10. DISABILITY IN THALASSAEMIA

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ABSTRACT

Thalassaemia can be a disability-inducing disease if poorly treated or as complications increase with age, determined by the quality of medical management and social and personal factors. The ongoing debate on whether thalassaemia is a disability or not is thus complex and inconclusive and has created a vast heterogeneity of policies and approaches across the globe. Given that the risk to develop disabilities is subject to individualised assessment, the Thalassaemia International Federation (TIF) proposes a specific disability risk assessment model for thalassaemia (DRAM-Thal), based on the findings of a targeted literature review and of the TIF Survey 2022–2023. The model considers both clinical features and social parameters and is addressed to national social services and all other relevant stakeholders. At the same time, this work invites further research on the understudied topic of disability in thalassaemia that heavily affects the rights and daily life of people living with the disease.

INTRODUCTION

In the last half century, the life expectancy of beta-thalassaemia patients has dramatically increased mostly due to appropriate management as per the recommendations of the international guidelines, including provision of regular blood transfusions, chelation treatments, and multidisciplinary care. The improved survival rate, however, has increased the need to promote well-structured and co-ordinated multidisciplinary care for addressing existing and emerging comorbidities, such as cardiovascular disease, liver disease, diabetes mellitus, increasing pain, and hearing loss [1, 2,-3], with a non-negligible impact on the patients' quality of life. While thalassaemia itself is not defined or percieved as a disability to date, its complex, lifelong clinical needs impact on an individual's health, everyday life, and social integration and can lead to various complications that may be considered disabilities, i.e., the loss, to a smaller or greater level, of the patient's ability and competency to achieve professional, education, personal, social, and other goals.

The debate on whether thalassaemia is a disability or not has been ongoing and inconclusive for decades. People with thalassaemia do not wish, on the one hand, to be considered disabled persons to avoid being stigmatised and consequently losing opportunities to achieve social inclusion in all paths of life. On the other hand, they are in need of appropriate, lifelong disease-specific health and social care, through disability allowances and schemes in order to be able to smoothly integrate into society and all other life settings. Successful social integration has been achieved in settings where optimal multidisciplinary health and social care schemes are available, easily accessible, and tailored to patients, i.e., in Greece [4], Italy [5], and Cyprus [6].

In this work, TIF aims at shedding some new light on the different types of disability, identifying those types that may be part of the thalassaemia syndromes and suggesting a disability risk assessment model that may be used by social services of each country to assess each person with thalassaemia. It also aims at encouraging researchers to focus on this understudied and controversial topic that is closely linked to the socioeconomic situation of each country.

METHODOLOGY

To be able to define disability, identify how it is associated with thalassaemia, and develop a disability risk assessment model, we conducted a targeted literature review on the existing definitions of disability and identified those parameters of the disease (clinical and social) that relate to disability. After verifying those parameters through the findings of the TIF Survey 2022–2023, we developed a disability risk assessment model for thalassaemia (DRAM-Thal) addressed to the social services of each country and other interested stakeholders.

FINDINGS

Targeted Literature Review – Defining Disability

Defining disability is a complex, evolving matter, as the term "disability" covers a broad range and degree of conditions. A disability may have been present at birth, caused by an accident, or developed over time. The most well-known definition of disability is included in the International Classification of Functioning, Disability and Health (ICF) [7], a framework published by the World Health Organization in 2001 for defining and measuring functioning and disability. According to the ICF, "disability is an umbrella term for impairments, activity limitations and participation restrictions, referring to the negative aspects of the interaction between an individual (with a health condition) and that individual's contextual factors (environmental and personal factors)".

In 2006, the United Nations [8], in the *Convention on the Rights of Persons with Disabilities*, gave a more elaborated definition, stating that "persons with disabilities include those who have long-term physical, mental, intellectual or sensory impairments, which in interaction with various barriers may hinder their full and effective participation in society on an equal basis with others". Based on existing definitions, different countries perceive and define disability differently in national legislation. For instance, the Centres for Disease Prevention and Control (CDC) consider disability as "any condition of the body or mind (impairment) that makes it more difficult for the person with the condition to do certain activities (activity limitation) and interact with the world around them (participation restrictions)" [9]. The CDC further specifies that disability can be "related to conditions that are present at birth and may affect functions later in life, including cognition (memory, learning, and understanding), mobility (moving around in the environment), vision, hearing, behaviour, and other areas. These conditions may be disorders in single genes, including thalassaemia".

In general, disability is linked to limitations, either physical or cognitive, in each person's daily activities. Disabilities can manifest in various forms and affect individuals in different ways. They are often categorised based on the nature of the impairment and its impact on a person's ability to perform daily activities. The UN definition of disability provides a broader framework for the categorisation of disability, that can be physical, mental, intellectual or sensory. The ICF Checklist [10] further elaborates these categories and refers to body functions and structures. Table 1 presents the different types of disability.

Table 1. Amalgamation of categories of disabilities

Physical	Mental
- Chronic health conditions (e.g., diabetes, cardiovascular conditions, respiratory conditions) - Mobility impairments (e.g., paralysis, cerebral palsy, limb loss) - Dexterity or fine motor skill impairments (e.g., arthritis) - Neurological disabilities (e.g., epilepsy, multiple sclerosis, Parkinson's Disease)	- Mental health conditions (e.g. depression, anxiety)
Intellectual	**Sensory**
- Learning disabilities (e.g. dyslexia, attention-deficit/hyperactivity disorder) - Memory impairments	- Visual impairments (e.g., blindness, low vision) - Hearing impairments (e.g., hearing loss, deafness)
Communication	**Invisible**
- Speech impairments (difficulties in articulation, fluency, or voice production) - Language disorders (challenges in understanding or using language effectively)	- Invisible disabilities (e.g., chronic pain, chronic fatigue syndrome)

Thalassaemia as A Disability-Including Disease – Legislation and Other Official Documents

The diversity of opinions and practices concerning disability in various countries and in the minds of both patients and physicians affects the policies on patient social support, such as disability pensions and age of retirement. It also has an effect on how patients perceive themselves, their body image, their social integration and general psychosocial adjustment. In addition, the concept of disability is absent when describing patient outcomes in these conditions, yet it is possible that limitations to function may occur over time even in well treated patients, and such limitations may be more evident at a young age in poorly treated patients.

In 2005, the World Health Assembly, in its Resolution on Disability [11], had expressly recognised thalassaemia as a disability, calling Member States to contain the number of new affected births by implementing "as appropriate, family counselling programmes, including premarital confidential testing for diseases such as anaemia and thalassaemia, along with prevention counselling for intra-family marriages". Since then, according to available data, very few countries have explicitly recognised thalassaemia as a disability-inducing disease, incorporating it in national legislation.

In 2005, the Australian Government included thalassaemia and other haemoglobinopathies requiring chelation therapy in its "List of Recognised Disabilities" [12]. In 2007, the United Arab Emirates included people with thalassaemia in their Disability Act [13]. In India, the Rights of Persons with Disabilities (RPWD) Act [14], adopted in December 2016, recognised persons with blood disorders (thalassaemia, haemophilia and sickle cell disease) as "persons with disabilities". Those assessed with a benchmark disability of 40% are given a Disability Certificate and are entitled to several social benefits, including access to education, employment, and financial support.

In Greece, thalassaemia has also been directly associated with disability under national legislation that provides, inter alia, for social benefits such as early retirement and ease of access to public universities [15]. In Italy, thalassaemia has also been recognised as a disability through national legislation on disability that provides for several social benefits and allowances [16]. The United States and the United Kingdom provide thalassaemia patients with disease-specific allowances under the "Compassionate Allowances [17]" and the "Personal Independence Payment" [18] programmes, respectively, that address people with disabilities. In Cyprus, even if thalassaemia is not officially recognised as a disability, the disease-specific allowances provided under the amended Social Insurance Law 59(I) of 2010 are a responsibility of the Department of Social Integration of People with Disabilities of the Deputy Ministry of Social Welfare.

The Medical Perspective

Based on the ICF model, the effects of a health condition on a patient's life start from the body structures and functions and progresses to the person's participation in activities to varying degrees. The final effects are influenced by personal factors (i.e., education, adaptation, and adherence) and social and environmental factors (i.e., family support and socio-economic status). Therefore, we must refer to the *TIF Guidelines for the clinical management of transfusion-dependent thalassaemia* [19] to identify whether and which body structure defects exist and how these affect function. In fact, thalassaemia does not a priori come with any defects except for anaemia and, if this is treated early, thalassaemia cannot be termed a disability. Disabilities appear if the patient is poorly treated or as complications increase with age [20], again determined by the degree and quality of medical management and qualified by social and personal factors. For these reasons, there can be no generalised claim of thalassaemia as a disability. Individuals with these syndromes can become disabled, according to the quantity and quality of clinical management [21]. The possible somatic consequences of the thalassaemia syndromes, as derived by the underlying pathophysiology, are described in Figure 1.

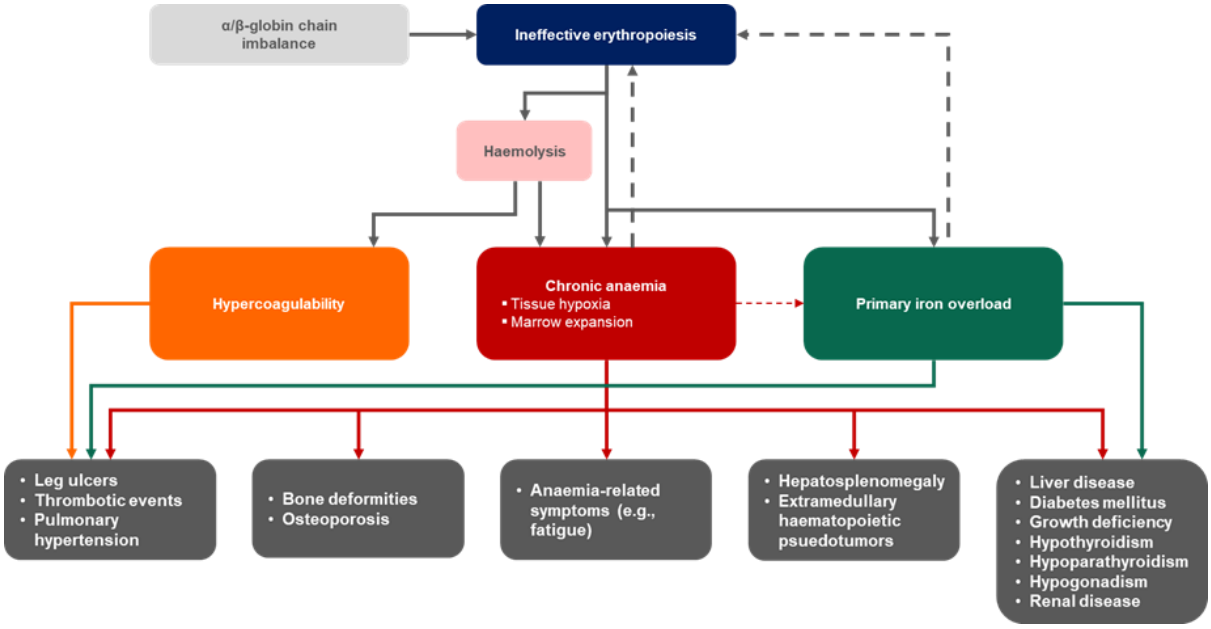


Figure 1. Comorbidities in TDT and NTDT – Source: Cappellini et al., 2021; Taher et al., 2023

Anaemia

Anaemia results directly from the main pathophysiology of the disease and may cause symptoms, such as fatigue, exercise intolerance, enlarged spleen, or child irritability. In acute anaemia, these are prominent, but in anaemia, which is congenital and chronic, the patient may not feel any symptoms. A rapid fall in haemoglobin (acute on chronic) may, however, cause more subjective symptoms.

- In transfusion-dependent thalassaemia (TDT), diagnosis leads to blood transfusion, and symptoms may appear before the next transfusion and eliminated by the transfusion. If not treated, a TDT individual will become progressively debilitated with extreme fatigue and weakness, compounded by splenomegaly and the effects of ineffective erythropoiesis (described below). Extreme anaemia will also result in high-output heart failure [22], which is both debilitating and lethal. The prevalence of cognitive impairment is high amongst patients and is associated with low haemoglobin and increasing age [23].

- In non-transfusion dependent thalassaemia (NTDT), there is chronic anaemia, which alone causes few symptoms in the majority of patients, given that the haemoglobin does not usually fluctuate very much, except in the event of acute episodes, such as intercurrent infections [24]. Such episodes prompt blood transfusions and correction of the anaemia. Nevertheless, chronic anaemia will have other consequences which include tissue hypoxia affecting various organs that may lead to disability and death, such as high-output heart failure and pulmonary hypertension [25].

Bone Marrow Expansion

Expansion of the erythropoietic tissue to compensate for ineffective erythropoiesis is a basic feature of the thalassaemia syndromes. This tissue expansion has various consequences.

- Bone deformity: Within the bone marrow the tissue expansion from early life will disrupt bone microarchitecture and cause bone deformity, growth retardation, and low bone mineral density. This can be extreme in poorly treated patients affecting long bones, spinal column, skull, and facial bones. Deformity can affect body image and patient psychology, especially in adolescence; in this way, it can play a negative role in patient participation and social adjustment. Moreover, deformity of the facial and especially maxillary bones, which exceed the growth of the mandible, may lead to malocclusion with functional difficulties in eating and dental disease, besides aesthetic considerations [26].

- Osteoporosis is a major contributor to poor quality of life, causing bone pain and spinal deformities with collapsed vertebrae, which may result in nerve compression. Fractures are also a consequence and can occur at all ages with minimal trauma. Severe bone disease of this type can be regarded as disability, as it can limit one's ability to participate in activity.

- Extramedullary haemopoietic masses (pseudotumors) may occur at various sites, and any contribution to disability will depend on location and size of the mass. In TDT, regular transfusions suppress abnormal haemopoiesis if the haemoglobin is maintained above 9 g/dl. If this level is not achieved in TDT, and especially in NTDT in which there is a persistent anaemia, such masses are encountered more frequently. Clinical debility is most often the result of paraspinal masses that cause compression of the spinal nerves, resulting in back pain and paraesthesia, which may progress to paraparesis and paraplegia, with effect on mobility. Such neurological effects may become permanent if not treated early (e.g., by blood hypertransfusions, hydroxyurea, irradiation).

Iron Overload

- Iron overload, resulting from increased intestinal iron absorption due to ineffective erythropoiesis and particularly due to repetitive blood transfusions, may lead to vital tissue injury by free unbound iron radicals, but rarely to the extent that the label disability can be adopted.
- Heart disease due to iron overload cardiomyopathy is frequent in TDT patients and later in life, and it may also affect NTDT patients. The clinical effects include ventricular dysfunction, which can progress to heart failure and severe arrhythmias [27]. These can severely limit daily function and restrict social participation.
- Liver disease is rarely debilitating in thalassaemia patients unless very advanced, including liver cirrhosis and hepatocellular carcinoma.
- Endocrine complications are common in thalassaemia, but the effects on quality of life are rarely disabling since diagnosis is usually prompt and hormonal replacement effective. Delayed puberty and hypogonadism can seriously affect adolescents' psychological maturation. Hypothyroidism even if untreated causes non-specific symptoms but can contribute to heart complications. Diabetes can have serious disabling complications, including visual impairment, cardiac arrhythmias, and stroke. Hypoparathyroidism can cause paraesthesia, prolonged QT interval, tetany, seizures, and even heart failure [28]. In all endocrine complications, a degree of disability can be experienced in thalassaemia patients depending on the quality of monitoring and response from clinical experts.
- Fertility can be affected in both males and females [29], mainly causing psychological effects.

Vascular Complications and Hypercoagulability

These are more common in NDTD patients, especially if splenectomised. The most common effects include leg ulcers and thromboembolic events.

Leg ulcers are a complication which increases with age and can severely limit a patient's freedom to move and participate, reducing quality of life [30]. There is ischaemia of the skin, leading to ulceration, which cannot heal easily and causes local pain. Such ulcers often take several months to heal and may require surgical intervention (skin grafting).

Thromboembolic events are related to a hypercoagulable state which is related to splenectomy and NTDT [31]. These phenomena cause mainly venous thromboses, such as deep vein thromboses, but they are also associated with cerebrovascular events, which range from silent infarcts to overt stroke [32]. Pulmonary hypertension may also be related to hypercoagulability even though this may not be the only causative factor [33].

Drug Toxicity

Several medications are taken regularly by thalassaemia patients, and almost universally taken are the iron chelating agents desferrioxamine, deferiprone, and deferasirox. All these can cause long-term adverse effects, including ocular, auditory, bone growth retardation, allergic reactions, gastrointestinal disturbance, renal toxicity, liver toxicity, debilitating arthralgia, and finally agranulocytosis/neutropenia, which is mainly caused by deferiprone and can make one susceptible to severe infections. Hydroxyurea, even though generally well tolerated, can cause bone marrow suppression. This may cause bleeding (mainly gastrointestinal) and susceptibility to severe infections. Other reported side effects include mental/mood changes (such as confusion, hallucinations), seizures, dyspnoea, and renal toxicity. Bisphosphonates may cause osteonecrosis of

the jaw, but also hypocalcaemia, bone and joint pain, and renal toxicity have been reported. Finally, recently approved therapies may cause bone pain, arthralgia, hypertension, and hyperuricaemia. In addition, thromboembolic events have been reported, which include DVT, pulmonary emboli, portal vein thromboses, and strokes [19].

In summary, from a medical perspective, the thalassaemia syndromes (especially TDT) that are optimally treated cannot be classified as disability. They allow a full range of activities and participation, including education, employment, marriage and raising a family. Involvement in most sports is possible including isolated reports of individuals completing marathon runs. Such extreme sports, however, should be undertaken after medical assessment. NTDT should be viewed with caution since even carefully followed patients can develop complications from young adulthood. Complications of the condition and its treatment are in fact possible initiators of disabling, activity limiting developments. For this reason, it is usually the undertreated thalassaemia patient that can be classified as disabled but only after taking into account the nature and degree of disability.

The Patients' Perspective

Thalassaemia patients experience chronic fatigue and weakness due to the reduced oxygen-carrying capacity of their blood. While this is not always observable by others, it may impact patients' ability to engage in daily activities, energy levels, and overall well-being, leading to depression, anxiety, and other mental health challenges. Patients also need to address low self-esteem, especially when bone deformities and skeletal abnormalities are present due to bone marrow expansion. Moreover, progressive organ damage in the heart, liver, and spleen, which is linked to iron overload, may affect physical function and mobility, and lead to visible disabilities and a decreased quality of life.

These effects that adversely affect the lives of patients and may cause disabilities, are manageable when patients are adherent and have access to appropriate medical management and treatment. Nonetheless, once developed, they are usually permanent rather than transient and are best prevented by holistic care or detected early to reduce progression. Early access to disease-specific education, supportive care, including counselling and rehabilitation services, and social care schemes and allowances or benefits, may be beneficial for addressing the broader impact of the condition on an individual's life and reducing the likelihood of disability.

To better understand and clarify the health status of patients, and the correlation between each country's income level and the risk of patients to develop disabilities, TIF's Survey 2022–2023 addressed patients and their families, and it collected feedback from 2071 individuals from 48 countries, most of whom resided in lower income countries (1,134, 56%), according to the World Bank 2022 definition (Figure 2) [34].

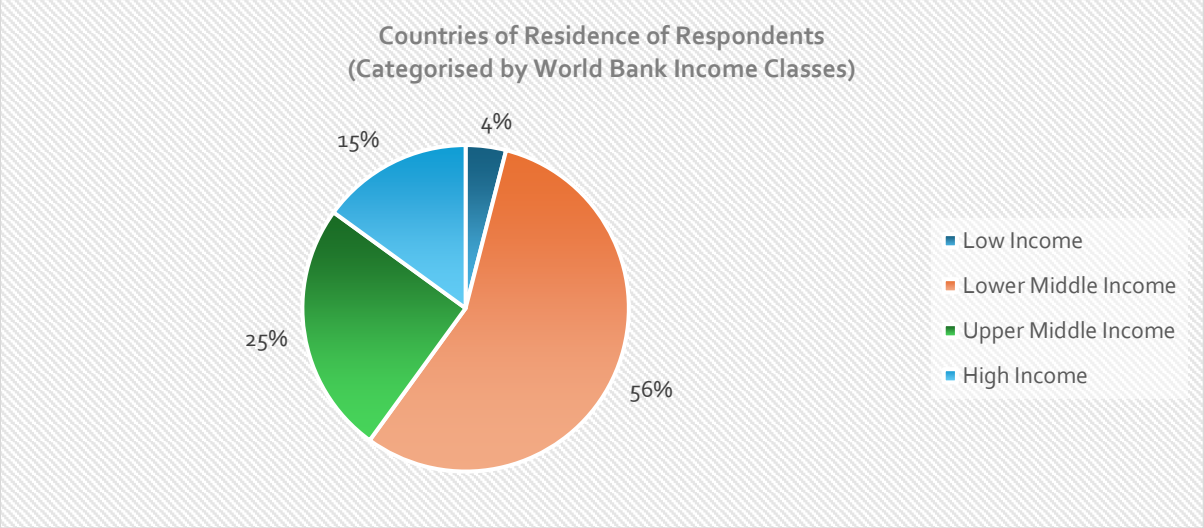


Figure 2. Countries of residence of respondents (Categorised by World Bank Income Classes) According to the World Bank, lower-middle-income economies are those with a gross national income (GNI) per capita between $1,136 and $4,465; upper-middle-income economies are those with a GNI per capita between $4,466 and $13,845; high-income economies are those with a GNI per capita of $13,846 or more.

Based on the parameters set by medical experts, as described above, we focused on specific questions that would reveal the quality of services in each country, whether patients are well treated and if they are prone to develop disabilities. The survey has indeed proven that people with thalassaemia, living in developing (low-income and lower-middle-income) countries, pay out of pocket to access health services and have a poorer clinical image compared to patients living in upper-middle- and high-income countries. Such expenses hit the poor the hardest and threaten decades-long progress on health, leading people with thalassaemia closer to disability.

Age

Survey findings show that an ageing thalassaemia population lives in high income countries, indicative of the level of healthcare patients receive and of the confined or manageable number of comorbidities (Figure 3).

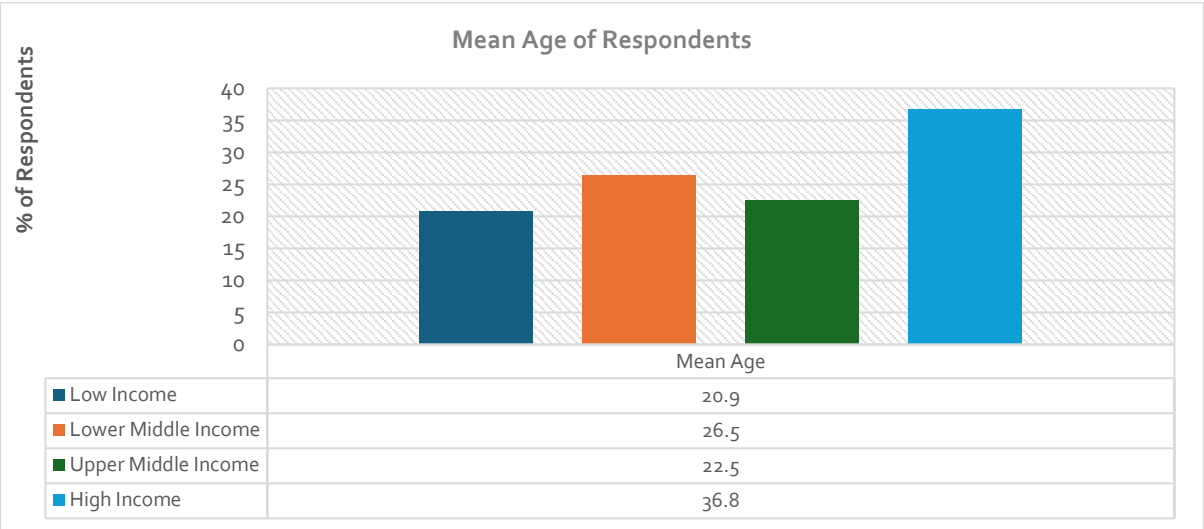
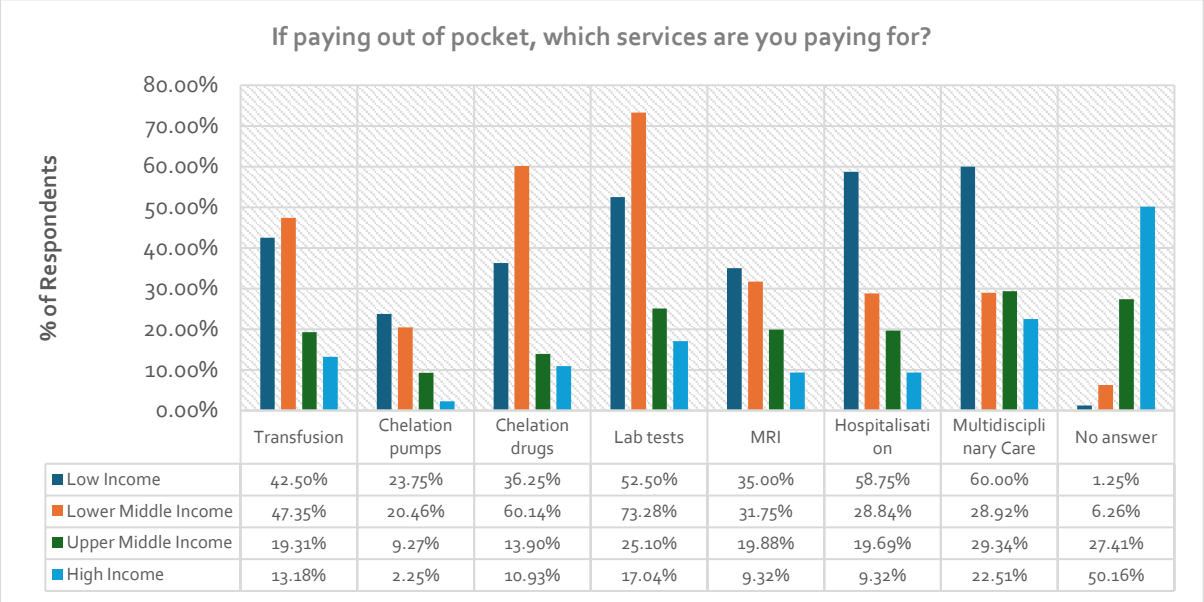


Figure 3. Mean age of respondents

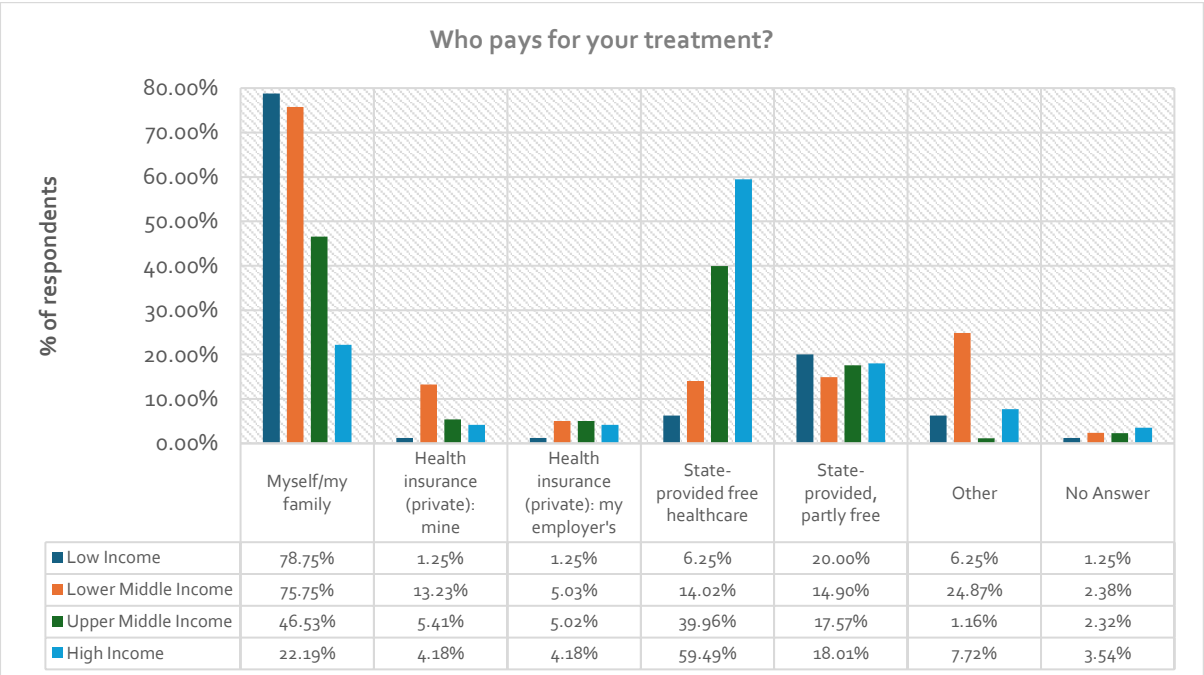
Accessibility of Healthcare

Survey respondents indicated that they themselves pay for access to essential care in low- and lower-middle-income countries, while multidisciplinary care remains challenging in such settings. Having to carry the burden of the treatment means that patients and their families need to have the financial means to do so (Figures 4 & 5). Based on the survey findings, almost half of the respondents living in low-income settings are unemployed and one third is already disabled at a very young age, given that the median age of respondents is 20.9 years old (Figure 6). On the contrary, people living in high-income countries have uninterrupted access to appropriate healthcare, without them or their families having to carry the burden of treatment. They are also employed, working full time and in position to have a better quality of life.



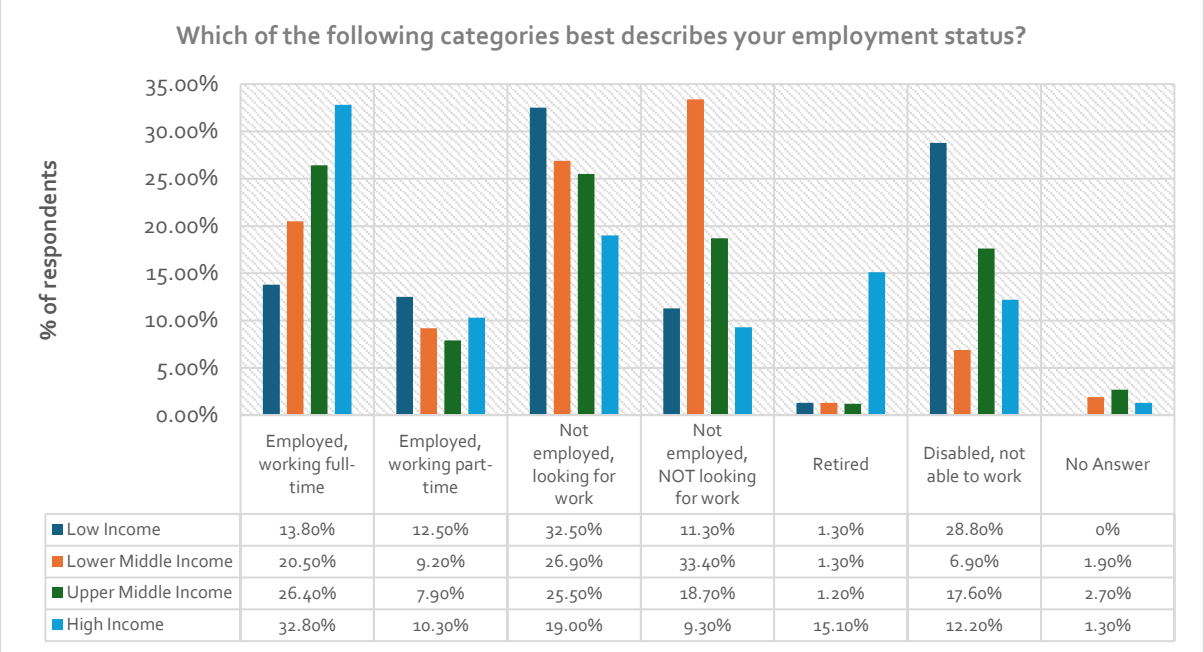
	Transfusion	Chelation pumps	Chelation drugs	Lab tests	MRI	Hospitalisation	Multidisciplinary Care	No answer
Low Income	42.50%	23.75%	36.25%	52.50%	35.00%	58.75%	60.00%	1.25%
Lower Middle Income	47.35%	20.46%	60.14%	73.28%	31.75%	28.84%	28.92%	6.26%
Upper Middle Income	19.31%	9.27%	13.90%	25.10%	19.88%	19.69%	29.34%	27.41%
High Income	13.18%	2.25%	10.93%	17.04%	9.32%	9.32%	22.51%	50.16%

Figure 4. Healthcare services paid out-of-pocket. by country income level



	Myself/my family	Health insurance (private): mine	Health insurance (private): my employer's	State-provided free healthcare	State-provided, partly free	Other	No Answer
Low Income	78.75%	1.25%	1.25%	6.25%	20.00%	6.25%	1.25%
Lower Middle Income	75.75%	13.23%	5.03%	14.02%	14.90%	24.87%	2.38%
Upper Middle Income	46.53%	5.41%	5.02%	39.96%	17.57%	1.16%	2.32%
High Income	22.19%	4.18%	4.18%	59.49%	18.01%	7.72%	3.54%

Figure 5. Coverage schemes of healthcare services

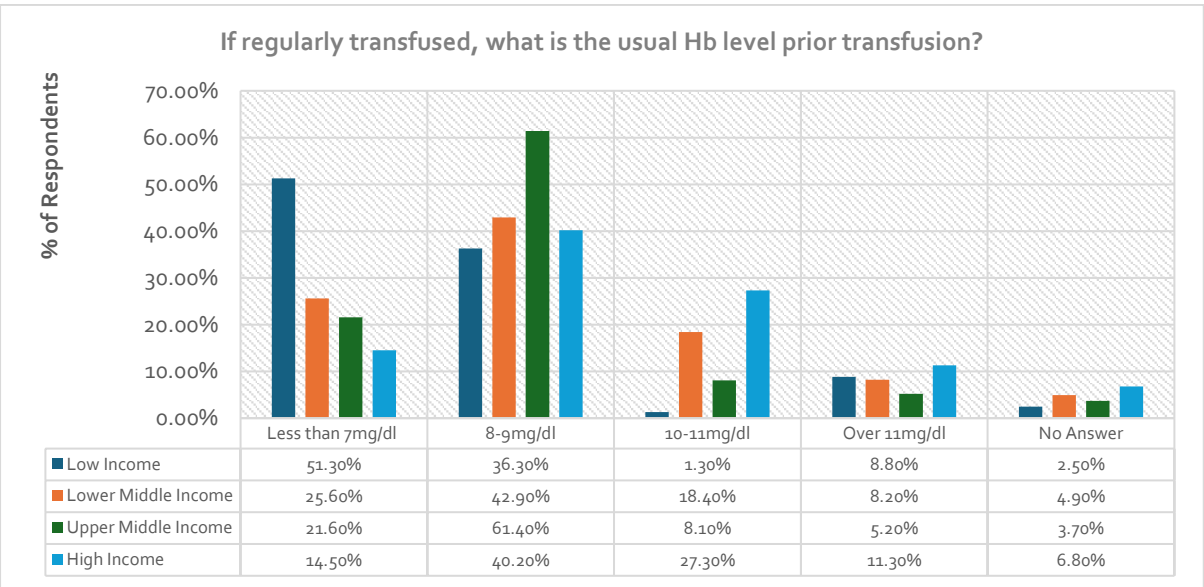


	Employed, working full-time	Employed, working part-time	Not employed, looking for work	Not employed, NOT looking for work	Retired	Disabled, not able to work	No Answer
Low Income	13.80%	12.50%	32.50%	11.30%	1.30%	28.80%	0%
Lower Middle Income	20.50%	9.20%	26.90%	33.40%	1.30%	6.90%	1.90%
Upper Middle Income	26.40%	7.90%	25.50%	18.70%	1.20%	17.60%	2.70%
High Income	32.80%	10.30%	19.00%	9.30%	15.10%	12.20%	1.30%

Figure 6. Employment status of patients with thalassaemia who responded to TIF Survey 2022–2023, by country income level.

Pre-Transfusion Hb

The majority of patients living in low-income countries report that are transfused when their haemoglobin drops below 7mg/dl (Figure 7), indicative of prolonged fatigue, weakness, shortness of breath, dizziness, or headaches that have a negative impact on the quality of life and cause cognitive and intellectual impairment. About one third of respondents living in lower-, middle-, and upper-middle-income countries face the same challenges and are at risk to develop anaemia-related disabilities.

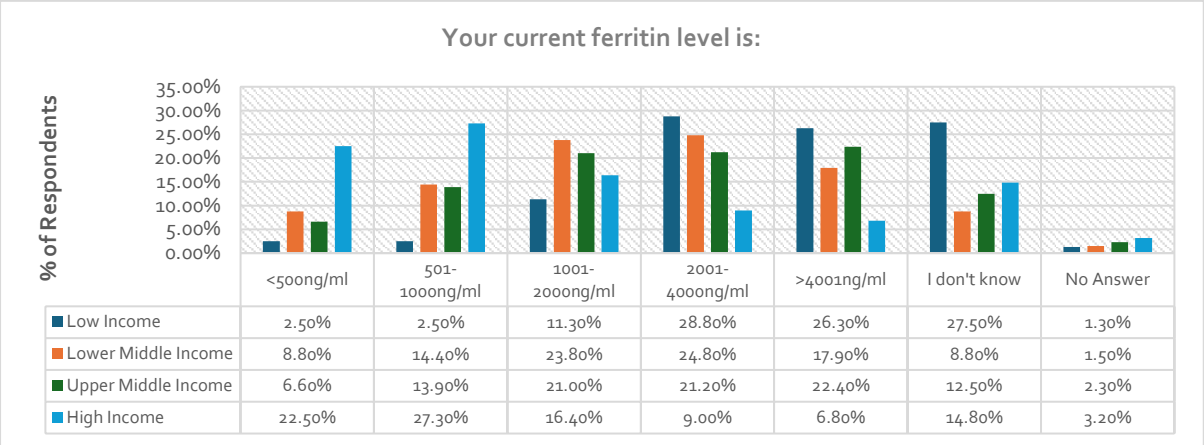


	Less than 7mg/dl	8-9mg/dl	10-11mg/dl	Over 11mg/dl	No Answer
Low Income	51.30%	36.30%	1.30%	8.80%	2.50%
Lower Middle Income	25.60%	42.90%	18.40%	8.20%	4.90%
Upper Middle Income	21.60%	61.40%	8.10%	5.20%	3.70%
High Income	14.50%	40.20%	27.30%	11.30%	6.80%

Figure 7. Quality of provided healthcare services, by country income level, and by pre-transfusional haemoglobin level

Serum Ferritin

According to TIF Guidelines, chelation therapy should be started after about one year of chronic transfusions, which correlates with a serum ferritin of approximately 1,000 ng/mL [19]. This means that people with thalassaemia who have a ferritin level higher than the 1,000 ng/mL threshold are not properly chelated. This is the case for more than half of the thalassaemia population living in low-income, lower-middle-income and upper-middle-income countries, while patients living in high-income countries report being appropriately chelated (Figure 8). Given that access to chelation drugs is essential to confine comorbidities linked to iron overload and that the majority of the global thalassaemia population lives in developing countries, it is evident that the majority of patients do not have access to chelation therapy and are thus prone to develop a wide range of disabilities.

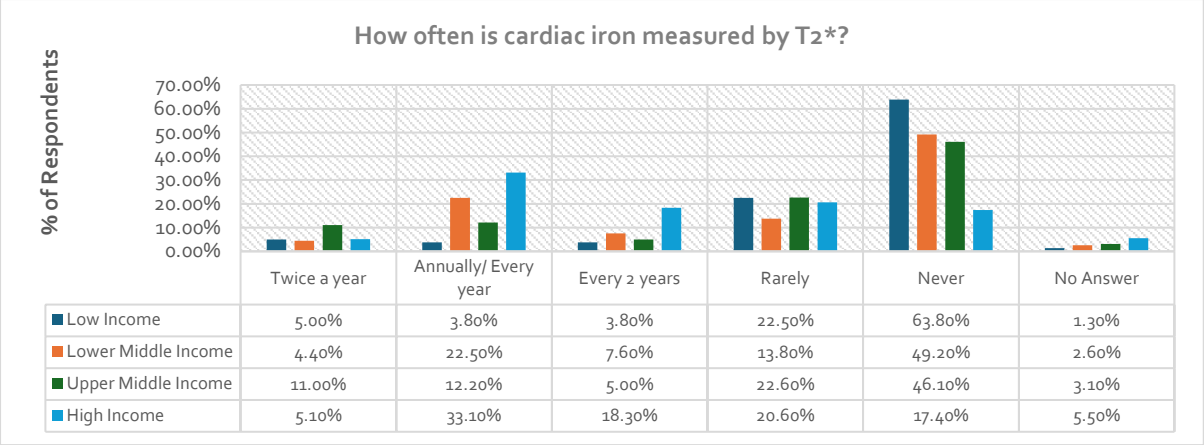


	<500ng/ml	501-1000ng/ml	1001-2000ng/ml	2001-4000ng/ml	>4001ng/ml	I don't know	No Answer
Low Income	2.50%	2.50%	11.30%	28.80%	26.30%	27.50%	1.30%
Lower Middle Income	8.80%	14.40%	23.80%	24.80%	17.90%	8.80%	1.50%
Upper Middle Income	6.60%	13.90%	21.00%	21.20%	22.40%	12.50%	2.30%
High Income	22.50%	27.30%	16.40%	9.00%	6.80%	14.80%	3.20%

Figure 8. Serum ferritin concentration

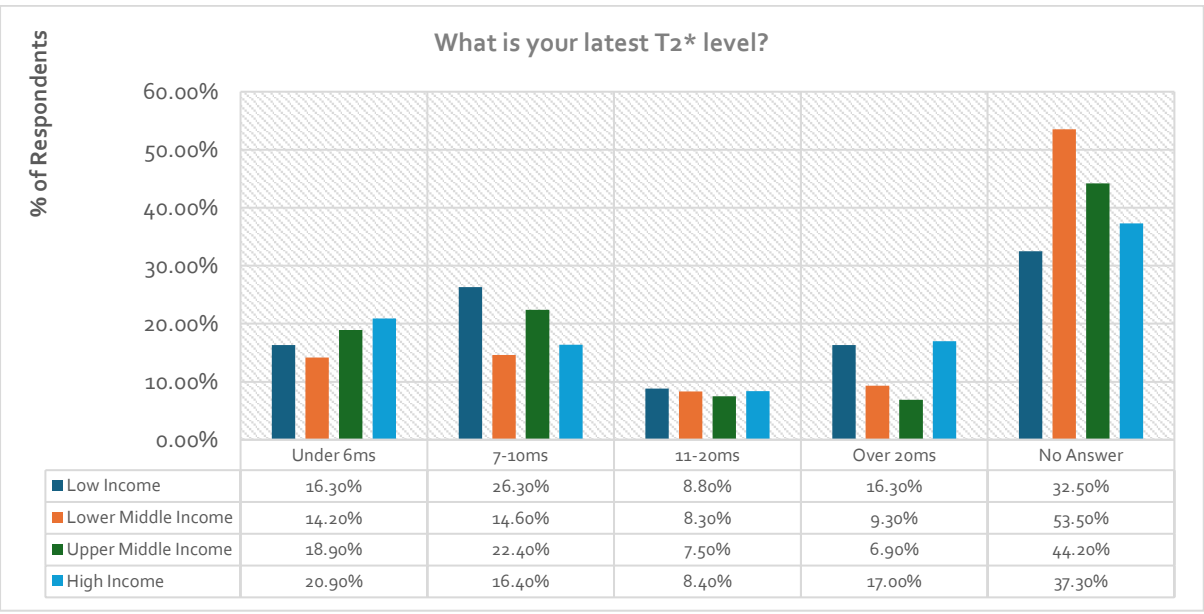
Magnetic Resonance Imaging (MRI) T2*

Magnetic resonance imaging (MRI) T2* technique is used to assess iron overload in the heart, liver, and pancreas of thalassaemic patients. It is a useful tool to evaluate the efficiency of iron chelators and monitor the health status of patients. In contrast to high-income countries, the vast majority of respondents from all other country income groups was never tested with the said technology (Figure 9). The majority of those tested globally had results lower than 20 ms (normal) which calls for the revision of thalassaemia clinical management protocols to effectively remove excess iron (Figure 10).



	Twice a year	Annually/ Every year	Every 2 years	Rarely	Never	No Answer
Low Income	5.00%	3.80%	3.80%	22.50%	63.80%	1.30%
Lower Middle Income	4.40%	22.50%	7.60%	13.80%	49.20%	2.60%
Upper Middle Income	11.00%	12.20%	5.00%	22.60%	46.10%	3.10%
High Income	5.10%	33.10%	18.30%	20.60%	17.40%	5.50%

*Figure 9. Access to magnetic resonance imaging (MRI) T2**

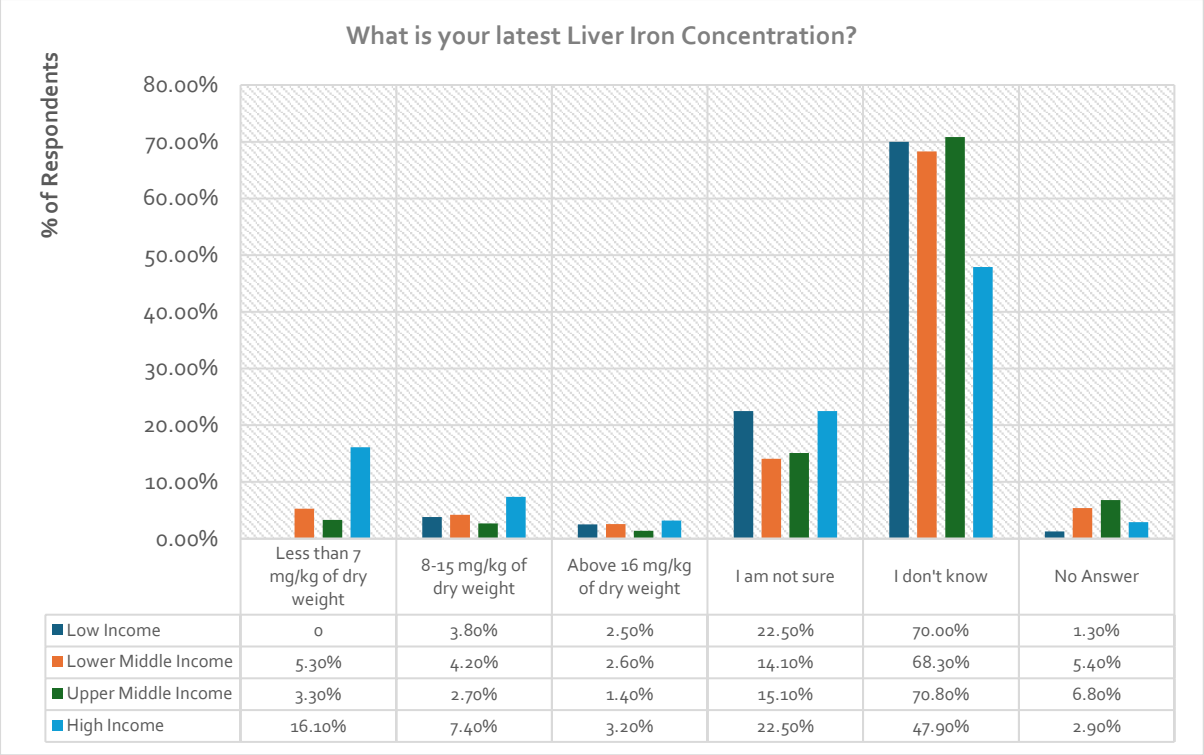


	Under 6ms	7-10ms	11-20ms	Over 20ms	No Answer
Low Income	16.30%	26.30%	8.80%	16.30%	32.50%
Lower Middle Income	14.20%	14.60%	8.30%	9.30%	53.50%
Upper Middle Income	18.90%	22.40%	7.50%	6.90%	44.20%
High Income	20.90%	16.40%	8.40%	17.00%	37.30%

Figure 10. Reported T2 value*

Liver Iron Concentration

Elevated liver iron concentration is a marker of increased comorbidities in patients with beta thalassaemia. Survey respondents reported not being sure of aware of this marker, which indicates the need for disease-specific education globally (Figure 11).

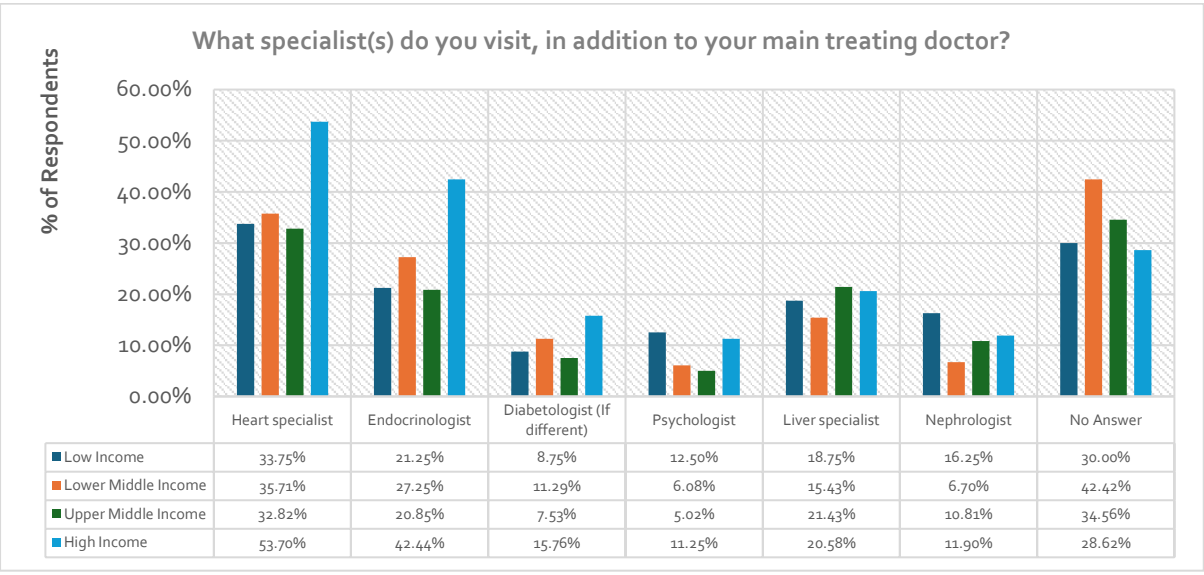


	Less than 7 mg/kg of dry weight	8-15 mg/kg of dry weight	Above 16 mg/kg of dry weight	I am not sure	I don't know	No Answer
Low Income	0	3.80%	2.50%	22.50%	70.00%	1.30%
Lower Middle Income	5.30%	4.20%	2.60%	14.10%	68.30%	5.40%
Upper Middle Income	3.30%	2.70%	1.40%	15.10%	70.80%	6.80%
High Income	16.10%	7.40%	3.20%	22.50%	47.90%	2.90%

Figure 11. Reported liver iron concentration value by country income level

Comorbidities

Survey respondents have verified that people with thalassaemia face, indeed, multiple challenges and comorbidities related to both their physical and mental health, as they need to visit different medical specialties at different intervals to address disease-related issues (Figure 12).

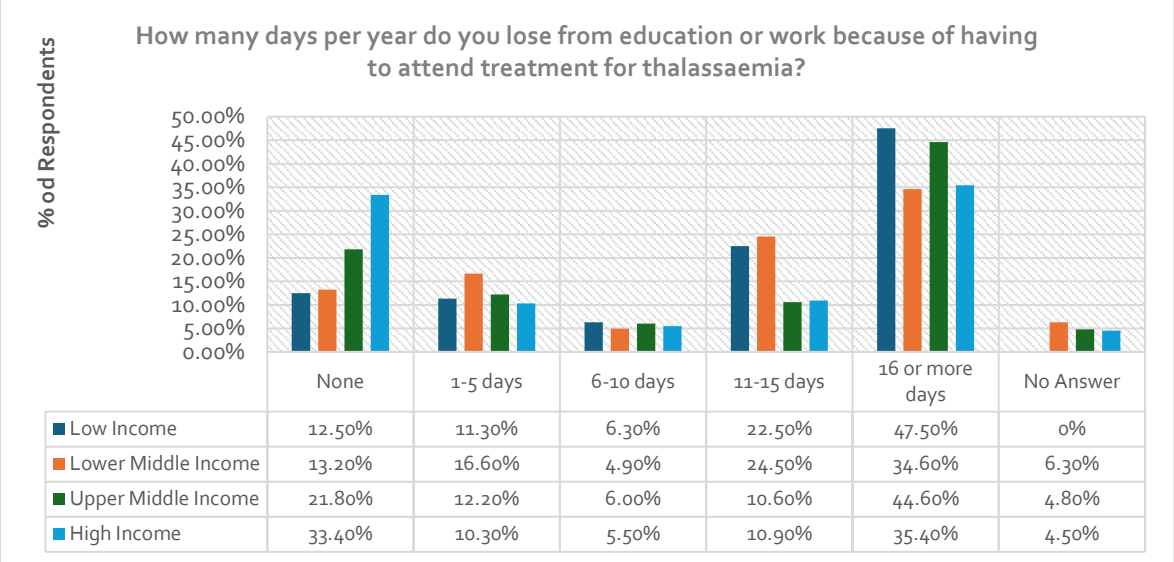


	Heart specialist	Endocrinologist	Diabetologist (If different)	Psychologist	Liver specialist	Nephrologist	No Answer
Low Income	33.75%	21.25%	8.75%	12.50%	18.75%	16.25%	30.00%
Lower Middle Income	35.71%	27.25%	11.29%	6.08%	15.43%	6.70%	42.42%
Upper Middle Income	32.82%	20.85%	7.53%	5.02%	21.43%	10.81%	34.56%
High Income	53.70%	42.44%	15.76%	11.25%	20.58%	11.90%	28.62%

Figure 12. Reported medical specialists visited, by income level

Days Lost from Education/Work

Losing days from school or work to receive treatment has a great impact on each patient's psychology and level of social integration. The vast heterogeneity of realities is depicted in Figure 13, with the majority of patients losing productive time of more than 16 days per year for treatment. Interestingly, inequalities exist even among patients living in high-income countries, as one third of respondents do not lose any days from school or work for treatment purposes (Figure 13).



	None	1-5 days	6-10 days	11-15 days	16 or more days	No Answer
Low Income	12.50%	11.30%	6.30%	22.50%	47.50%	0%
Lower Middle Income	13.20%	16.60%	4.90%	24.50%	34.60%	6.30%
Upper Middle Income	21.80%	12.20%	6.00%	10.60%	44.60%	4.80%
High Income	33.40%	10.30%	5.50%	10.90%	35.40%	4.50%

Figure 13. Number of days lost from education or work for treatment per year, by income level

DISCUSSION

TIF's Perspective

Disabilities may be general and common to many diseases, particularly chronic ones, but may also be disease-specific, e.g., due to transfusion-related infections, iron-related organ damage, or osteopenia or osteoporosis, the latter considered as old-age complications but appears in people with transfusion-dependent thalassaemia from a very young age. Given that affected patients in countries with optimal medical and social care are ageing [1], new disease-related disabilities are emerging that cannot be neglected or excluded from any policy addressing the needs of the thalassaemia community.

While it is clear that the appearance of disabilities in thalassaemia depends on the quality of care and provision of social benefits to ease adherence to treatment and social integration, countries have not yet focused on how to improve the access of people with thalassaemia to appropriate health and social care. Despite having signed or ratified the *Convention on the Rights of Persons with Disabilities* [35] and even addressing the needs of the ageing thalassaemics through disability acts and other policies, national healthcare systems still need to be strengthened, and social care services still need to become aware of the complexity of thalassaemia and why patients need individualised assessment and tailored measures to be active members of society. This is on account of the disorder's nature, genetic background, complicated pathophysiology, and consequently its vastly heterogeneous clinical outcome, which requires personalised management tailored to individual needs. The key responsibility for management lies with the physician specialised in the long-term treatment of

thalassaemia. Such complexity hence calls for targeted policy measures, so that no person with thalassaemia is left behind.

For all the above reasons, TIF has built on the ICF definition and developed the Disability Risk Assessment Model for Thalassaemia (DRAM-Thal) to provide national competent authorities with a tool to recognise disabilities in thalassaemia and successfully assess each individual case, based on personal and social factors. The DRAM-Thal may serve as (i) a statistical tool in the collection and recording of outcome data; (ii) a research tool; (iii) a measure for needs assessment and vocational assessment and for planning rehabilitation services; (iv) a social policy tool in social security planning, affecting legislation development; and (v) an educational tool.

In the thalassaemia syndromes, whether an impairment develops or a function is affected depends on several factors that extend from the healthcare system to patients themselves. These factors may be used to assess the risk and status of disability:

Accessibility of Healthcare

If a child is not treated or treated poorly due to limited access to treatment, with transfusions given at a low haemoglobin level, there is impaired function and fatigue due to anaemia. In time, bone deformities, fractures, and extramedullary haemopoiesis can occur, which may cause pressure on vital structures such as the spinal canal and nerves. Later in life, poor iron chelation can lead to organ failure causing heart disease, liver and endocrine damage.

Quality of Healthcare

The quality of healthcare services may be assessed through a set of clinical features, including each patient's:

- ***Age:*** Without close monitoring and regular treatment, beta thalassaemia may cause serious organ damage and be life threatening. With multidisciplinary care, people are likely to live into their 50s, 60s, and beyond but with the risk to develop multiple disability-inducing comorbidities.
- ***Pre-transfusional haemoglobin:*** A level of 9.0–10.5 g/dl has been shown to promote normal growth, allow normal physical activities, adequately suppress bone marrow activity, and minimise transfusional iron accumulation [19].
- ***Serum ferritin:*** It generally correlates with body iron stores and is relatively easy and inexpensive to determine repeatedly. Serum ferritin is most useful in identifying trends: an increasing trend implies an increasing iron burden that requires further clinical investigation.
- ***Cardiac iron concentration:*** T2* is an MRI technique to measure liver and cardiac iron, recommended as part of yearly monitoring of multi-transfused patients at risk of developing myocardial or liver iron loading. It requires shorter acquisition times and allows the early identification of patients at high risk of developing organ deterioration and complications.
- ***Liver iron concentration (LIC):*** It is measured to identify whether body iron is adequately controlled, as it is linked to the risk of hepatic/ extrahepatic damage. Normal LIC values are up to 1.8 mg/g dry wt, with levels of up to 7 mg/g dry wt seen in some non-thalassaemic populations without apparent adverse effects. Sustained high LIC (above 15–20 mg/g dry wt) have been linked to worsening prognosis, liver fibrosis progression, or liver function abnormalities. The most common methods to measure LIC is through biopsy, SQUID, and MRI.
- ***Splenectomy:*** If the clinical management of transfusion-dependent thalassaemia is inadequate, the increased destruction of red blood cells by reticuloendothelial system, in particular by the spleen, results in the spleen's enlargement (splenomegaly). Splenectomy, the surgical removal of the spleen is a treatment option with major adverse effects, including sepsis, thrombophilia, pulmonary hypertension and iron overload [19], affecting both the survival and quality of life of patients.
- ***Comorbidities:*** Bone disease is common at all ages, causing pain, fractures (osteopenia, osteoporosis) and limiting mobility. Iron overload causes a number of co-morbidities including vascular disease (deep vein thrombosis and cerebrovascular events), pulmonary hypertension, heart cardiomyopathy leading to heart failure; pituitary damage leading to hypogonadism, growth retardation, and delayed puberty; endocrine complications, namely diabetes, hypothyroidism and hypoparathyroidism; and liver disease, namely fibrosis, cirrhosis, and hepatocellular carcinoma, particularly if concomitant chronic hepatitis is present. Arthralgia, infections, and neurological deficits may appear, such as paraparesis and paraplegia with effects on mobility, paraesthesia, and stroke. The presence of these co-occurring conditions should be regarded as causing disability.

The Patient's Social Environment and the Social Determinants of Health

For people with chronic diseases, including thalassaemia and sickle cell disease, the social determinants of health are crucial for their overall health status, as ageing fully exposes patients to social factors and is linked to the appearance of a number of disabilities [1]. The social determinants of health (SDH) are the non-medical factors that influence health outcomes. They are the conditions in which people are born, grow, work, live, and age, which follow a social gradient: the lower the socioeconomic position, the worse the health. The factors that determine the socioeconomic position are income and social protection; education; unemployment and job insecurity; working life conditions; food insecurity; housing; basic amenities and the environment; early childhood development; social inclusion and non-discrimination; structural conflict; and access to affordable health services of decent quality. These have been analysed in the Chapter 9 of the Global Thalassaemia Review.

Pain Level

The degree of pain experienced is usually related to bone disease, but is of multifactorial aetiology. The main manifestations are osteoporosis and fractures, as well as deformities. Whatever the cause of pain, it will affect quality of life but also social function, and it may lead to depression and other mental health issues.

Mental Health Concerns: The DRAM-Thal Model

Patients with thalassemia may have at least one psychological disorder, such as depression, anxiety, psychosomatic illness, and social problems and isolation.

The above parameters may be assessed using a scoring-based system, with 1 point being given to satisfactory outcomes and 3 to poor outcomes, either clinical or social. In DRAM-Thal (Table 2), Column A includes patients who receive optimal or nearly optimal medical care and appropriate social support and have very confined chances of developing disabilities. Columns B and C include patients who are more likely to develop disabilities. These patients receive less than optimal to inappropriate medical care and weak to very poor social care and protection.

Acknowledging that medical and social care need to act synergistically for optimal outcomes, we suggest the integration of a disease-specific classification system into the disability assessment criteria of each country to assess each patient's risk to develop a disability based on their clinical perspective or status and potential health outcomes, and to best address their needs. The suggested scoring model could substantially ease national competent authorities in disability assessment, as people with either a high- or very high-risk level are deemed more vulnerable and in need of strengthened social support. Given that the vast majority of people with thalassaemia live in low- and lower-middle-income countries and have a poor clinical image, according to the literature and TIF Survey findings, immediate action needs to be taken for the benefit of such a vulnerable population.

Table 2. Disability Risk Assessment Model for Thalassaemia (DRAM-Thal) (proposed by TIF)

Disability Risk Assessment Model for Thalassaemia *Calculate points to assess risk level*		**A** **1 point** **No Risk** **None, Absent, Negligible** **Good Clinical Perspective**	**B** **2 points** **Moderate Risk** **Medium, Fair** **Moderate Clinical Perspective**	**C** **3 points** **Severe Risk** **High, Extreme** **Poor Clinical Perspective**
1	**Accessibility of Healthcare**			
	Multidisciplinary Care: *When professionals from a range of disciplines work together to deliver comprehensive care that addresses as many of the patient's needs as possible.* ***Essential Health Care:*** *For thalassaemia, it comprises of regular blood transfusions and chelation therapy.*	Free Access to Multidisciplinary Care through Universal Health Coverage or Insurance-based systems	Free Access to Essential Health Care + Paid Access to Multidisciplinary Care	Limited / No Access to Essential Health Care
2	**Quality of Health Care Services**			
i	**Age** *While disability risk increases with age, it is considered inevitable if patients are undertreated, at any age.*	<30 years old	30-45 years old	>45 years old
ii	**Pre-transfusion Hb** *A pre-transfusion haemoglobin of 9.0-10.5 g/dl has been shown to promote normal growth, allow normal physical activities, adequately suppress bone marrow activity and minimise transfusional iron accumulation.*	9.0-10.5 g/dl	7.0-9.0 g/dl	<7 mg/dl
iii	**Serum Ferritin** *Serum ferritin (SF) generally correlates with body iron stores, and is relatively easy and inexpensive to determine repeatedly. Serum ferritin is most useful in identifying trends: an increasing SF trend implies an increasing iron burden that requires further clinical investigation.*	<1000 mg/L	1001-3000 mg/L	>3000 mg/L
iv	**Cardiac MRI T2*** *T2* is an MRI technique to measure liver and cardiac iron, recommended as part of yearly monitoring of multi-transfused patients at risk of developing myocardial or liver iron loading. It requires shorter acquisition times and allows the early identification of patients at high risk of developing organ deterioration and complications.*	>20 ms	10-15 ms	<10ms
v	**LIC** *Liver iron concentration (LIC) is measured to identify whether body iron is adequately controlled, as it is linked to the risk of hepatic/ extrahepatic damage. Normal LIC values are up to 1.8 mg/g dry wt, with levels of up to 7 mg/g dry wt seen in some non-thalassaemic populations without apparent adverse effects. Sustained high LIC (above 15-20 mg/g dry wt) have been lined to worsening prognosis, liver fibrosis progression or liver function abnormalities. The most common methods to measure LIC is through biopsy, SQUID and MRI.*	<7 mg/gdw	7-10 mg/gdw	>11 mg/gdw
vi	**Splenectomy** *If the clinical management of transfusion-dependent thalassaemia is inadequate, the increased destruction of red blood cells by reticuloendothelial system, in particular by the spleen, results in its enlargement (splenomegaly). Splenectomy, the surgical removal of the spleen is a treatment option with major adverse effects, including Sepsis, Thrombophilia, Pulmonary hypertension and Iron overload, affecting both the survival and quality of life of patients.*	No	Yes	
vii	**Co-morbidities** *Iron overload causes a number of co-morbidities including vascular disease, pulmonary hypertension, heart cardiomyopathy leading to heart failure; pituitary damage leading to hypogonadism, growth retardation, and delayed puberty; endocrine complications, namely diabetes, hypothyroidism and hypoparathyroidism; liver disease, namely fibrosis, cirrhosis and hepatocellular carcinoma, particularly if concomitant chronic hepatitis is present. Bone disease is common at all ages, causing pain, fractures (osteopenia, osteoporosis) and limiting mobility. The presence of these co-occurring conditions should be regarded as causing disability.*	None	1-2	2+

3	**Social Determinants of Health**			
i	**Days lost from school per year**	None	5-15 days	16+ days
ii	**Days lost from work per year** *(over and above annual statutory or contractual sick leave entitlement)*	None	5-15 days	16+ days
iii	**Access to social protection allowances**	Yes	Partly	No
iv	**Financial Situation**	Satisfactory	Poor	Very Poor
v	**Level of social integration**	High	Moderate	Low
4	**Pain Level**			
	Pain Scale *1 to 3: Mild and minor pain that is noticeable and possibly distracting.* *4 to 6: Moderate to moderately strong pain that is enough to disrupt normal daily activities.* *7 to 10: Debilitating, intense pain that prevents a person from living a normal life.*	1-3	4-6	7-10
5	**Mental Health Concerns**			
	Co-appearance of mental health issues *a. Depression* *b. Stress/Anxiety* *c. Psychosomatic issues* *d. Isolation*	1 issue (a or b or c or d)	Any combination of 2 issues (a-d)	Any combination of >2 issues (a-d)
	SCORING SCALE **Risk to develop disability**	***Total Number of Points*** **<10** ***Risk Level*** **Medium**	**11-20** **High**	**>20** **Very High**

CONCLUSION

Disabilities can be diverse and intersect with one another, and their impact on an individual's life can vary widely. Thalassaemia encompasses all types of disability that may manifest at any age if a patient is poorly treated or develops multiple comorbidities due to ageing. Where people with thalassaemia have free and unrestrictive access to quality multidisciplinary care, they have a better quality of life, an increased lifespan, and less complications, and they are less prone to develop any type of disability. The TIF Disability Risk Assessment Model for Thalassaemia may serve as a compass for national authorities to improve disease-specific policies. Nonetheless, to better understand how each stakeholder perceives the correlation of thalassaemia and disability, more data on national settings and policies are needed.

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