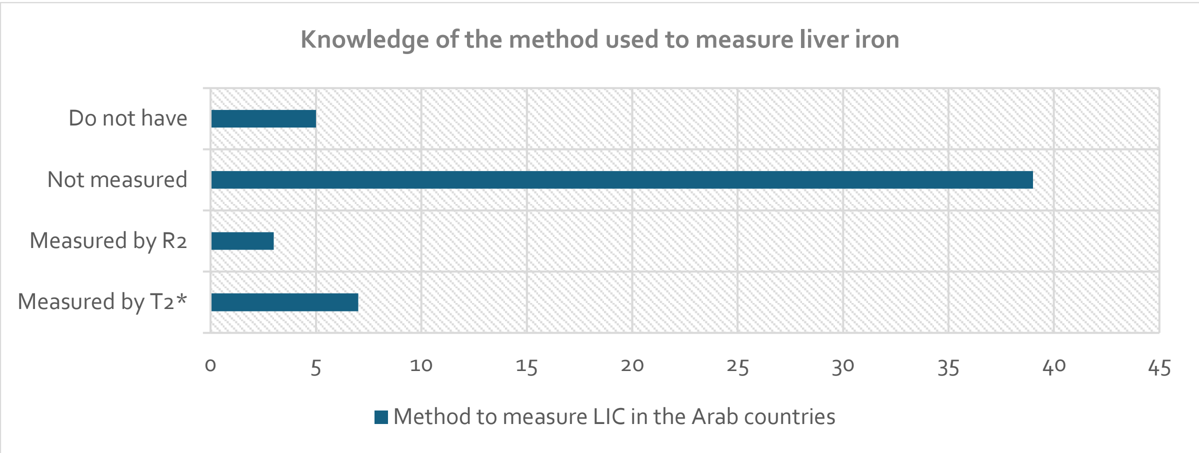

Figure 14. Patient's knowledge of the method used to measure liver iron (Americas and Western Europe)

✓ Patient's knowledge of their liver and cardiac iron level

It is expected, that since the majority of patients in Arab countries do not have their LIC measured that very few patients will know their result. In fact, only 4 patients (7.4%) were able to give a figure for LIC (3 had <7mg/g dry weight and one had >15). Likewise, only 11 (20.4%) gave a result for cardiac iron (3 had <20ms, 2 had 10-29ms, 1 6-10ms and 5 had <6ms), while the rest could not give a result.

Overall, the MRI services in the Arab countries are very different from those in European/American countries, from the patients' view. Unmet needs and inequalities are becoming more obvious.

Iran (Islamic Rep. of)

This country is treated separately since it developed comprehensive services for its large thalassaemia population earlier that most other Middle Eastern countries. 26 patients responded to the questionnaire, which is a reasonable number for a single country. The results are very different from the Arab countries with only few patients not knowing their MRI results. From these results (Figures 15-19), it appears that Iranian patients have outcomes concerning iron load in liver and heart that are comparable to those of the traditional parts of Europe. It must be remembered, however, that results concern small samples of patients who may not be representative of the total number of patients across each country or country group. However, in the absence of official registries and electronic patient records, patients' view is an important indicator of patient-reported outcomes, and as an indicator of unmet needs that must be taken seriously. In Iran, university centres provide data using MRI measurements on various aspects of clinical research, including the correlation of cardiac biomarkers and myocardial iron overload [38], evaluating heart function in iron overloaded patients [39], predicting pulmonary hypertension [40] and others.

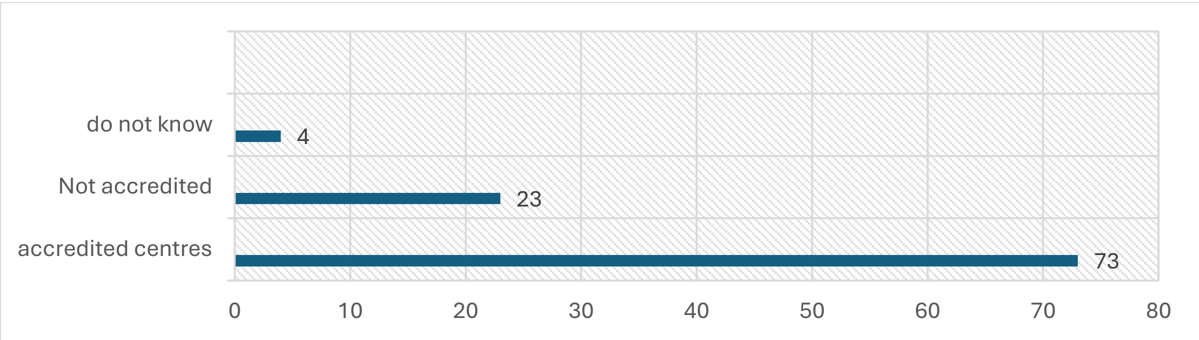

Figure 15. Patients' knowledge of whether the MRI centre serving them is accredited or not (Iran)

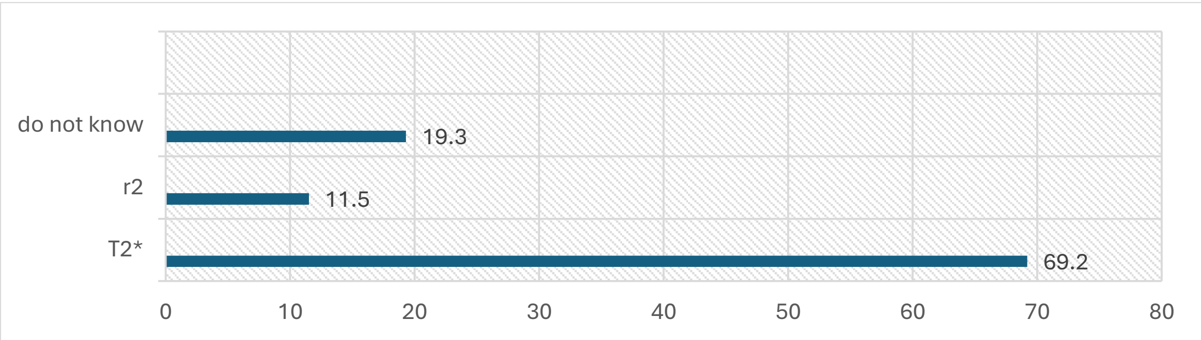

Figure 16. Patients' knowledge of the method used to measure liver iron (Iran)

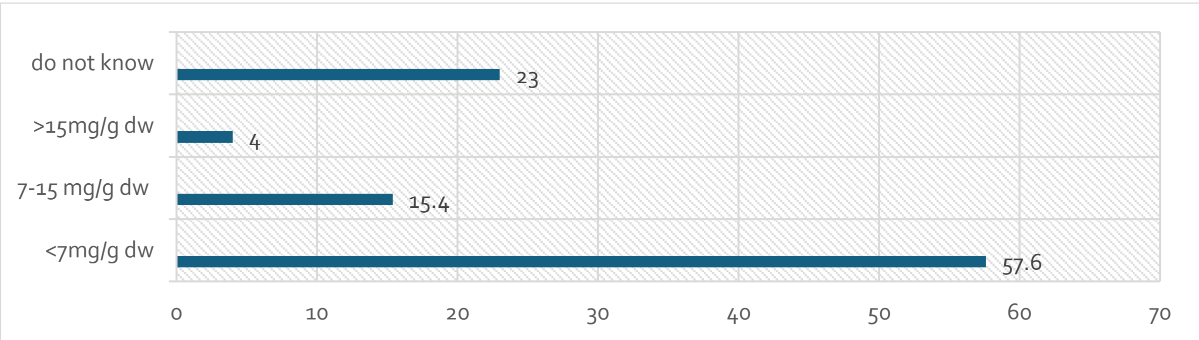

Figure 17. Patients' knowledge of their liver iron level (Iran)

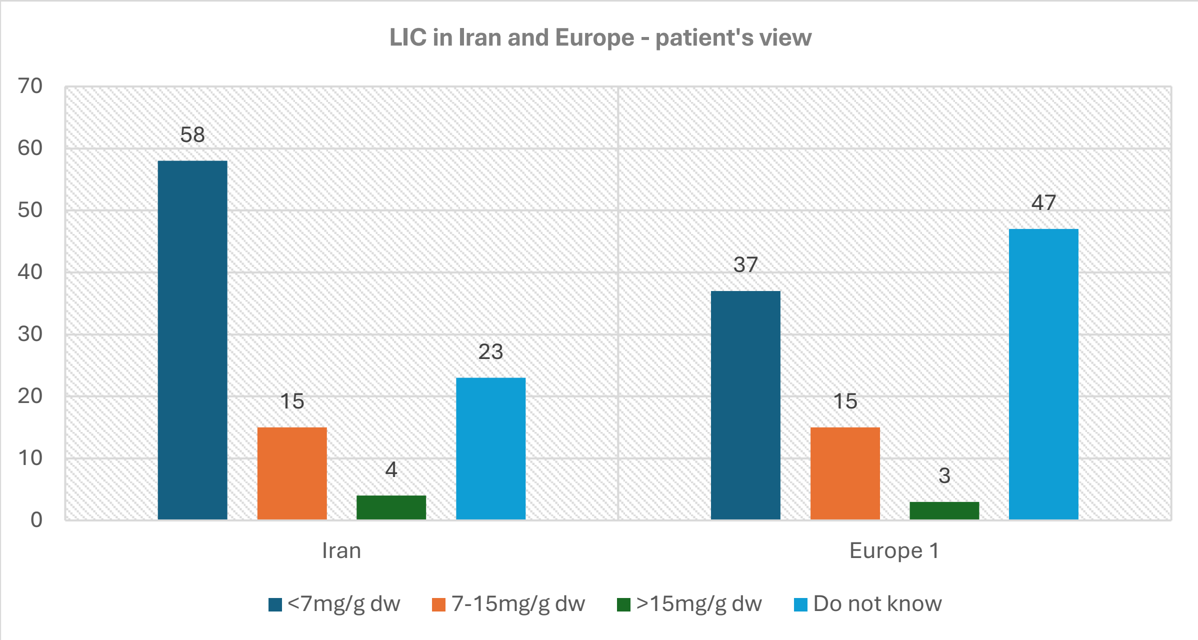

Figure 18. Patients' knowledge of their liver iron level (Iran versus European country group 1)

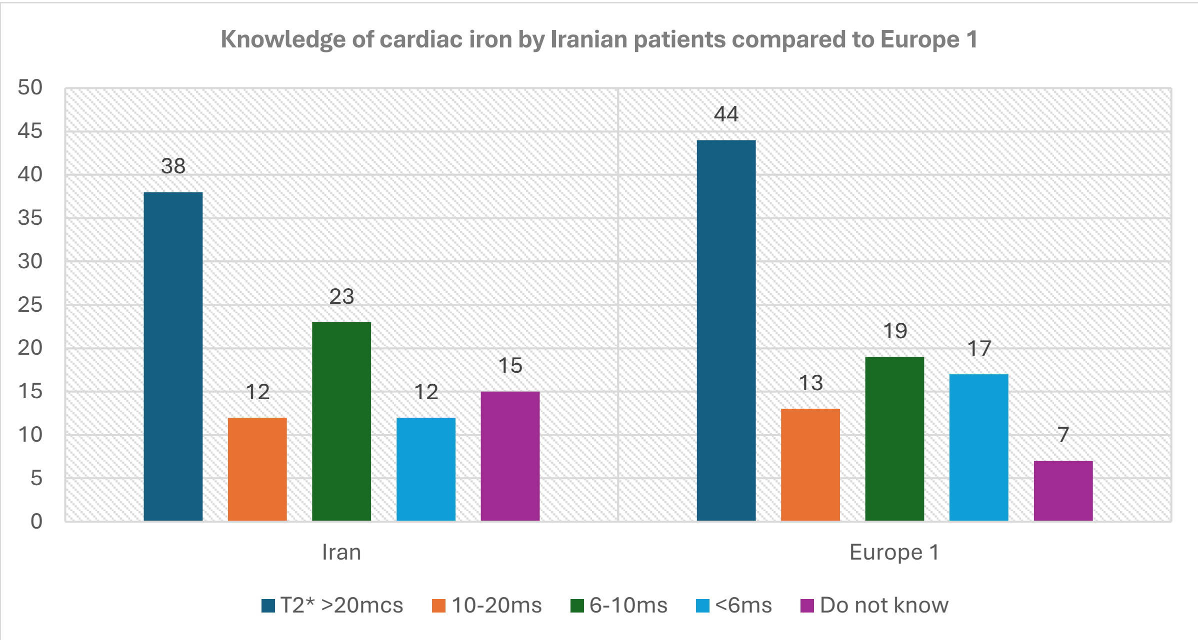

Figure 19. Patients' knowledge of their cardiac iron level (Iran versus European country group 1)

Indian Subcontinent

The Indian Subcontinent consists of India, Pakistan, Nepal, Bangladesh, Sri Lanka and the Maldives. Concerning the thalassaemia syndromes and haemoglobin disorders in general, this is the global hub. The estimated number of beta thalassaemia patients is around 35-40% of the world thalassaemia population, given the inaccuracies in data recording. In this survey, 183 patients responded with the following results.

✓ Patient's knowledge of whether the MRI centre serving them is accredited or not

Faith that MRI centres have gone through an accreditation process is probably not within the patients' scope; however, the positive responses reflect the patients' impression and confidence in the results that this technology is bringing. The vast majority either do not know or are sure that there is no accreditation (Figure 20).

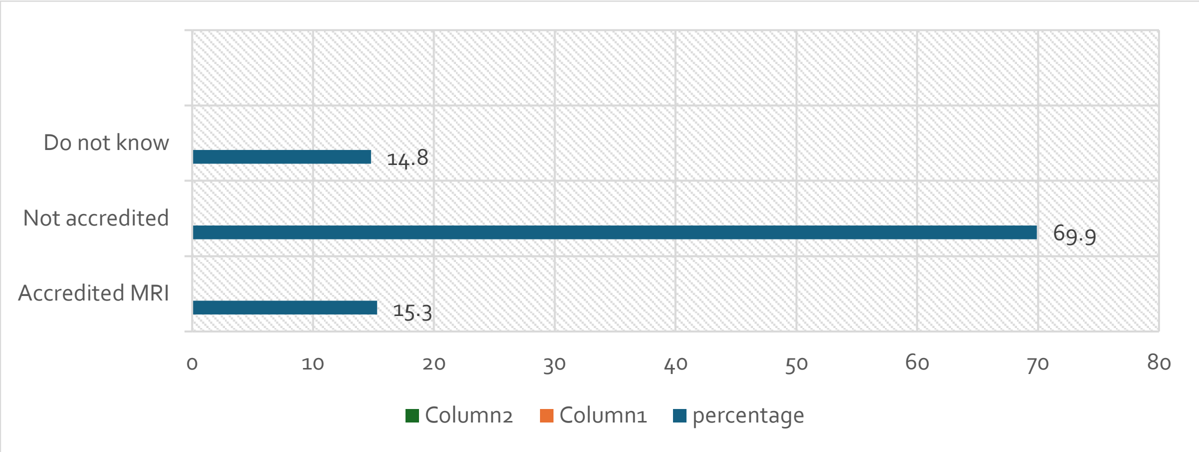

Figure 20. Patients' knowledge of whether the MRI centre serving them is accredited or not (Indian Subcontinent)

✓ Patient's knowledge of the method used to measure liver iron

Measurement of liver iron, if measured at all, it is mostly by T2*. R2 has been used only where sponsorship was offered or for the purposes of a clinical trial. Patient responses are based on practical experience and may not just be impressions. This is reflected also in the knowledge of their results (Figure 21).

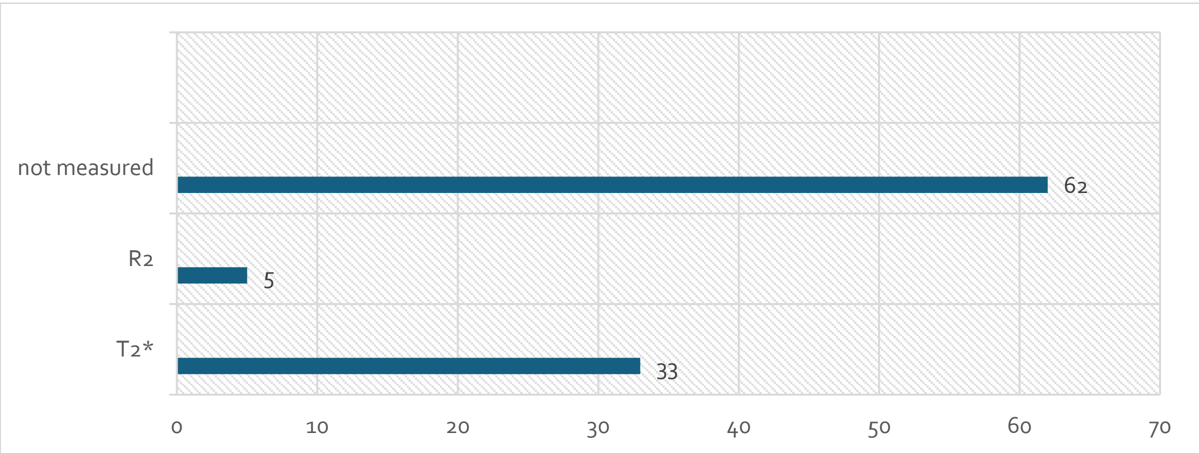

Figure 21. Patients' knowledge of the method used to measure liver iron (Indian Subcontinent)

✓ Patient's knowledge of their liver iron level

The vast majority of patients cannot give a result since LIC is not measured (Figure 22). This also demonstrates the great inequality, in which a minority of patients benefit from limited services, because they can afford such services and often go abroad to find the service they need.

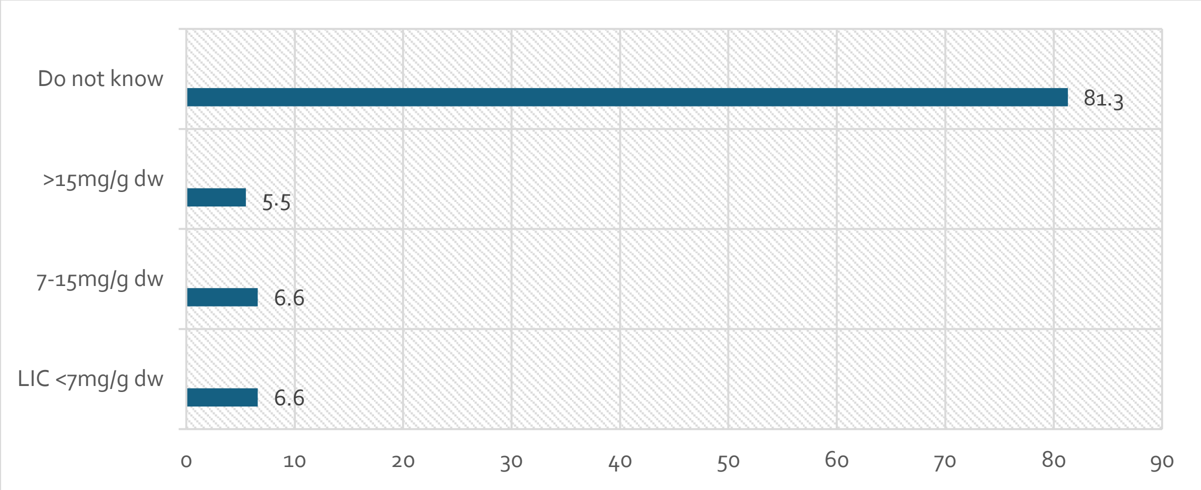

Figure 22. Patients' knowledge of their liver iron level (Indian Subcontinent)

✓ **Patient's knowledge of their cardiac iron level**

Unlike LIC, more patients have knowledge of their cardiac iron measured by MRI (Figure 23). However, in the Indian subcontinent, this still applies to only 40% of respondents, who represent an adult group of survivors and so selected for age and education. The total picture of the subcontinent is much worse.

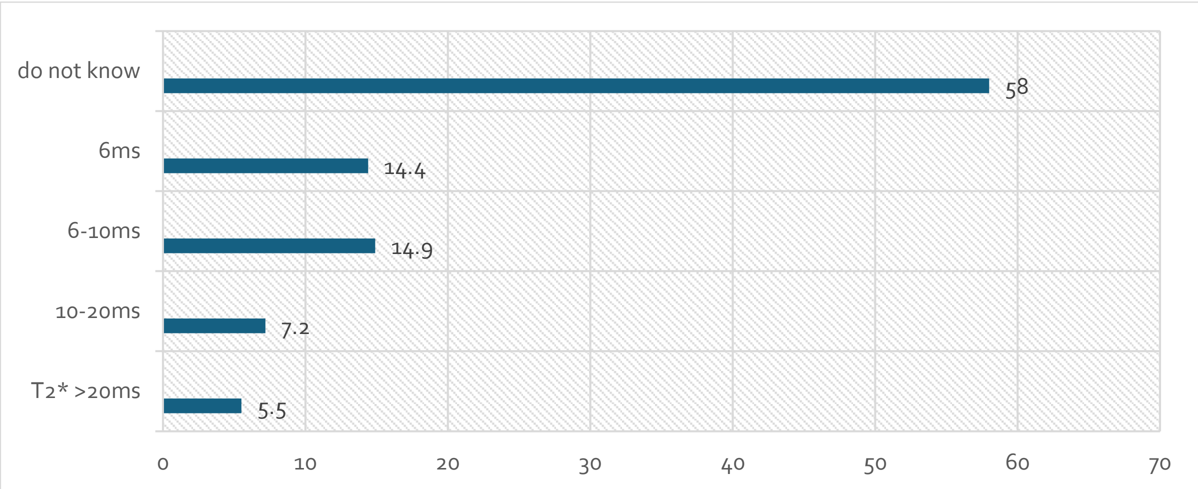

Figure 23. Patients' knowledge of their cardiac iron level (Indian Subcontinent)

The Far East

The responses from this part of Asia were very few from each country, mostly single case, with the exception of Malaysia, from which 31 patients responded. Even though these countries are at very different levels of economic and social development, it was not possible to divide them and so the results reflect mostly Malaysia. Patients that have responded include Malaysia (31), Chinese territories (mainland, Hong Kong SAR and Taiwan, 6 patients), Indonesia (6), Singapore (1), Philippines (1), Thailand (1), Viet Nam (3), making a total of 50 responses.

✓ Patients' knowledge of whether the MRI centre serving them is accredited or not

Concerning accreditation of MRI centres, 52% of patients thought that their centres were accredited, while 20% thought not; only 28% stated that they did not know.

✓ Patients' knowledge of the method used to measure liver iron

Half of patients (50%) were aware that T2* is used to measure liver iron, while 15.7% had been tested by R2 (this reflects the limited use of R2 globally); 35% did not know what is used.

✓ Patients' knowledge of their liver iron level

In this part of the world, LIC is either not measured in the majority of patients or they are not informed (Figure 24).

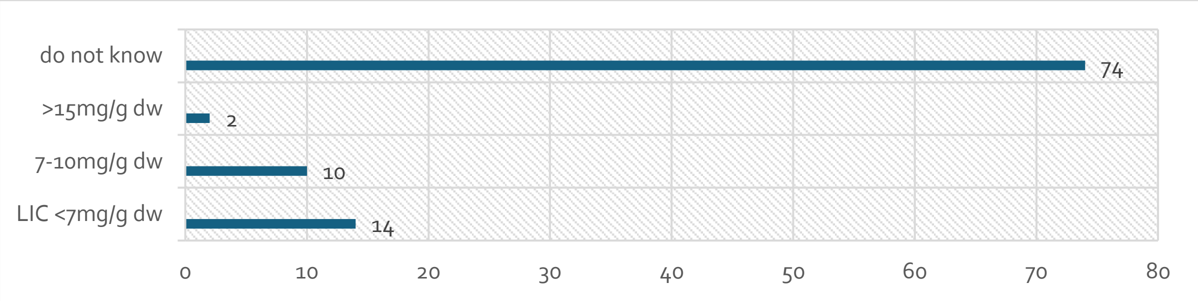

Figure 24. Patients' knowledge of their liver iron level (Far East)

In this part of the world, LIC is either not measured in the majority of patients or they are not informed (Figure 24).

✓ Patients' knowledge of their cardiac iron level

As in other parts of the world, patients in Asian countries have better knowledge of the heart results compared to liver iron. Considering again the nature of this sample of patients (selected for age and education), the fact over 30% are ignorant or have not had MRI testing Is a reflection of the inequities in the availability and use of services. Ignorance in itself reflects a dependency on the medical provider and a lack of self-reliance, with all the consequences.

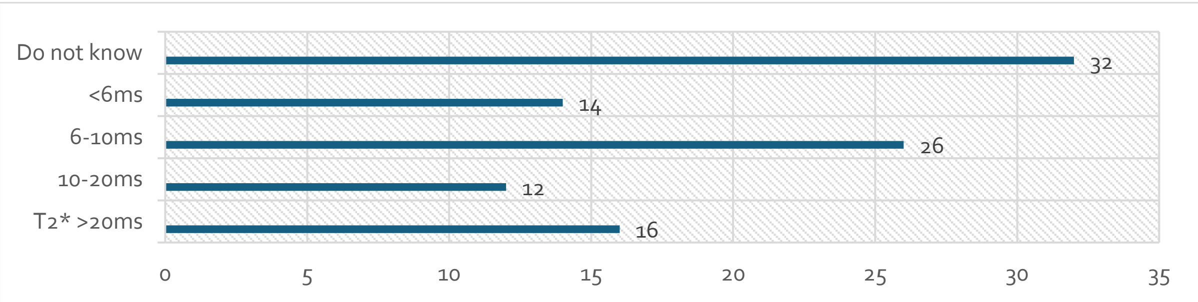

Figure 25. Patients' knowledge of their cardiac iron level (Far East)

Global Comparative Results

The results of the present patient survey are indicative of serious deficiencies in the use of MRI services to monitor iron load, at least from the patients' views. Importantly, there deficiencies are not totally related to the lack of resources and infrastructure, since European and American countries still seem to have serious gaps in the MRI service provision to thalassaemia patients. In addition, even though the above results have been derived by an educated adult group of patients, they reflect to a great extent what patients have learnt from their caretakers. Ignorance of the MRI methods used to measure LIC (Figure 26) or failure to report the liver or cardiac iron level (Figures 27 and 28) indicate that educated patients are not being well informed by their treating physicians, thus being in a poor position to partner in decisions concerning their care.

Despite the inherited selection bias of this survey and the small sample sizes compared to the global thalassaemia population, the depicted patient views are of value and the identified service and information gaps must be regarded as significant.

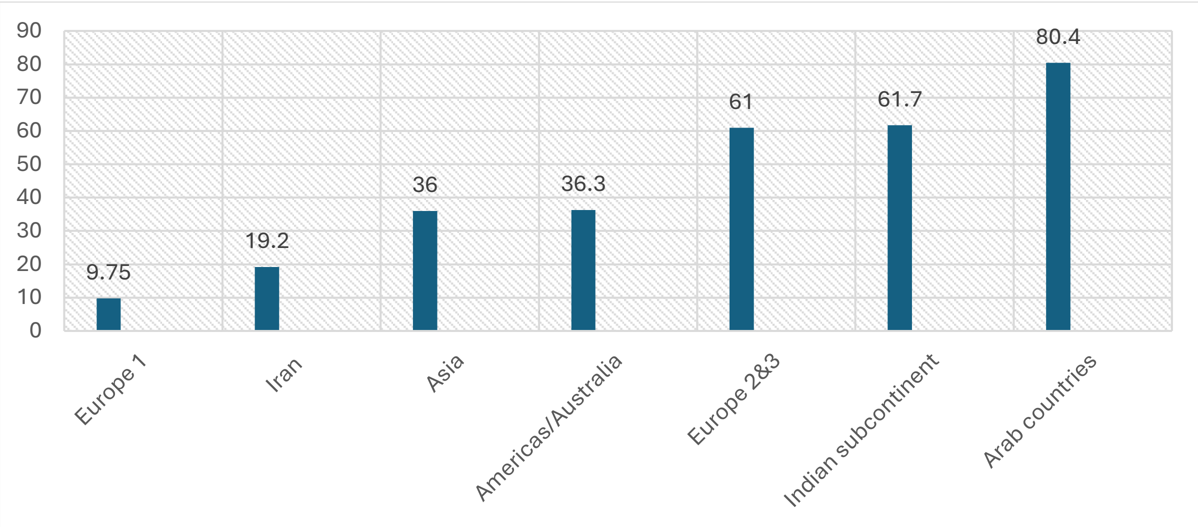

Figure 26. Patients' knowledge of the method used to measure liver iron (global comparison)

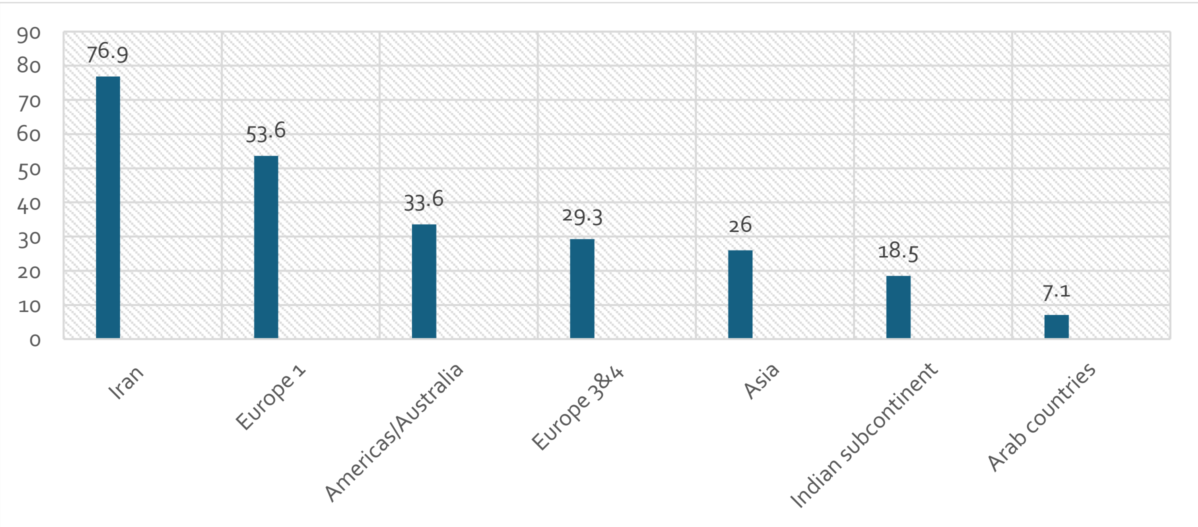

Figure 27. Patients' knowledge of their liver iron level (global comparison)

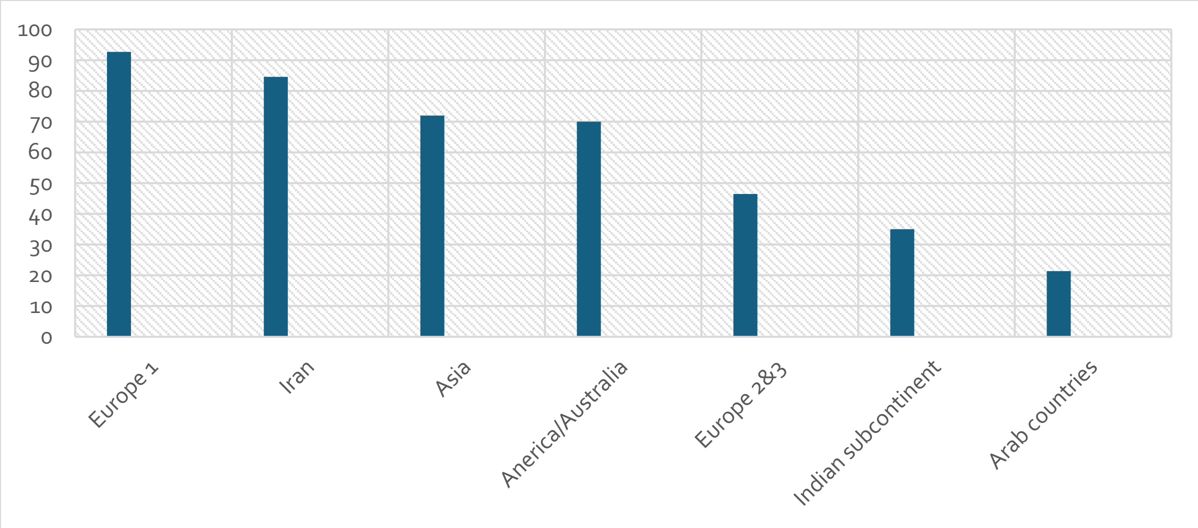

Figure 28. Patients' knowledge of their cardiac iron level (global comparison)

TIF MRI SURVEY – PART 2: THE PHYSICIAN'S VIEW

TIF conducted in 2014 a questionnaire-based survey involving physicians from 111 reference centres providing care to thalassaemia patients in 33 countries. According to this survey, physicians stated that that MRI T2* for cardiac iron was available to all 111 centres (100%). Ferriscan (R2, Figure 29) was available to 57 centres (51%); the distribution of these centres were: Europe 45.6%, Americas & Australia 29.8%, Arab countries 12.3%, Asia 5.3%, Iran 7%; no centres reported having R2 in the Indian subcontinent.

TIF experience today is not very different from what is depicted form the above figures, and it is still not possible to tell from the reports provided by professionals or treatment centres whether all or selected patients are benefitting from MRI services. These pieces of evidence should therefore be examined in parallel to the corresponding patient-reported data, previously presented in this chapter.

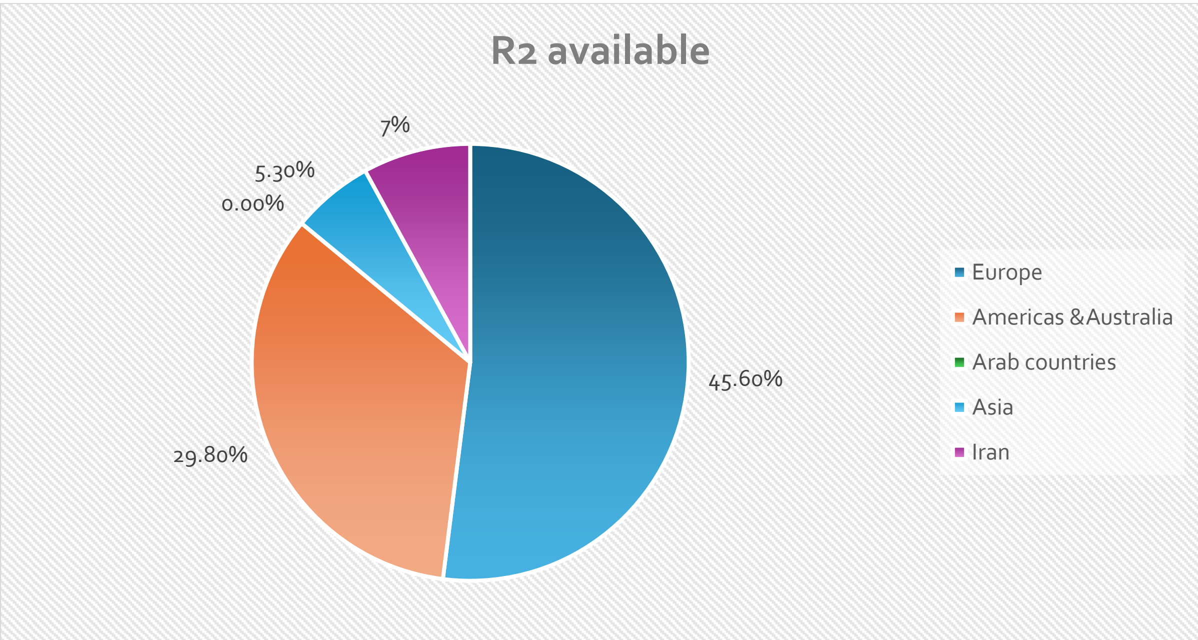

Figure 29. Availability of Ferriscan (R2) for liver iron monitoring across the world

A literature survey on MRI results in thalassaemia patients, published data were derived by centres from the following countries: USA, UK, Italy, Greece, France, Iran, Turkey, China (mainland, Hong Kong, Taiwan), Indonesia, Thailand, India, Qatar, Oman, Israel, Vietnam and Australia. Physicians from these countries have published studies on a limited number of patients, mostly treated in academic centres. There is no indication of whether the total thalassaemia population in these countries is served by MRI monitoring according to guidelines, or whether only selected patients have been included in these studies.

It is still interesting to report results of MRI iron measurements, in particular, the proportion of patients with either normal-range results or those with severe iron overload, as these are good indicators of outcomes (Table 2).

Table 2. Reported cardiac MRI T2 values examples from different countries; also indicating the different range of results from older to more recent reports.*

Country	Source	Sample size	T2* <10ms	T2* 10-20ms	T2* >20ms
United Kingdom	Anderson Eur Heart J 2001[5]	109	20	43	37
Hong Kong SAR	Au WY Haematol 2008[41]	180	26	24	50
Turkey	Karakus, Indian J Hematol Blood Transfus. 2017[42]	95 TDT	12.6%	18.9%	65.3%
Thailand	Chaosuwannakit, Tomography. 2021[43]	119 TDT+NTDT	3.5%	14.2%	82.35%
Egypt	Batouty, Cardiovasc Imaging. 2024[44]	57 TDT	5.3%	14%	80.7%
Italy	Longo, Blood Transfus. 2021[45]	756	3%	12%	85%
Malaysia	Hoe, Front Radiol. 2022[46]	39	7.7%	15.4%	76.9%
Indonesia	Atmakusuma, Acta Med Indones. 2021[47]	62	11.3%	27.4%	61.3%
Greece	Kattamis, EJHaem. 2023[48]	208	2.5%	4.5%	90.5%

CONCLUSION

Although MRI measurement of cardiac and liver iron has proven as an invaluable tool to guide effectively iron load monitoring and importantly chelation therapy, this service remains far from reaching all patients; in fact, validated MRI measurements seem to be accessible to only a small minority of them. Patients lack, in their majority across most countries with medium to high disease prevalence as well as in those with low disease prevalence but large populations, adequate and appropriate knowledge on the value of not only the availability and use of MRI technology but very importantly of any accurate and reliable measurements of iron overload. Unavailability is of particular concern but so is the need for patients and families to either fully or partially cover the cost of MRI measurements. In addition, unreliable and inaccurate measurements resulting from the lack of appropriate and regular software validation/calibration may seriously mislead treatment decisions. NGOs like TIF have a duty to advocate for the increased availability and accessibility of patients to validated MRI services, while alternative solutions must be considered, where this is possible. In this context, a group of thalassaemia specialist have suggested an algorithm to be followed in the latter case (Figure 30).

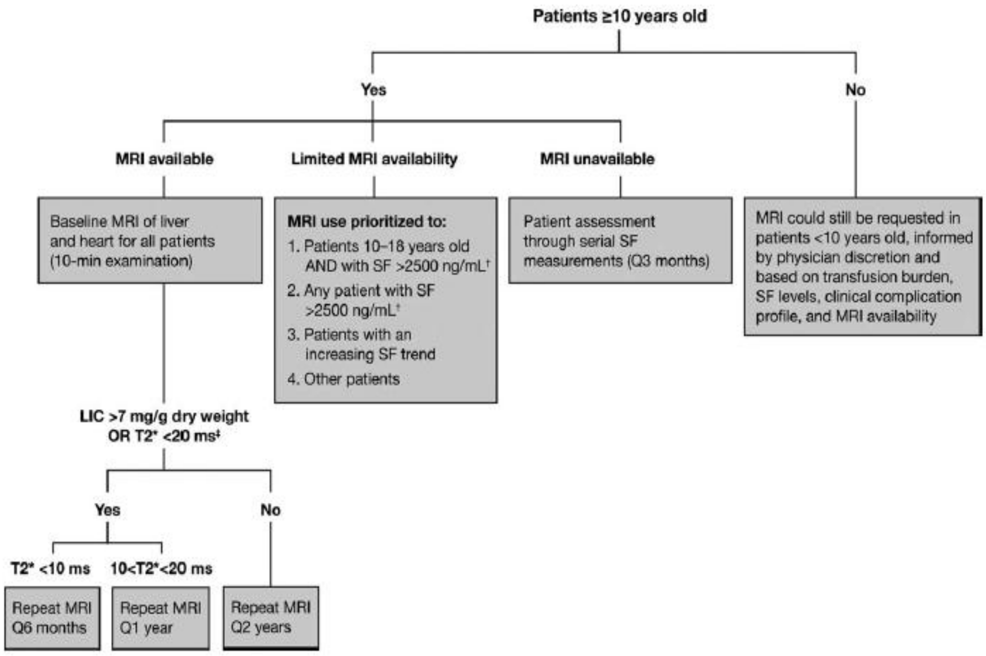

FIGURE 1 Algorithm to guide MRI use in TDT across countries with limited resources. †Based on serial measurements of at least three SF readings; ‡Irrespective of SF levels and heart-failure status. LIC, liver iron concentration; MRI, magnetic resonance imaging; Q, every; SF, serum ferritin; T2*, cardiac T2*

Figure 30. An algorithm to guide clinical use of MRI for the diagnosis of cardiac and liver iron overload in patients with transfusion-dependent thalassaemia when availability is limited (from Viprakasit V, Ajlan A, Aydinok Y, et al. Am J Hematol. 2018;93:E135-E1

REFERENCES

1. Zurlo MG, De Stefano P, Borgna-Pignatti C, Di Palma A, Piga A, Melevendi C, Di Gregorio F, Burattini MG, Terzoli S. Survival and causes of death in thalassaemia major. Lancet. 1989; 2(8653): 27-30

2. Borgna-Pignatti C, Cappellini MD, De Stefano P, Del Vecchio GC, Forni GL, Gamberini MR, Ghilardi R, Origa R, Piga A, Romeo MA, Zhao H, Cnaan A. Survival and complications in thalassa3emia. Ann N.Y. Acad Sci. 2005; 1054: 40-7 doi: 10.1196/annals.1345.006.

3. Ladis V, Chouliaras G, Berdousi H, Kanavakis E, Kattamis C. Longitudinal study of survival and causes of death in patients with thalassemia major in Greece. Ann N Y Acad Sci. 2005; 1054:445-50. doi: 10.1196/annals.1345.067.

4. Aldouri MA, Wonke B, Hoffbrand AV, Flynn DM, Ward SE, Agnew JE, Hilson AJ. High incidence of cardiomyopathy in beta-thalassaemia patients receiving regular transfusion and iron chelation: reversal by intensive chelation. Acta Haematol. 1990; 84: 113-7 doi: 10.1159/000205046.

5. Anderson LJ, Holden S, Davis B, Prescott E, Charrier CC, Bunce NH, Firmin DN, Wonke B, Porter J, Walker JM, Pennel DJ. Cardiovascular T2-star (T2*) magnetic resonance for the early diagnosis of myocardial iron overload. Eur Heart J. 2001; 22:2179 DOI: 10.1053/euhj.2001.2822

6. Modell B, Khan M, Darlison M, Westwood MA, Ingram D, Pennell DJ. Improved survival of thalassaemia major in the UK and relation to T2* cardiovascular magnetic resonance. J Cardiov Mag Resonance. 2008; 10:42 doi: 10.1186/1532-429X-10-42

7. Chouliaras G, Berdoukas V, Ladis V, Kattamis A, Chatziliami A, Frangodimitri C, Karabatsos F, Youssef J, Karagiorga-Lagana M. Impact of magnetic resonance imaging on cardiac mortality in thalassaemia major. J Magn Reson Imaging. 2011; 34(1): 56-9 doi: 10.1002/jmri.22621.

8. Jensen PD, Jensen FT, Christensen T, Ellegaard J. Non-invasive Assessment of Tissue Iron Overload in the Liver by Magnetic Resonance Imaging. Br J Haematol, 87 (1): 171-84 doi: 10.1111/j.1365-2141.1994.tb04888.x

9. Brittenham GM, Sheth S, Allen CJ, Farrell DE. Transfusional Iron Overload in Sickle Cell Disease. Semin Hematol. 2001; 38 (1 Suppl 1), 37-56 doi: 10.1016/s0037-1963(01)90059-9

10. St Pierre TG, Clark PR, Chua-anuson W, Fleming AJ, Jeffrey GP, Olynyk JK, Pootrakul P, Robins E, Lindeman R. Noninvasive measurement and imaging of liver iron concentration using proton magnetic resonance. Blood. 2005; 105(2): 855- 861 doi: 10.1182/blood-2004-01-017

11. Angelucci E, Brittenham GM, McLaren CE, Ripalti M, Baronciani D, Giardini C, Galimberti M, Polchi P, Lucarelli G. Hepatic Iron Concentration and Total Body Iron Stores in Thalassemia Major. N Engl J Med. 2000; 343 (5): 327-31doi: 10.1056/NEJM200008033430503

12. Lidén M, Adrian D, Widell J, Uggla B, Thunberg P. Quantitative T2* imaging of iron overload in a non-dedicated centres - Normal variation, repeatability and reader variation. Eur J Radiol Open. 2021 May 24;8:100357. doi: 10.1016/j.ejro.2021.100357

13. Labranche R, Gilbert G, Cerny M, Vu KN, Soulières D, Olivié D, Billiard JS, Yokoo T, An Tang. Liver Iron Quantification with MR Imaging: A Primer for Radiologists. RadioGraphics. 2018; 38(2): 392-412 doi: https://doi.org/10.1148/rg.2018170079

14. Henninger B, Alustiza J, Garbowski M, Gandon Y. Practical Guide to Quantification of Hepatic Iron With MRI. Eur Radiol. 2020; 30 (1), 383-393 doi: 10.1007/s00330-019-06380-9

15. Wood JC, Enriquez C, Ghugre N, Tyzka JM, Carson S, Nelson MD, Coates TM. MRI R2 and R2* mapping accurately estimates hepatic iron concentration in transfusion-dependent thalassemia and sickle cell disease patients. Blood. 2005; 106(4): 1460-1465 doi: 10.1182/blood-2004-10-3982.

16. Garbowski MW, Carpenter JP, Smith G, Roughton M, Alam MH, He T, Pennell DJ, Porter JB. Biopsy-based calibration of T2* magnetic

resonance for estimation of liver iron concentration and comparison with R2 Ferriscan. J Cardiovasc Magn Reson 16, 40 (2014). https://doi.org/10.1186/1532-429X-16-40

17. Wunderlich AP, Cario H, Bommer M, Beer M, Schmidt SA, Juchems MS. MRI-based liver iron content determination at 3T in regularly transfused patients by Signal Intensity Ratio using an alternative analysis approach based on R2* theory. Rofo.2016; 188(9): 846-52 doi: 10.1055/s-0042-108859

18. Georgiev PG, Sapunarova KG, Goranova-Marinova VS, Goranov SE. Reduction of Liver Iron Load in Adult Patients with β-Thalassemia Major Treated with Modern Chelation Modalities. Folia Med (Plovdiv). 2020 Jun 30;62(2):265-270. doi: 10.3897/folmed.62.e39518.

19. Atmakusuma TD, Lubis AM. Correlation of Serum Ferritin and Liver Iron Concentration with Transient Liver Elastography in Adult Thalassemia Intermedia Patients with Blood Transfusion. J Blood Med. 2021 Apr 15;12:235-243. doi: 10.2147/JBM.S303703.

20. Positano V, Ramazzotti A, Pepe A, Salvatori C, Marcheschi P, Meloni A, Mangione M, Santarelli MF, Cianciulli P, Caruso V, Maggio A, Landini L, Lombardi M. Magnetic Resonance T2* Technique for Segmental and Global Quantification of Myocardial Iron : Multi-Centre Validation in the MIOT (Myocardial Iron Overload in Thalassemia) Network. Blood, 2008. 112 (11): 5420, doi.org/10.1182/blood.V112.11.5420.5420.

21. Fernandes JL, Sampaio EF, Verissimo M, Pereira FB, da Silva JA, de Figueiredo GS, Kalaf JM, Coelho OR. Heart and liver T2 assessment for iron overload using different software programs. Eur Radiol. 2011; 21(12):2503-10. doi: 10.1007/s00330-011-2208-1

22. K-A Git, Fioravante LAB, Fernandes JL. An Online Open-Source Tool for Automated Quantification of Liver and Myocardial Iron Concentrations by T2* Magnetic Resonance Imaging. Br J Radiol. 2015; 88 (1053), 20150269 doi: 10.1259/bjr.20150269

23. Nadar SK, Daar S, Abdelmottaleb WA, Shaikh MM, Al Mahrouqi H, Al-Raiisi M, Hassan M, Al Rawahi B, Al Rahbi S. Abnormal diastolic function and Global longitudinal strain in patients with Thalassemia Major on long term chelation therapy. Int J Cardiovasc Imaging. 2021 Feb;37(2):643-649. doi: 10.1007/s10554-020-02036-8.

24. Ojha V, Ganga KP, Seth T, Roy A, Naik N, Jagia P, Gulati GS, Kumar S, Sharma S. Role of CMR feature-tracking derived left ventricular strain in predicting myocardial iron overload and assessing myocardial contractile dysfunction in patients with thalassemia major. Eur Radiol. 2021 Aug;31(8):6184-6192. doi: 10.1007/s00330-020-07599-7.

25. Das KM, Baskaki UMA, Pulinchani A, Ali HM, Almanssori TM, Gorkom KV, Das A, Dewedar H, Sharma S. Significance of Cardiac Magnetic Resonance Feature Tracking of the Right Ventricle in Predicting Subclinical Dysfunction in Patients with Thalassemia Major. Diagnostics (Basel). 2022 Aug 9;12(8):1920. doi: 10.3390/diagnostics12081920.

26. Bonios MJ, Fountas E, Delaporta P, Kyrzopoulos S, Kattamis A, Adamopoulos SN, Tsiapras D. Left ventricular deformation mechanics over time in patients with thalassemia major with and without iron overload. BMC Cardiovasc Disord. 2021 Feb 9;21(1):81. doi: 10.1186/s12872-021-01897-8

27. Barbero U, Fornari F, Gagliardi M, Fava A, Giorgi M, Alunni G, Gaglioti CM, Piga A, Ferrero GB, Longo F. Myocardial longitudinal strain as the first herald of cardiac impairment in very early iron overload state: an echocardiography and biosusceptometry study on beta-thalassemia patients. Am J Cardiovasc Dis. 2021 Oct 25;11(5):555-563.

28. Meloni A, Pistoia L, Ricchi P, Allò M, Rosso R, Cuccia L, Casini T, Cecinati V, Serra M, Rossi V, Righi R, Renne S, Vallone A, Positano V, Cademartiri F. Prospective changes of pancreatic iron in patients with thalassemia major and association with chelation therapy. Blood Adv. 2022 Nov 4:bloodadvances.2022008805. doi: 10.1182/bloodadvances.2022008805.

29. Meloni A, Pistoia L, Gamberini MR, Ricchi P, Cecinati V, Sorrentino F, Cuccia L, Allò M, Righi R,

Fina P, Riva A, Renne S, Peritore G, Dalmiani S, Positano V, Quaia E, Cademartiri F, Pepe A. The Link of Pancreatic Iron with Glucose Metabolism and Cardiac Iron in Thalassemia Intermedia: A Large, Multicentres Observational Study. J Clin Med. 2021 Nov 26;10(23):5561. doi: 10.3390/jcm10235561

30. Huang J, Shen J, Yang Q, Cheng Z, Chen X, Yu T, Zhong J, Su Y, Guo H, Liang B. Quantification of pancreatic iron overload and fat infiltration and their correlation with glucose disturbance in pediatric thalassemia major patients. Quant Imaging Med Surg. 2021 Feb;11(2):665-675. doi: 10.21037/qims-20-292.

31. Nayak AM, Choudhari A, Patkar DP, Merchant RH. Pituitary Volume and Iron Overload Evaluation by 3T MRI in Thalassemia. Indian J Pediatr. 2021 Jul;88(7):656-662. doi: 10.1007/s12098-020-03629-w.

32. Abdel-Gadir A, Vorasettakarnkij Y, Ngamkasem H, et al. Ultrafast Magnetic Resonance Imaging for Iron Quantification in Thalassemia Participants in the Developing World: The TIC-TOC Study (Thailand and UK International Collaboration in Thalassaemia Optimising Ultrafast CMR). Circulation. 2016;134(5):432–434. doi:10.1161/CIRCULATIONAHA.116.022803

33. Global Atlas of medical devices. WHO medical devices technical series. https://www.who.int/medical_devices/publications/global_atlas_meddev2017/en/

34. Hussain S, Hoodbhoy Z, Ali F, Hasan E, Alvi N, Hussain A, Ishrat K, Ur Rahman Z, Qamruddin A, Parvin A, Hasan BS. Reduction of cardiac iron overload by optimising iron chelation therapy in transfusion dependent thalassaemia using cardiac T2* MRI: a quality improvement project from Pakistan. Arch Dis Child. 2020 Nov;105(11):1041-1048. doi: 10.1136/archdischild-2020-319203.

35. Atmakusuma TD, Kalwani R, Nasution SA, Rumende CM. Correlation of Serum Ferritin and Cardiac Iron Toxicity with Cardiac Function in Transfusion Dependent Beta-Thalassemia Major Patients. Acta Med Indones. 2021 Jul;53(3):291-298.

36. Fianza PI, Rahmawati A, Widihastha SH, Afifah S, Ghozali M, Indrajaya A, Pratama DMA, Prasetya D, Sihite TA, Syamsunarno MRAA, Setiabudi D, Fucharoen S, Panigoro R. Iron Overload in Transfusion-Dependent Indonesian Thalassemic Patients. Anemia. 2021 Apr 15;2021:5581831. doi: 10.1155/2021/5581831

37. Dissanayake R, Samarasinghe N, Waidyanatha S, Pathirana S, Neththikumara N, Dissanayake VHW, Wetthasinghe K, Gooneratne L, Wickramasinghe P. Assessment of iron overload in a cohort of Sri Lankan patients with transfusion dependent beta thalassaemia and its correlation with pathogenic variants in HBB, HFE, SLC40A1, and TFR2 genes. BMC Pediatr. 2022 Jun 15;22(1):344. doi: 10.1186/s12887-022-03191-

38. Saadatifar H, Niayeshfar A, Mard-Soltani M, Bahrampour E, Khalili S, Alinezhad Dezfuli D, Pouriamehr S. The correlation of cardiac biomarkers and myocardial iron overload based on T2* MRI in major beta-thalassemia. Int J Cardiovasc Imaging. 2021 Nov 2. doi: 10.1007/s10554-021-02458-y.

39. Shiae Ali E, Bakhshali MA, Shoja Razavi SJ, Poorzand H, Layegh P. Cardiac MR images of thalassemia major patients with myocardial iron overload: a data note. BMC Res Notes. 2021 Aug 19;14(1):318. doi: 10.1186/s13104-021-05733-2.

40. Rezaeian N, Asadian S, Parsaee M, Toloueitabar Y, Hemmati Komasi MM, Shayan L, Hosseini L. The predictive role of cardiac magnetic resonance imaging in determining thalassemia patients with intermediately to highly probable pulmonary hypertension. Echocardiography. 2021 Oct;38(10):1769-1777. doi: 10.1111/echo.15210.

41. Au WY, Lam WW, Chu WW, Yuen HL, Ling AS, Li RC, Chan HM, Lee HK, Law MF, Liu HS, Liang R, Ha SY. A cross-sectional magnetic resonance imaging assessment of organ specific hemosiderosis in 180 thalassemia major patients in Hong Kong. Haematologica. 2008 May;93(5):784-6. doi: 10.3324/haematol.12367

42. Karakus V, Kurtoğlu A, Soysal DE, Dere Y, Bozkurt S, Kurtoğlu E. Evaluation of Iron Overload in the Heart and Liver Tissue by Magnetic Resonance Imaging and its Relation to Serum

Ferritin and Hepcidin Concentrations in Patients with Thalassemia Syndromes. Indian J Hematol Blood Transfus. 2017 Sep;33(3):389-395. doi: 10.1007/s12288-016-0735-2

43. Chaosuwannakit N, Makarawate P, Wanitpongpun C. The Importance of Cardiac T2* Magnetic Resonance Imaging for Monitoring Cardiac Siderosis in Thalassemia Major Patients. Tomography. 2021 Apr 18;7(2):130-138. doi: 10.3390/tomography7020012.

44. Batouty NM, Tawfik AM, Sobh DM, Gadelhak BN, El-Ashwah S, Hussein MA, Gad M, Aziz AAAE, El-Shahed MA, Karam R. Global and regional cardiac magnetic resonance feature tracking left ventricular strain analysis in assessing early myocardial disease in β thalassemia major patients. J Cardiovasc Imaging. 2024 Aug 3;32(1):18. doi: 10.1186/s44348-024-00026-1.

45. Longo F, Corrieri P, Origa R, Barella S, Sanna PMG, Bitti PP, Zuccarelli A, Commendatore FV, Vitucci A, Quarta A, Lisi R, Cappellini MD, Massei F, Forni GL, Piga A. Changing patterns of thalassaemia in Italy: a WebThal perspective. Blood Transfus. 2021 May;19(3):261-268. doi: 10.2450/2020.0143-20.

46. Hoe HG, Git KA, Loh CK, Abdul Latiff Z, Hong J, Abdul Hamid H, Wan Sulaiman WNA, Mohd Zaki F. Magnetic resonance imaging T2* of the pancreas value using an online software tool and correlate with T2* value of myocardium and liver among patients with transfusion-dependent thalassemia major. Front Radiol. 2022 Sep 6;2:943102. doi: 10.3389/fradi.2022.943102.

47. Atmakusuma TD, Kalwani R, Nasution SA, Rumende CM. Correlation of Serum Ferritin and Cardiac Iron Toxicity with Cardiac Function in Transfusion Dependent Beta-Thalassemia Major Patients. Acta Med Indones. 2021 Jul;53(3):291-298.

48. Kattamis A, Voskaridou E, Delicou S, Klironomos E, Lafiatis I, Petropoulou F, Diamantidis MD, Lafioniatis S, Evliati L, Kapsali E, Karvounis-Marolachakis K, Timotheatou D, Deligianni C, Viktoratos P, Kourakli A. Real-world complication burden and disease management paradigms in transfusion-related β-thalassaemia in Greece: Results from ULYSSES, an epidemiological, multicentre, retrospective cross-sectional study. EJHaem. 2023 May 23;4(3):569-581. doi: 10.1002/jha2.695.

49. Viprakasit V, Ajlan A, Aydinok Y, Al Ebadi BAA, Dewedar H, Ibrahim AS, Ragab L, Trad O, Wataify AS, Wong LLL, Taher AT. MRI for the diagnosis of cardiac and liver iron overload in patients with transfusion-dependent thalassemia: An algorithm to guide clinical use when availability is limited. Am J Hematol. 2018 Jun;93(6):E135-E137. doi: 10.1002/ajh.25075.