# 14. UNMET NEEDS OF PATIENTS WITH THALASSAEMIA: TIF'S PERSPECTIVE

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## INTRODUCTION

Understanding the unmet needs of patients across the world, is translated as understanding and recognizing the rights to standards of services which are not reached or satisfied, so that basic human and patients' rights are violated. To understand the unmet needs of patients with haemoglobin disorders and more particularly, those with Transfusion Dependent Thalassaemia (TDT), one must first recognize those needs, which if addressed appropriately, will contribute to patient survival, growth, and control of complications; thus facilitating integration into society and promoting a near normal and productive life. This is the ultimate goal that each government, and national competent authority should be aiming to achieve for the patients under their care; this is after all also what the UN Sustainable Development Goals (UN SDG) 2030 aim to achieve. To recognize these needs however, it is necessary to know the standards of care that must be met in order to achieve the best possible outcomes. For complex, multi-organ disorders these standards affect many levels of care and begin at the organizational level and include not only the health and social care services, but also the community at large as well as the individual patient and his/her family.

The methods and services for addressing both TDT and Non-Transfusion Dependent Thalassaemia (NTDT) effectively have been identified over many years through clinical and other research; they have been adopted and applied, albeit mainly in a few high prevalence countries and initially those of the Mediterranean basin. These countries with the support of the World Health Organisation (WHO) have demonstrated successful results of their control programmes, both in the area of prevention (since the 1980s) [1] and of clinical management (since the 1990s) [2,3], thus constituting examples for all who aim to achieve successful outcomes.

- ✓ Increased survival rate with an increasingly ageing patient population,
- ✓ Reduction of annual affected births,
- ✓ Reduction of morbidity and mortality rates, and
- ✓ Improved social integration.

A few high prevalence countries recognized early on the huge medical, public health, social and economic repercussions that these disorders would entail if left unaddressed or sub-optimally managed. Suboptimal care would contribute to an increased national health burden and acceptance of premature death as an inevitable consequence. This realization was the true driving force for the governments of the Mediterranean countries, to move fast in the search for solutions. Moreover, the high disease prevalence in these countries brought with it increased needs in blood, medications and other clinical and social challenges which, in the absence of any effective policies to address their control, they inevitably expected to continue to increase in numbers and multiply in unmet needs. Hence, the assimilation of the political commitments to address their effective prevention and management was considered a one-way solution.

The success of the programmes, initiated in the 1970s in the Mediterranean countries, was thus a consequence of:

1. The early recognition of needs, that led to political commitment – a necessary element to effectively address the control of these disorders and,
2. The development and implementation of nationally coordinated, supported and fully funded disease-specific control programmes for prevention and management.

### What were the prerequisites for the establishment of disease-specific programmes and what components did they include?

The existence of:

1. A healthcare system that provided universal coverage, without leaving out-of-pocket expenses for the patients or families, bearing in mind the chronicity and the multiple elements involved in monitoring and treatment of this disorder,
2. Strong public health and paediatric / haematology clinical infrastructures,
3. Quality, centrally coordinated transfusion services (including haemovigilance systems),
4. Epidemiological information based on surveys and Disease-specific patient registries,
5. Ongoing continual analysis of patient outcomes and results for tailoring policies, programmes (surveillance programmes) and actions, and
6. National guidelines, based on international consensus and evidence-based recommendations, and their nationwide adoption and implementation.

Important prerequisites for effective clinical management are outlined below. More extended and comprehensive information is provided in TIF's Guidelines for the Clinical Management of Transfusion Dependent and Non-Transfusion Dependent Thalassaemia. (For more information, see the relevant Chapters on Blood Transfusion, Management of Iron Overload and Multidisciplinary Care in this Global Review/Report).

*Table 1. Prerequisites for effective clinical management*

| | |
|---|---|
| 1. | Dedicated areas/clinics within paediatric/haematology departments of hospitals or independent day care units attached to hospitals |
| 2. | **Blood transfusion** services, with special attention to:<br>• Adequacy – To maintain an acceptable level of haemoglobin to suppress endogenous erythropoiesis and address the severe anaemia.<br>• Safety – To avoid transmission of blood-borne infections, as well as alloimmunisation and other transfusion-related adverse/unwanted events/reactions.<br>• Special processing– To ensure RBC concentration and RBC viability, as well as adequate leukodepletion to prevent or minimize related adverse effects.<br>• Appropriate storage – To safeguard the functional properties of RBCs and their appropriate and safe distribution, maintaining the cold chain and preventing contamination. |

3. **Iron Chelation** of patients:
   - Availability of all three (3) authorized and approved iron chelating agents.
   - Support for patient adherence.
   - Medical expertise in managing iron overload and tailoring treatment to address individual patient needs.

4. Well standardized **iron load monitoring** to keep iron levels within acceptable limits (the goal of iron chelation therapy), as described in consensus guidelines (such as TIF's Guidelines):

For example:

- Serum Ferritin levels measured regularly every 3 months or more frequently
- MRI measurements of iron in heart and liver at least annually in all patients

(frequency is based on individual needs)

5. **Multidisciplinary Care (MDC)** is an essential component of the medical care given that:
   - The various specialties see patients proactively for early detection of organ involvement and are well coordinated with the paediatric/haematology team responsible for patient care.
   - A single clinical record is maintained (patient healthcare record) and shared with all medical/health specialists involved in the care of the patient.
   - Mutually agreed treatment decisions are taken as a result of meetings and regular interactions between the paediatric/haematology team and other medical specialists following the patient.

6. **Existence of Reference Centres** that:
   - Have the ability to provide expert diagnosis and patient management, resulting in optimal care according to international guidelines.
   - Are able to support patients that undergo routine treatment in smaller peripheral centres (even with less expertise) with official networking and data sharing facilities.
   - Have an appropriate governance and organizational structure with clear cut professional roles.
   - Have well designed spaces for patient treatment (e.g. privacy) and medical consultations.
   - Maintain a patient registry.
   - Are involved in teaching and research.

Today, all the above elements are included in the recommendations of international guidelines, which if and when adopted, can contribute significantly to the planning of appropriate services by national competent authorities and the provision of quality care by treating physicians.

*Multidisciplinary Care (MDC)* is given a special reference in this section because it constitutes an important need that has not been fully appreciated by service providers across the world to-date.

The multi-organ involvement seen in thalassaemia is significant and increases with age across countries even in well treated patients [1, 2]. It is thus expected that the treating physicians (i.e., a haematologist, or an experienced paediatrician or internist) will supervise the provision of care services and make every effort to coordinate with other medical specialists and healthcare professionals including at least the following:

- **SPECIALISED NURSES.** The important and wide-ranging responsibilities and competences of haemoglobinopathy nurses include the supervision of blood transfusions, practical aspects of iron chelation therapy, patient support and communication, provision of information, encouragement of self-management, and symptom control amongst others [3, 4]. To develop the kind of expertise required there is need for continuity of care and not the frequent rotation of staff that is often witnessed in hospital services. The specialist nurse is generally the closest contact to the patient in the clinic and often acts as liaison between the patient and the medical team.

- **CARDIOLOGIST.** In view of the importance of cardiac monitoring and timely management of heart complications, the cardiologist forms a central figure in the team. Heart complications are closely related to anaemia, iron overload, iron chelation, endocrinopathies, nutritional factors, and other issues in this multi-organ condition. It is therefore important that cardiologists proactively monitor and understand the broader issues of concern, and be able to discuss their findings, not only with colleagues on the same team but also with patients, so that treatment decisions or modifications can be taken in agreement. Cardiologists with special interest in thalassaemia should therefore be identified and invited to supervise monitoring and treatment of patients in close collaboration with the team [5, 6].

- **HEPATOLOGIST.** In both TDT and NTDT there is increasing development of liver complications, which are responsible for an increasing proportion of morbidity and mortality. These are due to iron toxicity to the liver, often with a contribution from viral infections. Management of liver disease is also complicated by the presence of iron overload, with or without the contribution of chronic viral hepatitis [7,8]. Matters such as the role of intensifying iron chelation, the use of anti-viral agents, and preventing the progression of liver disease to cirrhosis and carcinoma make it imperative that the paediatric/haematology team works for example in close collaboration with the hepatologist.

- **ENDOCRINOLOGIST.** Endocrine complications are almost universally seen in thalassaemia patients. They affect the patients' quality of life as well as having serious consequences to vital organs [9]. It is therefore important, from an early age, that all transfusion-dependent patients be assessed by an endocrinologist who is able to supervise all treatment that may be necessary. The importance of the endocrinologist in the multidisciplinary team is wide-reaching, as illustrated by the psychological impact of endocrine disorders (including delayed puberty) and the need for frequent liaison with the team.

- **DIABETES SPECIALIST.** The prevalence of diabetes is high in thalassaemia and rising as patients grow older; in some cases, reaching rates as high as 20%. A joint diabetes/thalassaemia clinic on a regular basis may be recommended as part of the multidisciplinary care [10].

- **PSYCHOLOGIST.** Patients who live with a lifelong disorder since infancy, that requires constant monitoring and care, are subject to many challenges and stress, along with their families [11]. The need for the involvement of a psychologist thus on the team should not require further emphasis, the role of whom is extended to support and advise the care team, including the patients' families.

- **SOCIAL WORKER.** The role of a social worker frequently overlaps with that of a psychologist. There are however specific problems that arise in the family, particularly of financial and social nature, which fall clearly in the realm of the social worker. This is of course dependent on the role of the social and welfare system in each country and. it is the role of the care team to decide whether there is a need for input from social workers or not on the circumstances of each case.

- **OBSTETRICIAN.** In cases of pregnancy, obstetric specialists should be involved and collaborate closely with the thalassaemia treating team from the stage of pre-pregnancy counselling right through to labour and post-partum management [12, 13].

**Regrettably, published information (which is quite confined and largely sporadic) and data accumulated by the Thalassaemia International Federation (TIF) throughout its three decades of work (by means of field visits, reports and interactions with stakeholders at the local level), have shown that the needs of the greatest majority of the patients who live in the developing economies are not addressed effectively. In fact, even basic services that are the cornerstones to the survival and management of these patients are**

**in many instances inadequately addressed. Other needs, including support for adherence to prescribed treatment that is lifelong, taken on a daily basis, cumbersome and often painful, are generally not appropriately appreciated or prioritized. This holds true also for the necessary support required by patients and families in their transition from paediatric to adult care. Moreover, elements such as MDC and Reference Centres (as described briefly above) are grossly neglected; only a very small percentage of patients globally benefit from such essential components of care and these live mainly in 5 – 6 countries that have a high disease prevalence in their indigenous or immigrant population and usually very developed economies.**

The global inequalities in thalassaemia care, reflect mainly the economic and social inequalities that characterize today's world. An improvement certainly can be achieved by reaching out to policymakers and those responsible for allocating resources to particular services. It is necessary for policies and action plans to improve access to quality care in these complex disorders. Promoting universal health coverage and recognizing that access is a multidimensional concept which includes availability, and affordability. [Cu A, Meister S, Lefebvre B, Ridde V. Assessing healthcare access using the Levesque's conceptual framework- a scoping review. Int J Equity Health. 2021 May 7;20(1):116. doi: 10.1186/s12939-021-01416-3. PMID: 33962627]. A recent study in Greece investigated barriers that patients with beta-thalassaemia face in accessing the care they include socioeconomic influences. Even though thalassaemia patients faced no barriers in accessing the transfusion centre or the hospital, all medications for an associated condition have to be prescribed by a specialist outside the transfusion unit and this results in additional expense incurred by the patient; they also face challenges in accessing laboratory test services, and blood shortages, which is a serious challenge affecting blood transfusions in Greece. These conclusions from a survey among the patient population indicate that even high-income countries, with a tradition in managing thalassaemia, face perceived access issues [Souliotis K; Golna C; Nikolaidi S; Vatheia G; Hasurdjiev S. Access to health care for patients with thalassaemia in Greece: a cross-sectional study. East Mediterr Health J. 2020;26(12):1482–1492. https://doi.org/10.26719/emhj.20.118]

Chronic disorders, especially if rare in a particular population, are often invisible to national health authorities, and even more so when resources are limited. These issues are not easily addressed. Services for haemoglobin disorders often have to compete with other chronic conditions, and so lobbying and advocacy are required to gain the resources needed to upgrade existing or even create new services. Such advocacy cannot be the responsibility of the treating expert alone. Empowered national thalassaemia associations have historically succeeded in promoting policies and gaining the attention of health authorities, and in fact TIF was created based on this experience.

However, in order to become equal and productive partners at the decision-making table, support groups must be armed with epidemiological data and provide meaningful and evidence-based policy suggestions that will ultimately lead to the considerable reduction of the burden of disease to both patients and families as well as the wider national public health environment. Indeed, for most countries as this global review/report is revealing, a major unmet need is the existence of updated, nationwide data, patients' registries and electronic health records from which accurate and reliable information can be derived and appropriately analysed. Morbidity and mortality data must be presented so that health planners know where there are gaps in the services that are provided, which incur additional expenses caused by preventable complications and contribute to the premature death of patients instead of enabling longevity and survival with adequate social integration of patients and their families.

An awareness and understanding of the social determinants, the social and economic environment and factors which impact daily living; such influences may influence significantly patient outcomes and may be forgotten. Malnutrition in thalassaemia patients has been described in various environments but may be expected to more obvious in low-income settings. In a study from India 48.2% of patients (mean age 8.0±2.3) were malnourished

[ Biswas B, Naskar NN, Basu K, Dasgupta A, Basu R, Paul B. Malnutrition, Its Attributes, and Impact on Quality of Life: An Epidemiological Study among β-Thalassemia Major Children. Korean J Fam Med. 2021 Jan;42(1):66-72. doi: 10.4082/kjfm.19.0066. 31955549]. The family environment is of primary importance and often ignored in service provision. Yet family members may be seriously affected both in physical and psychological health [ Angane AY, Kadam KS, Ghorpade GS, Unnithan VB. Who will guard the guardians? Cross-sectional study on prevalence of psychiatric morbidity, quality of life, and coping skills in caregivers of children with thalassemia major. J Postgrad Med. 2022 Apr-Jun;68(2):72-77. doi: 10.4103/jpgm.JPGM_1128_20. PMID: 34708694]

One factor that must be recognized where rare diseases are concerned is the lack of physician experience outside academic and reference centres. In a study conducted in the USA comparing knowledge and clinical practices of physicians treating thalassaemia in centres of excellence and secondary centres, the findings suggest practice gaps and barriers to optimal care in the transition from paediatric to adult care, the ongoing management of adult patients, knowledge of the disease state, and familiarity with emerging treatments with the potential to improve clinical outcomes. The conclusion is that the level of participation in CME activities needs to be improved for all healthcare professionals involved in the care of patients with beta thalassemia [Stacy S, Sheth S, Coleman B, Cerenzia W. An assessment of the continuing medical education needs of US physicians in the management of patients with beta thalassemia. Ann Hematol. 2021 Jan;100(1):27-35. doi: 10.1007/s00277-020-04246-5. PMID: 32870368]

# METHODOLOGY USED BY TIF FOR SCORING THE EFFECTIVENESS OF THALASSAEMIA-RELATED SERVICES ACROSS ITS MEMBER COUNTRIES

TIF has made an effort to score the 'anticipated' performance of each member country (through its National Thalassaemia Associations), based on the services the country provides to its patients. In this context, six (6) essential components (1 – 6) of clinical management and two other relevant elements (A+B) were considered together referred to as from now 'Service' (Table 1), the existence or availability of which supports and contributes significantly to the extent the care provided to the patients meets their needs as described above.

These are as follows:

*Table 2. Service components (1-6) and elements (A & B)*

| | |
|---|---|
| 1. | Blood transfusion services |
| 2. | Iron monitoring tools and services |
| 3. | Iron chelation therapy |
| 4. | MDC services |
| 5. | Reference/Expert Centres |
| 6. | National Guidelines for the Prevention and Management of Thalassaemia |
| A. | Healthcare professionals' expertise |
| B. | National Thalassaemia Patients/Parents Associations/support groups |

Information regarding the above was extracted and used (mainly after the year 2010) from:

i. Published information (mainly PubMed)

ii. Reported information to TIF

iii. Patients' responses to TIF's specifically structured surveys

It was not possible to assess the quality standard of the service in the absence of any relevant well documented data or information. The only indication that TIF felt safe to associate with quality were the survival rates and/or age distribution of patients and/or morbidity rates, where reliable such data existed.

The following symbols (see Table 3 below) were used in assessing and scoring the services (as described in Table 2)

*Table 3. Definition of scoring symbols*

| | |
|---|---|
| ✓ | denotes recognition that the service was applied (i) nationwide (covering >70% of the population), and (ii) as a governmental disease programme or policy, and as such only published information was taken into consideration for this symbol. |
| • | describes the identified service (according to the methodology described earlier) as being provided partially (covering only a proportion of the population) e.g., hospital/clinic/centre based, city/region based but NOT nationwide, as a governmental disease programme or policy (based on absence of published information and/or TIF's collected information) |
| × | describes the absence or very confined existence of the service (based on absence of published information and/or TIF's database) |

Each country's scoring was a combination of the three symbols as shown below (Table 4):

*Table 4. TIF's scoring and grading system*

| Scoring | Category / Grade |
|---|---|
| 8 √ | A |
| 7 √ + 1 • | |
| 6 √ + 2 • | |
| 5 √ + 2 • | |
| 4 √ + 4 • | |
| 3 √ + 5 • | B |
| 2 √ + 6 • | |
| 1 √ + 7 • | |
| 0 √ + 6 - 8 • | C |
| 0 √ + 4 - 6 • | D |
| 0 √ + 2 - 4 • | E |
| 0 √ + 0 - 2 • | F |

**Some explanatory notes for the scoring and grading used:**

One symbol (from these described in Table 2) had to be assigned (as per the assessment process) to each of the 8 services (1-6 and A+B) described above in Table 1.

The numbers before the symbol indicate the number of services that are given the particular symbol.

Grading between **A – F** of countries was thus related to the numbers of symbols a country scored/received. The bigger the number of the 'favorable' symbols i.e. √ and • the better the grade a country received.

Table 5 below describes how the grading of each country was reached. In addition, and to help us understand perhaps better the different approaches of the countries in addressing thalassaemia needs, other useful information was included e.g. the country's Income Group (World Bank 2020), Human Development Index (HDI), level of effectiveness of its Thalassaemia Prevention Programme (see Chapter on Prevention), the country's GDP Health Expenditure (% of GDP), any reported / estimated national β-thalassaemia prevalence data (based on TIF's reports/calculations and/or published data), anticipated/expected β-thalassaemia births/ year (based on TIF's calculations and/or published data), infant mortality rate and under-5 years of age mortality rates (as published). Further to these, and with the view of supporting our scoring and grading, survival rates and age distribution information amongst patients with thalassasemia, were marked as 'existing' according to the same scoring symbols (i.e. √ for nationwide published data; • for partially available data, either published or available from reliable sources; x for no available data).

| Country | World Bank | UNDP | TIF | | Country Information | | | Thalassaemia Services | | | | | | | | Thal- related Indicators | | World Bank Development Indicators | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Income Group | HDI | Prevention | Thalassaemia Services | GDP Health Expenditure (% of GDP) | Reported / Estimated National β-thalassaemia | Expected β-thalassaemia births/ year | Transfusion | Iron Load Monitoring | Iron Chelation provided | MDC | Ref. Centre(s) | HCP Expertise | National Guidelines | National Thalassaemia | Survival Rate | Age Distribution | Infant Mortality rate (per 1,000 live births) | Under 5 mortality rate (per 1,000 live births) |
| **Albania** | Upper Middle | Very High | D | C | 5.26 | 356 | 0.625/ 1000 | I | I | I | x | x | I | I | I | x | I | 9 | 9.7 |
| **Greece** | High | Very High | A | A | 7.72 | 3,241 | 1.64/ 1000 | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | 3 | 3.8 |
| **Italy** | High | Very High | A | A | 8.67 | 7,044 | 0.46/ 1000 | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | 3 | 3.1 |
| **Iran** | Upper Middle | High | A | B | 8.66 | 20,777 | 0.43/ 1000 | √ | I | I | I | I | I | √ | √ | √ | √ | 12 | 13.9 |
| **Cyprus** | High | Very High | A | A | 6.77 | 659 | 5.55/ 1000 | √ | √ | √ | I | I | √ | I | √ | √ | √ | 2 | 2.3 |
| **Palestine** | Lower Middle | Medium/ Low | A | C | x | 689 | 0.4/ 1000 | I | I | I | x | x | I | I | √ | x | I | 17 | 19.4 |
| **Singapore** | High | Very High | A | A | 4.46 | 258 | 0.2/ 1000 | √ | √ | √ | | I | √ | √ | √ | x | √ | 2 | 2.5 |
| **Oman** | High | Very High | B | C | 4.13 | 591 | 1.06/ 1000 | I | I | I | x | x | √ | I | x | x | | 10 | 11.4 |
| **Azerbaijan** | Upper Middle | High | B | C | 3.51 | 3,300 | 0.344/ 1000 | I | I | I | x | I | I | I | √ | x | I | 18 | 20.4 |
| **UK** | High | Very High | B | A | 7.72 | 1,564 | 0.042/ 1000 | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | 4 | 4.3 |
| **Lebanon** | Upper Middle | High | B | A | 8.35 | 375 | 0.132/ 1000 | √ | √ | √ | I | √ | √ | √ | I | x | √ | 6 | 7.2 |
| **Turkey** | Upper Middle | High | B | B | 4.12 | 5,500 | 0.121/ 1000 | I | I | I | I | I | √ | I | I | x | √ | 9 | 10.0 |
| **Jordan** | Upper Middle | High | B | B | 7.79 | 1,300 | 0.306/ 1000 | I | I | I | x | x | √ | I | √ | x | | 13 | 15.6 |
| **Maldives** | Upper Middle | High | B | B | 9.41 | 670 | 8.97/ 1000 | I | I | I | x | I | I | I | √ | √ | √ | 7 | 7.6 |
| **France** | High | Very High | B | A | 11.26 | 666 | 0.0016/ 1000 | √ | √ | √ | I | √ | √ | √ | I | √ | √ | 4 | 4.5 |
| **UAE** | High | Very High | B | A | 4.23 | 2,000 | 0.23/ 1000 | √ | √ | √ | I | √ | √ | √ | √ | x | √ | 6 | 7.5 |
| **Sri Lanka** | Lower Middle | High | B | B | 3.76 | 4,000 | 0.18/ 1000 | I | I | I | x | I | √ | √ | x | x | I | 6 | 7.1 |
| **Thailand** | Upper Middle | High | B | B | 3.79 | 98,460 | 3.7/ 1000 | √ | I | I | I | √ | √ | √ | I | √ | √ | 8 | 9.0 |

| Country | World Bank | UNDP | TIF | | Country Information | | | Thalassaemia Services | | | | | | | | Thal- related Indicators | | World Bank Development Indicators | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Income Group | HDI | Prevention | Thalassaemia Services | GDP Health Expenditure (% of GDP) | Reported / Estimated National β-thalassaemia | Expected β-thalassaemia births/ year | Transfusion | Iron Load Monitoring | Iron Chelation provided | MDC | Ref. Centre(s) | HCP Expertise | National Guidelines | National Thalassaemia | Survival Rate | Age Distribution | Infant Mortality rate (per 1,000 live births) | Under 5 mortality rate (per 1,000 live births) |
| **Kuwait** | High | Very High | B | C | 5.00 | 400 | 0.132/ 1000 | √ | I | I | x | x | √ | x | x | x | I | 7 | 7.9 |
| **Mauritius** | High | High | D | D | 5.83 | 200 | 0.37/ 1000 | I | I | I | x | x | x | x | I | x | x | 14 | 16 |
| **Malaysia** | Upper Middle | High | B | C | 3.76 | 7,984 | 0.58/ 1000 | I | I | I | x | x | √ | I | | I | √ | 7 | 8.6 |
| **Qatar** | High | Very High | C | C | 2.49 | 163 | 0.225/ 1000 | I | I | I | x | √ | √ | I | x | x | I | 6 | 6.5 |
| **Vietnam** | Lower Middle | Medium / Low | C | E | 5.92 | 20,000 | 0.35/ 1000 | I | x | I | x | x | I | x | x | x | x | 16 | 19.9 |
| **KSA** | High | Very High | C | C | 6.36 | 8,919 | 0.17/ 1000 | √ | I | √ | I | x | √ | I | x | x | I | 6 | 6.6 |
| **Iraq** | Upper Middle | Medium / Low | C | C | 4.11 | 17,000 | 0.576/ 1000 | √ | I | √ | x | x | √ | I | I | x | I | 22 | 25.9 |
| **India** | Lower Middle | Medium / Low | D | C | 3.54 | 150,000 | 0.58/ 1000 | I | I | I | x | x | √ | I | √ | x | x | 28 | 34.3 |
| **Pakistan** | Lower Middle | Medium / Low | C | C | 3.20 | 50,000 | 1.0/ 1000 | I | x | I | x | x | I | I | √ | x | x | 56 | 67.2 |
| **Tunisia** | Lower Middle | High | C | C | 7.29 | 742 | 0.122/ 1000 | I | I | I | x | I | √ | x | x | x | x | 15 | 16.9 |
| **Bulgaria** | Upper Middle | High | D | C | 7.35 | 270 | 0.156/ 1000 | I | I | I | x | I | √ | I | I | x | I | 6 | 6.7 |
| **Egypt** | Lower Middle | Medium / Low | D | C | 4.95 | 9,258 | 0.7/ 1000 | I | I | I | x | I | √ | I | I | x | x | 17 | 20.3 |
| **Belgium** | High | Very High | D | C | 10.32 | 62 | 0.002/ 1000 | √ | I | √ | I | I | I | I | x | x | I | 3 | 3.4 |
| **Trinidad &Tobago** | High | High | D | C | 6.93 | 100 | 0.3/ 1000 | I | I | I | x | x | I | x | √ | x | I | 16 | 17.5 |
| **Bangladesh** | Lower Middle | Medium / Low | D | E | 2.34 | 30.000 - 50,000 | 2.1/ 1000 | I | x | I | x | x | I | x | I | x | x | 26 | 30.8 |
| **Germany** | High | Very High | D | C | 11.43 | 5 - 600 | 0.0017/ 1000 | √ | √ | √ | x | x | I | I | x | I | I | 3 | 3.8 |
| **Indonesia** | Upper Middle | Medium / Low | D | C | 2.87 | 10,555 | 2.13/ 1000 | I | I | I | x | x | I | I | √ | x | I | 20 | 23.9 |
| **Algeria** | Lower Middle | High | D | D | 6.22 | 3,000 | 0.1/ 1000 | I | x | I | x | x | I | I | x | x | x | 20 | 23.3 |

| Country | World Bank | UNDP | TIF | | Country Information | | | Thalassaemia Services | | | | | | | | Thal- related Indicators | | World Bank Development Indicators | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Income Group | HDI | Prevention | Thalassaemia Services | GDP Health Expenditure (% of GDP) | Reported / Estimated National β-thalassaemia | Expected β-thalassaemia births/ year | Transfusion | Iron Load Monitoring | Iron Chelation provided | MDC | Ref. Centre(s) | HCP Expertise | National Guidelines | National Thalassaemia | Survival Rate | Age Distribution | Infant Mortality rate (per 1,000 live births) | Under 5 mortality rate (per 1,000 live births) |
| **Sweden** | High | Very High | D | D | 10.90 | 140 | 0.0026/ 1000 | I | I | I | x | x | I | x | x | x | x | 2 | 2.6 |
| **Canada** | High | Very High | D | A | 10.79 | 1,200 | 0.006/ 1000 | √ | √ | √ | I | √ | √ | √ | √ | I | I | 4 | 4.9 |
| **USA** | High | Very High | D | A | 16.89 | 1,326 | 0.004/ 1000 | √ | √ | √ | I | √ | √ | I | √ | I | I | 6 | 6.5 |
| **Myanmar** | Lower Middle | Medium / Low | D | F | 4.79 | 4,079 | 0.66/ 1000 | I | x | I | x | x | x | x | x | x | x | 36 | 44.7 |
| **Romania** | High | Very High | D | D | 5.56 | 200 - 300 | 0.025/ 1000 | I | I | I | x | x | I | I | I | x | I | 6 | 7.0 |
| **Yemen** | Low | Medium/ Low | D | F | 4.88 | 800 | 0.484/ 1000 | ? | ? | ? | x | x | x | x | x | x | x | 44 | 58.4 |
| **Cambodia** | Lower Middle | Medium / Low | D | F | 6.03 | U/A | 0.34/ 1000 | I | x | I | x | x | I | I | x | x | x | 23 | 26.6 |
| **Laos (Lao PDR)** | Lower Middle | Medium / Low | D | F | 2.25 | 275 | 4/ 1000 | ? | ? | ? | x | x | x | x | x | x | x | 36 | 45.5 |
| **Nepal** | Lower Middle | Medium/ Low | D | D | 5.84 | 600 | 1.28/ 1000 | I | x | I | x | x | I | I | I | x | x | 26 | 30.8 |
| **Austria** | High | Very High | D | D | 10.33 | 60 | 0.0014/ 1000 | I | I | I | x | x | I | x | x | x | x | 3 | 3.5 |
| **Afghanistan** | Low | Medium/ Low | D | F | 9.40 | 16,500 | 0.361/ 1000 | ? | ? | ? | x | x | x | x | x | x | x | 47 | 60.3 |
| **Morocco** | Lower Middle | Medium / Low | D | C | 5.31 | 500 | 0.07/ 1000 | I | I | I | x | x | I | I | I | x | I | 18 | 21.4 |
| **Brazil** | Upper Middle | High | D | B | 9.51 | 662 | 0.042/ 1000 | I | I | I | I | I | √ | √ | √ | x | I | 12 | 13.9 |
| **Argentina** | Upper Middle | Very High | D | C | 9.62 | U/A | 0.046/ 1000 | I | I | I | x | I | √ | √ | √ | x | I | 8 | 9.3 |

**FOR STATISTICAL ANALYSIS SEE ANNEX 1**

# DISCUSSION AND CONCLUSIONS

Four (4) countries received grade **A** with regards to their effectiveness in both the prevention and management programmes; all four (4) are high income countries, with low infant and under-5 mortality rates and with nationwide survival and age distribution data reported in published literature.

Five (5) countries had a combination of **A** and **B** grading between their prevention and clinical related services, two (2) of which are in Europe; both high income countries, and three (3) in the Eastern Mediterranean Region; two (2) upper-middle and one (1) high income country. All five (5) countries have low infant and under-5 mortality rates, and four (4) had nationwide survival and age distribution data reported in published literature.

Five (5) countries scored **BB** on prevention and clinical related services; four (4) upper-middle and one (1) lower-middle income countries, all with low infant and under-5 mortality rates. Two (2) did not have and three (3) had nationwide survival and age distribution data reported in published literature.

One may safely assume that all the above countries are providing adequate to nearly optimal services for their patients, optimal in **AA**'s to near optimal in **AB**, and good potential to reach near optimal care for countries scoring **BB**.

Scoring **B** of prevention programme with scoring **C** of clinical services describes the practices in four (4) countries in the extended European Region, two (2) in the Eastern Mediterranean Region, and one (1) in the West Pacific Region. These are countries which focused for some time now on addressing haemoglobin disorders in the context of both prevention and clinical management; and have the potential and interest to improve both their prevention programmes to reach nationwide coverage and the medical care services to reach better quality standards. More possibilities lie with the two (2) Eastern Mediterranean Region countries on account of their small population size, lower disease prevalence and better economic conditions.

Five (5) countries have a scoring combination of **C** for prevention and **C** for clinical services all of which in the Eastern Mediterranean Region (1 located in North Africa). These are countries in which clinical services were given more focus than prevention policies. Some disease-specific prevention policies in these countries may exist but these are mainly associated with a region of the country or are related to hospital-based services (mainly screening) and absence of other essential components of effective prevention (including genetic counselling, obstetric and prenatal diagnosis services). At the same time, and although focus has been given on clinical services, there is to-date no published information to document the quality of services or the nationwide existence of adequate and appropriate blood transfusion, iron load monitoring, chelation and MDC services in these countries.

Large populations and/or high disease prevalence and/or poor economies and/or political instability and/or simply low disease prevalence (and thus rarity of the disease), and/or other heath priorities have not allowed prioritization of these disorders on their national health agendas.

Ten (10) countries scored a combination of **D** for prevention, suggesting severe absence or the presence of very confined policies for prevention, while their clinical services score **C,** suggesting that more focus was given by governments on the medical care of the patients. This is a very interesting group of countries that span across five different regions of the world (as defined by WHO): Two (2) in the American Region (south), four (4) in the European Region (three (3) in the EU and one (1) in the extended Europe region), two (2) in the South East Asia Region and two (2) in the Eastern Mediterranean Region. These are countries of different population sizes, disease prevalence, healthcare systems and economies. Two (2) of those in the EU are of low to medium disease prevalence, robust economies and healthcare infrastructures, while the third one and the one (1) in the extended European region are in the upper middle-income group of countries, with low to medium disease prevalence and weaker public health and medical/social care infrastructures. The two (2) Eastern Mediterranean countries belong to the lower middle-income group, have medium disease prevalence and weak public and

medical/social care services. Of the two South East Asia countries, one (1) is in the upper middle and the other is in the lower middle-income groups. Both of these countries have large populations and medium to high disease prevalence. Public and medical/social services are weak and in transition to universal coverage. The two (2) countries of the American Region (located in the southern part of the region) belong to the high and upper middle-income groups respectively and have low to medium disease prevalence.

Five (5) countries exhibit poor prevention and clinical care services scoring **D+D** on both components Amongst them two (2) are very high-income group countries and have robust medical and public health infrastructures (e.g. Sweden and Austria) and recent introduction through migration and/or rarity of the disease may "justify" the current grading. Of the remaining three (3) countries of this scoring group, one (1) is in the EU amongst high income group countries and two (2) are in the Eastern Mediterranean and Southeast Asia Regions respectively, both with lower middle-income status, medium disease prevalence and weak public and health/social infrastructures.

Six (6) countries score **D** for prevention and **E** or **F** for clinical services, suggesting very poor and limited disease-specific programmes of both prevention and management. High numbers of annual affected births and high rates of morbidity and early death of patients are thus anticipated in these countries.

Weak economies and/or large populations, political instability, health and/or social and/or environmental priorities have not permitted national health authorities in these countries to focus on any level, and certainly not to prioritize haemoglobin disorders on their national health agendas.

Three (3) countries stand out in *Table 4* as a result of their contradicting profile with respect to the control of haemoglobin disorders. These countries score **A** with documented great focus on the medical care (and active research) of thalassaemia and its inclusion on their national health agendas, but their work on prevention is severely lagging behind and have been scored with a **D** (all three in the American Region). Two (2) of these are of very high HDI and have very robust medical, public health and research infrastructures, and hence have great potential for improving national prevention efforts. The third one is of high HDI (upper-middle income) but weaker healthcare infrastructures and economy, thus posing potential challenges in promoting effective disease specific prevention programmes.

# UNMET NEEDS: FOCUS ON α-THALASSAEMIA

## INTRODUCTION

Similar to β-thalassaemias, α-thalassaemia syndromes are among the most common inherited blood disorders, significantly affecting patients' health and imposing a substantial burden on healthcare systems. However, α-thalassaemia has historically received less attention compared to β-thalassaemias. This disparity can be attributed to several factors: the difficulty in identifying carriers and sometimes, individuals with clinically significant α-thalassaemia syndromes (such as HbH disease) using widely available and inexpensive laboratory tests, which has led to an underestimation of the condition's prevalence; the historical misconception that HbH disease is a benign condition; the relatively lower burden of HbH disease on public health resources compared to β-thalassaemias, as individuals with HbH disease are typically non-transfusion dependent, making it a lower public health priority; the universal intrauterine demise of the most severe form of the disease (α-thalassaemia major) before the availability of intrauterine transfusions; and the prevalence of HbH disease in regions where limited resources have historically been allocated to more pressing health challenges, such as communicable diseases.

Recognizing this gap, this section aims to specifically highlight the current unmet needs of individuals with α-thalassaemia and provide a roadmap for future directions.

## UNDERSTANDING THE EPIDEMIOLOGY OF A-THALASSAEMIA

It is no surprise that the first step toward improving care for a condition with significant regional and global impact is understanding its epidemiology. A better understanding of the distribution of α-thalassaemia, both regionally and globally, enables more effective allocation of resources and the development of better-tailored public health policies. However, this task is particularly challenging due to the diversity of inherited genotypes (e.g., α+ deletions, αo deletions, and non-deletional mutations) and their interactions which lead to varied clinical phenotypes. Additionally, the presence of other genetic disease modifiers common in endemic areas, such as β-thalassaemia, β-globin variants, and G6PD deficiency, further complicates the picture. The challenge is compounded by the fact that carriers of the most common form of α-thalassaemia (α+ thalassaemia) often exhibit a completely normal haematological profile. Therefore, well-designed epidemiological studies on a regional scale are essential to accurately identify the prevalence and specific genetic mutations in α-globin genes which will in turn help setting up designing appropriate diagnostic tools (e.g. genetic panels) and setting up screening programs. While efforts to address this issue have been made in certain countries, significant further work is needed in regions where resources remain limited.

## SCREENING PROGRAMS

Once a better understanding of the prevalence and underlying genetic mutations is achieved, region-specific diagnostic procedures can be developed. The focus should be on identifying carriers of αo deletions and non-deletional forms of α-globin gene mutations, which can lead to clinically significant forms of α-thalassaemia, including HbH disease and α-thalassaemia major. Screening programs for α-thalassaemia include prenatal carrier screening and neonatal screening for individuals affected with HbH disease. Neonatal screening is particularly valuable because the electrophoretic detection of Hb Bart's during the neonatal period allows for early and cost-effective diagnosis of affected individuals.

Similar to β-thalassaemias, neonatal screening for α-thalassaemia is not widely implemented. Only certain countries or regions with high prevalence have established such programs (e.g. Thailand, Taiwan, Hong Kong, southern provinces of China, Cyprus, and certain states in the US or provinces in Canada, and others). Similarly, prenatal screening is employed only in regions where α-thalassaemia is known to be prevalent. This leaves thousands of at-risk couples undiagnosed in areas without established prenatal screening programs as carriers of α-thalassaemia are often misdiagnosed with other microcytic anaemias, such as iron deficiency anaemia, due to overlapping haematological features.

## UNDERSTANDING THE CLINICAL OUTCOMES OF HBH DISEASE AND A-THALASSEMIA MAJOR

Despite its prevalence and clinical significance, high-quality research on the clinical outcomes and factors influencing these outcomes in α-thalassaemia remains limited. Most studies are constrained by their

retrospective or cross-sectional designs, a lack of true representation of older populations, and insufficient differentiation between the various forms of the disease (e.g., deletional vs. non-deletional mutations). A recent review of the literature highlighted significant variability in clinical phenotypes across different published reports, likely due to differences in study design, patient selection in various settings, and the underlying genotypes and other unaccounted factors in the cohorts examined. Currently, there is very limited data on thalassaemia-related complications in older age or the mortality rates of individuals with HbH disease. Furthermore, while the pathophysiology of deletional HbH disease is primarily driven by a uniform α-to-β globin chain imbalance, non-deletional mutations lead to variable pathophysiological effects that warrant special attention. Not all non-deletional forms of HbH disease follow similar clinical trajectories, and unlike β-thalassaemias where clinical severity correlates with beta-globin output, non-deletional α-thalassaemias exhibit diverse disease mechanisms that are not solely predicated on globin imbalance. As a result, different forms of α-thalassaemia can lead to varied clinical presentations and complications, which remain understudied.

To address these gaps, well-designed longitudinal studies focusing on specific forms of α-thalassaemia across all age groups are essential. Given the rarity and diversity of certain mutations, collaborative, multi-center studies are particularly needed. Within this process, understanding the clinical outcomes of deletional HbH disease, which affects millions of individuals primarily in Southeast Asia but also worldwide, should remain a priority. Critical questions remain unanswered, such as how deletional HbH disease impacts individuals as they grow older, and its effects on quality of life and potential avenues for health improvement.

α-Thalassemia major was once considered universally fatal, leading to intrauterine demise of affected fetuses. However, with the availability of intrauterine transfusions and advancements in perinatal care, many affected patients can now survive into adulthood. This presents a significant challenge to healthcare systems in regions where αo thalassemia deletions are most prevalent. Despite these advancements, the long-term outcomes of these patients, particularly into adulthood, and the burden on public health systems remain poorly understood. Given the rarity of the condition, it deserves specialized attention to address these gaps in knowledge and care.

## IMPROVING THE OUTCOME OF PATIENTS WITH α-THALASSAEMIAS

Identifying the specific needs of patients is fundamental to providing appropriate care and improving outcomes and quality of life. Given the limited research on the clinical outcomes of HbH disease, it is unsurprising that the management of individuals with HbH disease has remained stagnant and largely extrapolated from practices for β-thalassaemia. This approach overlooks the distinct features of the two conditions, often resulting in suboptimal care. Currently, therapeutic options for HbH disease are limited to transfusions (either on-demand or as part of a regular transfusion program) and splenectomy, with no approved disease-modifying therapies available for this population. Moreover, the optimal approach to these treatments remains unclear and is largely based on practices for β-thalassaemia. Concerted efforts are needed to specifically study different treatment approaches for various forms of α-thalassaemia. Critical question such as the long-term effects of splenectomy, specific transfusion initiation targets, tailored approaches to iron chelation, and surveillance guidelines for disease-specific or treatment-related complications in patients with α-thalassaemia remain largely unanswered.

Recently, newer disease-modifying treatments with various mechanisms of action have emerged, offering potential promise for managing HbH disease. Unfortunately, clinical trials for these novel therapies have included only a small minority of patients with α-thalassaemia, which may limit the applicability of the data to this group. As such, dedicated research focused specifically on patients with α-thalassaemia, rather than

treating them as a small subset within larger cohort of individuals with β-thalassaemia, is essential to fully understand the impact of these advances on the management of α-thalassaemias.

Curative therapies, such as haematopoietic stem cell transplantation, are important treatment options for selected patients with β-thalassaemia. However, data on the outcomes of haematopoietic stem cell transplantation in HbH disease is scarse. Similar to other aspects of management, current approaches are largely derived from β-thalassaemia practices. This is problematic, as the more severe forms of α-thalassaemia where stem cell transplantation may be beneficial often involve different pathophysiology, potentially requiring tailored approaches. Dedicated research is needed to evaluate the efficacy and safety of haematopoietic stem cell transplantation specifically in patients with α-thalassaemia, ensuring that treatment strategies are optimized for their unique clinical and biological characteristics. Similarly, while gene therapies are becoming a viable therapeutic option for patients with β-thalassaemia, this approach remains in the earliest phases of development for α-thalassaemia.

## ADVOCACY

Advocacy plays a pivotal role in improving care, clinical outcomes, and quality of life for people with chronic disease. This is well demonstrated by the significant progress made in β-thalassaemia. Strong advocacy efforts have led to increased awareness, securing much needed resources, better access to treatments, and the development of comprehensive care guidelines for patients with β-thalassaemia. However, similar advocacy initiatives are severely lacking for individuals with α-thalassaemia, leaving this group underserved and overlooked. Despite its prevalence and clinical significance, α-thalassaemia has not received the same level of attention. To address these disparities, there is an urgent need for stronger advocacy focused on α-thalassaemia. This includes raising awareness, mobilizing resources, and collaborations among healthcare providers, policymakers, patient organizations, and researchers. By amplifying advocacy efforts, we can ensure that patients with α-thalassaemia receive an appropriate level of care, support, and attention, ultimately improving their clinical outcomes and quality of life.

## FUTURE DIRECTIONS

To improve the clinical outcomes of individuals with α-thalassemia, a multifaceted approach is required. Collaborative efforts between clinicians, healthcare providers, funding organizations, governments, and industry across Eastern and Western regions are vital to advancing patient care and reducing the disease burden in resource-constrained areas. Prioritizing education, research, and the adoption of evidence-based, cost-effective strategies is critical. Conducting robust, prospective studies will help better understand patient outcomes and unmet needs. Furthermore, the creation of international collaborative registries can provide valuable insights into the less common forms of α-thalassemia, addressing key gaps in knowledge and care.

# CONCLUSION

The current state of affairs across the world with regards to the provision of appropriate medical care and effective prevention for thalassaemia is far from being a satisfactory one.

The countries where >80% of our global population is born and resides, present great challenges in providing access to appropriate medical, social and public health services. Most of these patients live in countries which score **C, D, E** and **F** in their clinical services thus suggesting suboptimal care, including poor access to adequate and safe blood, specialized and reliable iron load measurements and effective iron chelation; all of which constitute the cornerstone of the management of β-thalassaemia. The value and contribution of MDC and the existence of Reference Centres are elements of health services that are very underestimated in almost every county across the world; contributing to the anticipation of high rates of morbidity and mortality across these countries (for more information see Chapter on Disease Burden in this Global Review).

*Table 5* demonstrates well that in the majority of cases where prevention effectiveness scored A (i.e. very effective), the quality of treatment services provided to patients also scored high. As effectiveness of prevention drifted to low or very limited effectiveness, so did the level of effective of treatment services.

Basic statistical analysis (see Annex 1), where this was possible to be performed, confirmed to a great extent our findings and/or conclusions: wherever prevention score indicated effectiveness in a country, the survival rate of patients was higher. Similarly, wherever iron load monitoring services and iron chelation treatment were available, and their effectiveness anticipated or documented in literature, survival rates were higher. Certainly, the HDI level of the country was shown to be heavily related to the availability or not of iron load monitoring services (mainly MRI testing).

One can therefore only conclude that the rights of the patients with this disorder (which is the focus of this report) are to date tragically violated and TIF calls upon its member National Thalassaemia Associations to engage actively and productively with their national health and social decision makers and to join forces with the WHO and every relevant stakeholder in their country, importantly including the healthcare professionals community, for immediate action with regards to achieving improvements in the quality of services provided by their health care systems to patients with this thalassemia.
The unmet needs are many and multiple and unfortunately concern the majority of the patients with thalassaemia across countries in every Region of the world.

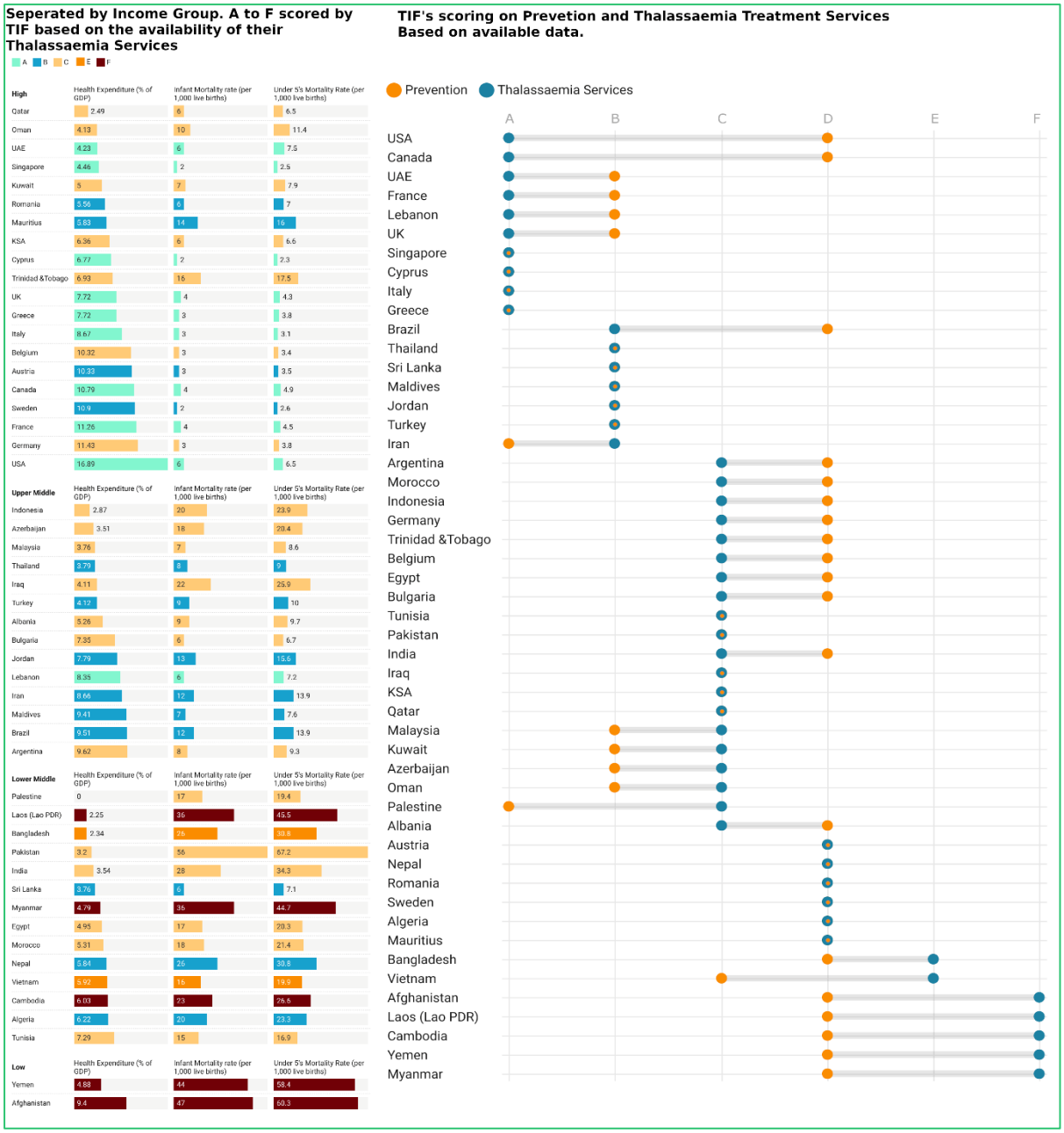



*Figure 1. Prevention and Thalassaemia Services*

# REFERENCES


1. Angastiniotis M, Petrou M, Loukopoulos D, Modell B, Farmakis D, Englezos P, Eleftheriou A. The Prevention of Thalassemia Revisited: A Historical and Ethical Perspective by the Thalassemia International Federation. Hemoglobin. 2021 Jan 18:1-13. doi: 10.1080/03630269.2021.1872612. PMID: 33461349.
2. Khandros E, Kwiatkowski JL. Beta Thalassemia: Monitoring and New Treatment Approaches. Hematol Oncol Clin North Am. 2019 Jun;33(3):339-353. doi: 10.1016/j.hoc.2019.01.003. PMID: 31030806.
3. Anionwu E, Leary A, Johnson K. Protecting specialist roles in haemoglobin disorders. Nurs Times. 2012 Jun 26-Jul 2;108(26):18. PMID: 22866484.
4. Tangayi S, Anionwu E, Westerdale N, Johnson K. A skills framework for sickle cell disease and thalassaemia. Nurs Times. 2011 Oct 18-24;107(41):12-3. PMID: 23251980.
5. Cogliandro T, Derchi G, Mancuso L, Mayer MC, Pannone B, Pepe A, Pili M, Bina P, Cianciulli P, De Sanctis V, Maggio A; Society for the Study of Thalassemia and Hemoglobinopathies (SoSTE). Guideline recommendations for heart complications in thalassemia major. J Cardiovasc Med (Hagerstown). 2008 May;9(5):515-25. doi: 10.2459/JCM.0b013e3282f20847. PMID: 18404006.
6. Kremastinos DT, Farmakis D, Aessopos A, Hahalis G, Hamodraka E, Tsiapras D, Keren A. Beta-thalassemia cardiomyopathy: history, present considerations, and future perspectives. Circ Heart Fail. 2010 May;3(3):451-8. doi: 10.1161/CIRCHEARTFAILURE.109.913863 . PMID: 20484195.
7. Di Marco V, Capra M, Angelucci E, Borgna-Pignatti C, Telfer P, Harmatz P, Kattamis A, Prossamariti L, Filosa A, Rund D, Gamberini MR, Cianciulli P, De Montalembert M, Gagliardotto F, Foster G, Grangè JD, Cassarà F, Iacono A, Cappellini MD, Brittenham GM, Prati D, Pietrangelo A, Craxì A, Maggio A; Italian Society for the Study of Thalassemia and Haemoglobinopathies; Italian Association for the Study of the Liver. Management of chronic viral hepatitis in patients with thalassemia: recommendations from an international panel. Blood. 2010 Oct 21;116(16):2875-83. doi: 10.1182/blood-2009-11-248724. PMID: 20551378.
8. Kountouras D, Tsagarakis NJ, Fatourou E, Dalagiorgos E, Chrysanthos N, Berdoussi H, Vgontza N, Karagiorga M, Lagiandreou A, Kaligeros K, Voskaridou E, Roussou P, Diamanti-Kandarakis E, Koskinas J. Liver disease in adult transfusion-dependent beta-thalassaemic patients: investigating the role of iron overload and chronic HCV infection. Liver Int. 2013 Mar;33(3):420-7. doi: 10.1111/liv.12095. PMID: 23402611.
9. 
10. De Sanctis V, Soliman AT, Elsedfy H, Skordis N, Kattamis C, Angastiniotis M, Karimi M, Yassin MA, El Awwa A, Stoeva I, Raiola G, Galati MC, Bedair EM, Fiscina B, El Kholy M. Growth and endocrine disorders in thalassemia: The international network on endocrine complications in thalassemia (I-CET) position statement and guidelines. Indian J Endocrinol Metab. 2013 Jan;17(1):8-18. doi: 10.4103/2230-8210.107808. PMID: 23776848.
11. Tzoulis P, Shah F, Jones R, Prescott E, Barnard M. Joint diabetes thalassaemia clinic: an effective new model of care. Hemoglobin. 2014; 38(2):104-10. doi: 10.3109/03630269.2013.862541. PMID: 24351096.
12. Rikos, N., Giannadaki, GK., Spontidaki, A. et al. Health status, anxiety, depression, and quality of life of patients with thalassemia. J Public Health (Berl.) (2020). https://doi.org/10.1007/s10389-020-01241-y
13. Tuck SM. Fertility and pregnancy in thalassemia major. Ann N Y Acad Sci. 2005;1054:300-7. doi:

10.1196/annals.1345.062. PMID: 16339678.

14. Origa R, Piga A, Quarta G, Forni GL, Longo F, Melpignano A, Galanello R. Pregnancy and beta-thalassemia: an Italian multicenter experience. Haematologica. 2010 Mar;95(3):376-81. doi: 10.3324/haematol.2009.012393. PMID: 19903676.
15. Forni GL, Puntoni M, Boeri E, et al. The influence of treatment in specialized centers on survival of patients with thalassemia major. Am J Hematol. 2009;84:317–318..

# ANNEX 1

## STATISTICAL ANALYSIS

Several statistical methodologies can be applied in order to examine the different aspects that could have an impact on thalassaemia patients. A group of countries across the globe has been categorised based on the score they received for prevention and thalassaemia services. Furthermore, some other measurements have been taken into account for the same countries such as income, HDI and the number of expected thalassaemia births.

From a statistical point of view, our goal is to determine how those factors can be related or how the answer 'YES' on survival rate of the A category of countries is more likely to be occurred than the D category for example.

The following results are based on the TIF database and the excel file 'UNMET NEEDS TABLE TEST'.

## THE WORDS

**"EXISTS"** – reflects presence of iron chelation treatment hospital/centre bases with no nationwide support or co-ordination

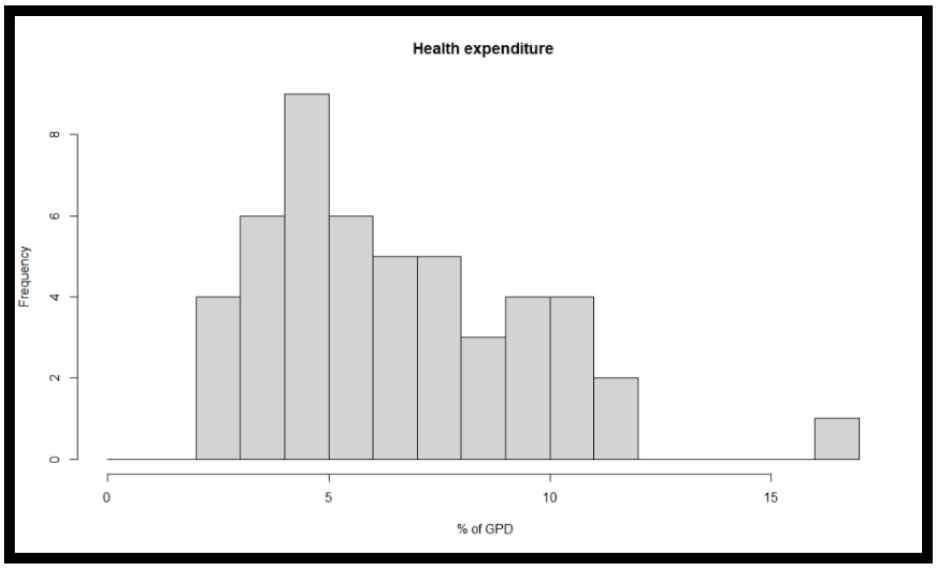
**"YES"** - reflects the nationwide co-ordination and support related to iron chelation treatment anticipated to have a certain level of effectiveness

**"NO"** – reflecting no published results which relate to low survival rates

To have a more sufficient understanding of our data, a brief analysis of the numerical variables is required. Below we write down the mean, standard deviation and some other indicators of the distribution of our data.

## HEALTH EXPENDITURE (% OF GDP)

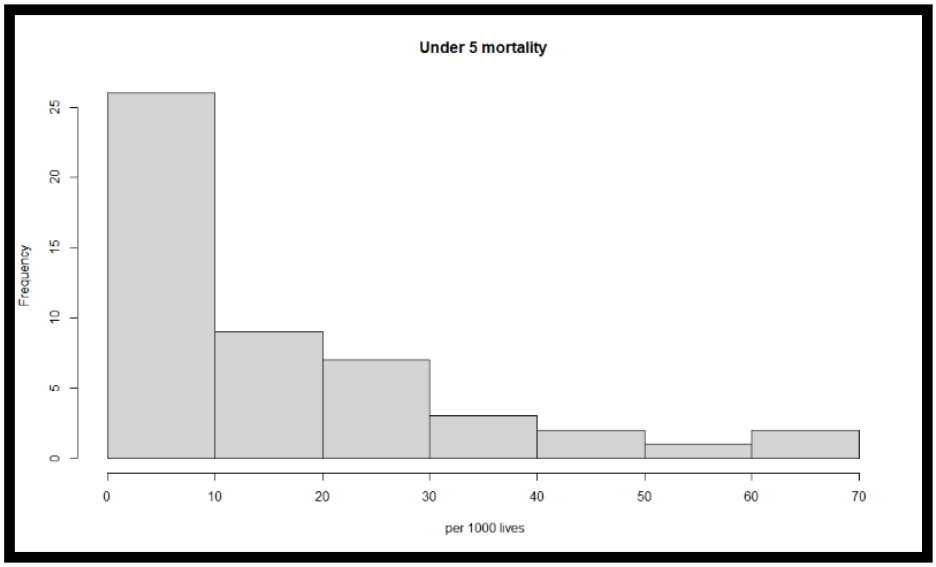
- The mean of the countries' health expenditure 6.56%
- The minimum value is 2.25% and it belongs to Laos
- The maximum value is 16.89% and it belongs to USA
- The median (the value which is in the middle of our sample) is 5.92%
- 75% of the countries have a health expenditure lower than 8.66%
- 25% of the countries have a health expenditure lower than 4.13%
- The variance is 9.04 while the standard deviation is 3.006
- The skewness of the sample is 0.92, something which demonstrates that the distribution of the sample is not completely symmetric.
- From the boxplot and the histogram of our data we find one outlier (a value that is much higher than the mean) and that is the USA while most of the other countries have a health expenditure very close to their mean
- From the Kolmogorov-Smirnov Statistical test we conclude that our sample of the health expenditure is normally distributed.
- In the graph below (histogram) we can see how many times we observe a specific value, and this is an indication about the sample's distribution.




*Note: From the statistical analysis Palestine removed because of not given value*

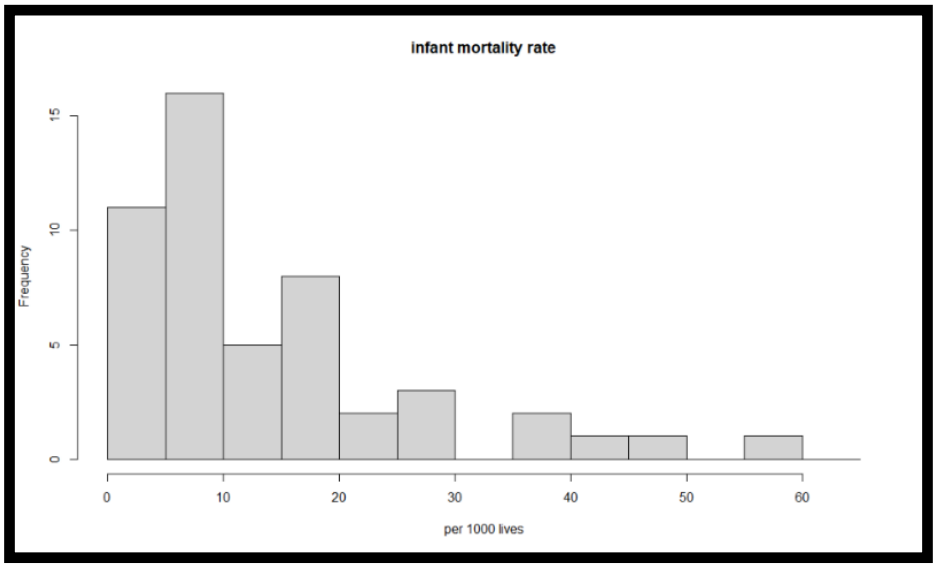
## UNDER 5 MORTALITY RATE (PER 1000 LIVES)

- The mean of the countries' under 5 mortality rate is 16.68
- The minimum mortality rate is 2.30 and it belongs to Palestine
- The maximum mortality rate is 67.2 and it belongs to Pakistan
- The median is 9.85
- 75% of the countries have an under 5 mortality rate lower than 21.15.
- 25% of the countries have an under 5 mortality rate lower than 6.52
- The variance is 245.4 while the standard deviation is 15.67
- The skewness of the sample is 1.65, and it shows that the distribution of the sample has a tale to the right (not symmetric)
- From the boxplot and histogram of the sample we can see that we have several outliers



## INFANT MORTALITY RATE (PER 1000 LIVES)

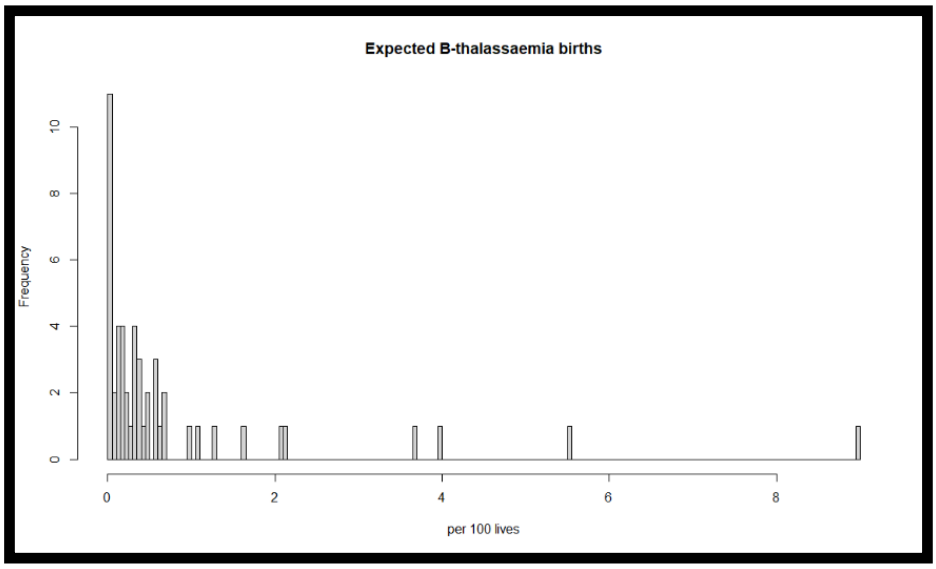
- The mean of the countries' infant mortality rate is 13.96
- The minimum mortality rate is 2 and it belongs to Cyprus, Singapore and Sweden
- The maximum mortality rate is 56 and it belongs to Pakistan
- 75% of the countries have an infant mortality rate lower than 18 lives per 1000
- 25% of the countries have an infant mortality rate lower than 6 lives per 1000
- The median of the sample is 9
- The variance is 155.6 while the standard deviation is 12.47
- From the boxplot and histogram of the sample it appears that there are a few extreme observations
- The skewness is 1.5 and the distribution is very similar with the under 5 mortality rate's one




## EXPECTED B-THALASSAEMIA BIRTHS (EBTB) PER YEAR (PER 1000 BIRTHS)

There are huge differences between the number of expected b-thalassaemia births and some countries must be excluded if we want to test a hypothesis later.

- The mean is 0.826
- The minimum is 0.0014 and it belongs to Austria
- The maximum is 8.97 and it belongs to Maldives
- The median is 0.32
- 75% of the countries have an EBTB lower than 0.6138
- 25% of the countries have an EBTB lower than 0.105
- The variance of the sample is 2.58 while the standard deviation is 1.6
- The skewness of the sample is 3.458
- The interquartile range of the sample is 0.5085
- As we can see by the histogram of the sample below there are a few countries with very high EBBT per year, much higher than the majority of the population of the other regions

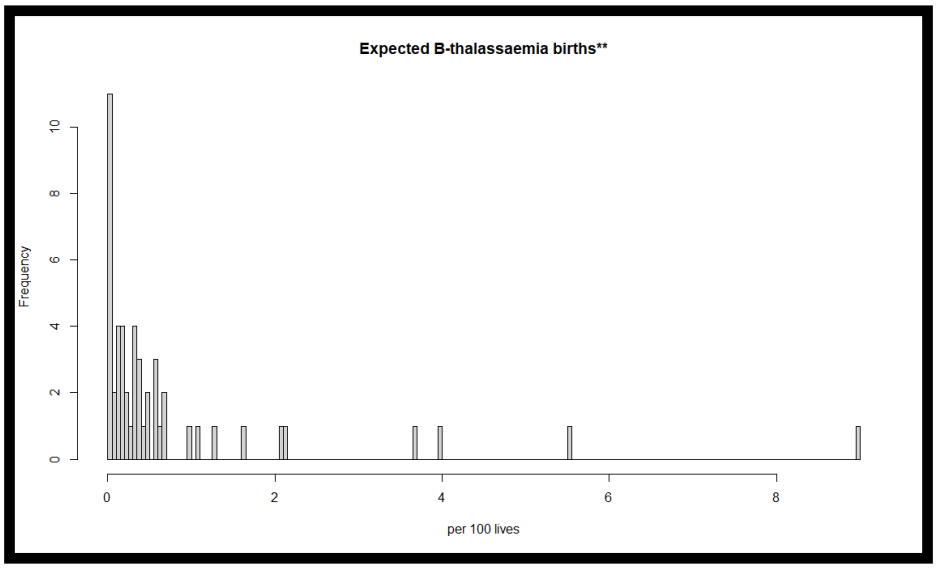



*** Some of the countries have an extremely small b-thalassaemia carrier rate and it is mainly defined by migration reasons. That results to a sharp decrease of expected b-thalassaemia births, with their numbers dramatically close to zero. Keeping that in mind, a more sufficient statistical analysis of that variable would be the one where we only include the countries whose EBTB is higher than 0.1. In fact, from the 50 countries in our data the 38 met this condition. ***

## **EXPECTED B-THALASSAEMIA BIRTHS (EBTB) PER YEAR (PER 1000 BIRTHS):

- The mean is 1.08
- The minimum is 0.1 and it belongs to Trinidad and Tobago
- The maximum is obviously 8.97 and it belongs to Maldives
- The median is 0.415
- 75% of the countries have an EBTB lower than 0.925
- 25% of the countries have an EBTB lower than 0.223
- The variance of the sample is 3.14 while the standard deviation is 1.77
- The skewness of the sample is 3.014 which is slightly reduced
- The interquartile range of the sample is 0.699
- The histogram of the new conditions of expected B-Thalassaemia births is very similar with the previous one

*Note: As expected, the mean of the second analysis on EBBT rose because of the reduced number of observations and the reduced number of values. Although the variance increased, the skewness had a slight dip comparing to the first analysis something that indicates that the new sample has a little smaller 'tale' to the right.*




## HYPOTHESIS TEST

With a theoretical background in statistics, we are going to be able to recognise the major issues that thalassaemia patients face. We will examine how the prevention of every country helps the survival rate or how the factors income and HDI influence the process. Moreover, analysis of the iron load monitoring or health expenditure's relation to the expected b-thalassaemia births per year, are also some topics of interest.

However, we must proceed with caution with the results we are going to produce. Any conclusions about the sample and the hypothesis we test every time should not be taken for granted. That's because in order to perform the statistical tests, some assumptions and conditions about the samples must be fulfilled. If these conditions are not satisfied, the results may be misleading and not reflect the reality, and our tests won't be valid. For example, we should have a clear picture about the theoretical distribution of our sample before using a specific mathematical model. Also, every observation (in this case every country) must be independent with each other. Many observations in the population, is a situation that offers much more secure results too. With all that in mind we begin to examine some of the issues where I mentioned before.

## PREVENTION-SURVIVAL RATE

The following test is offered to test the relation between prevention techniques and survival rate of each country. Our aim is to decide if every country, based on the category 'A-D' has an equal probability of having the statement 'NO' in survival rate. We are going to use the Chi square test of independence which is a non-parametric statistical test and does not assume something about the sample's distribution. The only requirement is that the countries are independent.

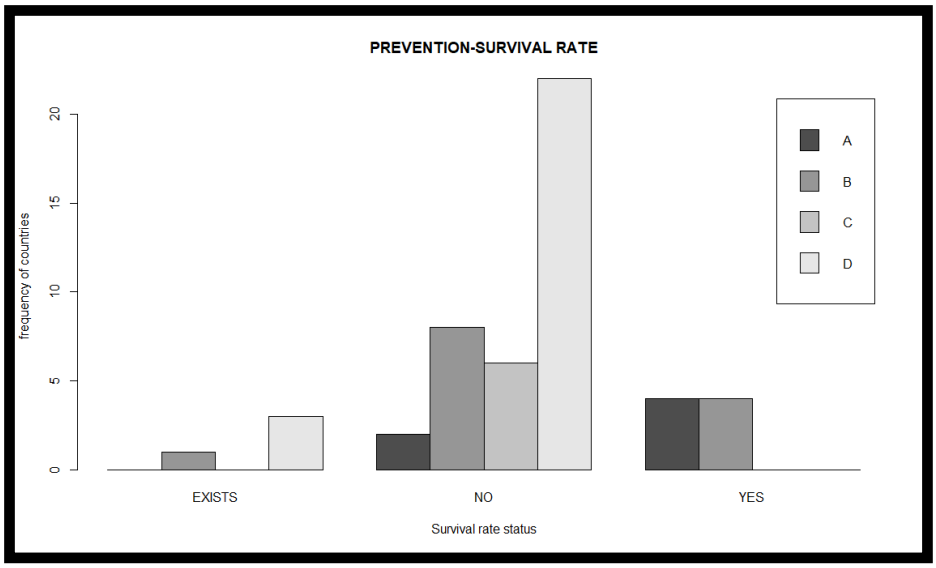
Our null hypothesis is: 'Variables Prevention and Survival Rate are independent'.

What we are trying to say by that is that if the null hypothesis is true, then Countries from any category have the same chance of answering yes to the survival rate and it does not depend on the prevention of each government.

*Note: This statistical test only examines if the two variables are related. It is not used to decide how they are related or how the levels of every variable are related. That we can figure it out by the graph and tables.*

The table and graph below sum up the data we have collected:

| Prevention Category/Survival Rate | Exists | No | Yes |
|---|---|---|---|
| **A** | 0 | 2 | 4 |
| **B** | 1 | 8 | 4 |
| **C** | 0 | 6 | 0 |
| **D** | 3 | 22 | 0 |




After performing the Chi-Square test of independence, we calculated the p-value of the test, and it was p=0.002215. This means that we have strong evidence against the null hypothesis and if we assume that the null hypothesis is true the probability of having a sample that extreme like the one we used now is 0.002215. Therefore, in a 95% level of confidence we reject the null hypothesis and conclude that there is a relation between the status of the countries' survival rate status and their prevention score category. From the table and graph, we can clearly see that countries with 'D' prevention category have a much higher ratio of 'NO' in the survival rate status than the others.

## IRON LOAD MONITORING-SURVIVAL RATE

Next up is the Iron Load Monitoring and Survival Rate relationship. According to TIF's surveys there are many inequalities in iron load monitoring and treatment of thalassaemia patients across the globe. In regions where optimal care is possible the effective control of iron toxicity has rocketed the survival rate in patients. In countries less financially developed this might not be the case.

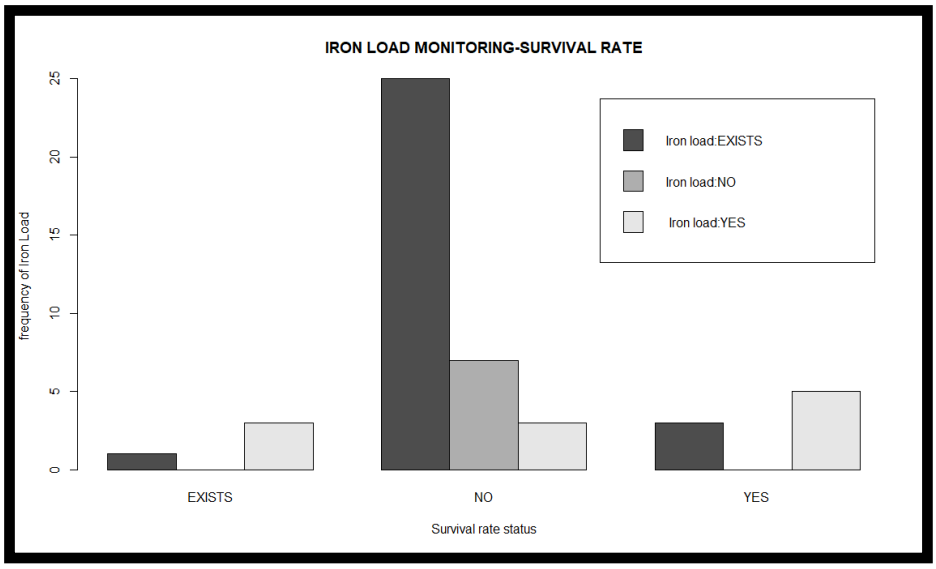
Using the same statistical test as before, we will test if the iron load monitoring is massively related to the survival rate of every country or if it is not statistical significand. The null hypothesis again is: 'Variables Iron Load Monitoring and Survival Rate are independent', which means that the survival rate of the thalassaemia patient does not depend on the successful iron load monitoring of his or her country.

- Note 1: In our database we have a particularly small sample of countries most of them not having a survival rate of NO. This does not reflect the situation in every country across the globe.

- Note 2: The countries Yemen, Laos and Afghanistan have been excluded from the test because of their unknown status.

| Survival Rate | Exists | No | Yes |
|---|---|---|---|
| **Iron Load** | | | |
| **Exists** | 1 | 25 | 3 |
| **No** | 0 | 7 | 0 |
| **Yes** | 3 | 3 | 5 |

The table and graph of those two variables are shown below:




Our p-value of the given test is p= 0.001455<0.05. So, we conclude, with a 95% level of confidence that we reject again the null hypothesis. Thus, there are statistically significant differences between the status of the survival rates depending on the Iron load monitoring of every country. If we had accepted the null hypothesis, we would imply that iron load monitoring is not related with the survival status of the patients of every country.

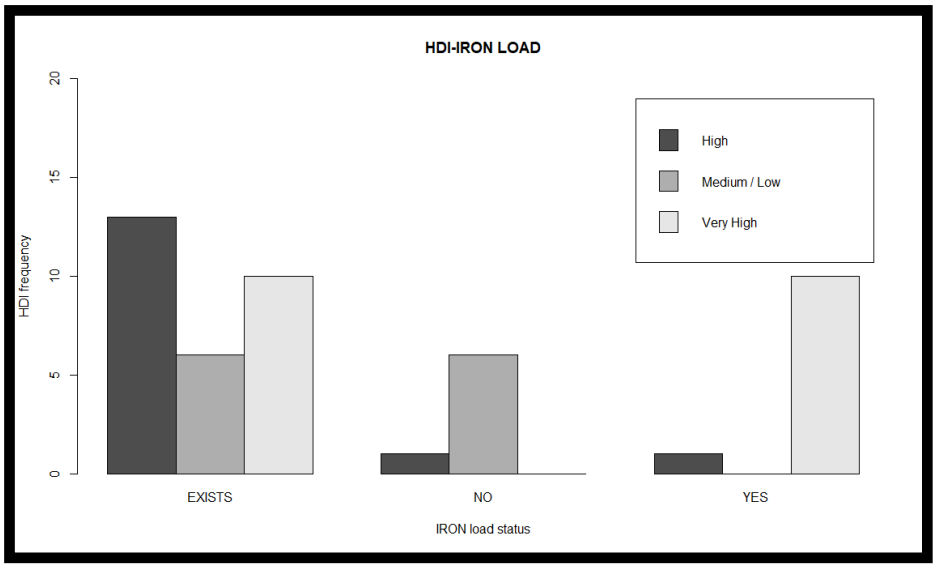
## HDI-IRON LOAD MONITORING

Based on the previous test's results, another interesting group of categories would be the HDI (Human Development Index) of every country and Iron load monitoring. It is important to understand that iron load monitoring could be quite an expensive process, and some countries have limited resources for their patient's healthcare. To test the effectiveness and availability of iron load monitoring TIF divided the countries in three separate HDI categories: Very High, High, Medium /Low.

Using the Chi-Squared test of independence again, we test the Null Hypothesis: 'Variables HDI and Iron Load Monitoring are independent'. More specifically, we are trying to determine if the Iron Load Monitoring status in every country has nothing to do with the country's HDI level. The table and graph of those two variables are shown below:

*Note: The countries Yemen, Laos and Afghanistan have been excluded from the test because of their unknown status.*

| Iron Monitoring/HDI Level | Exists | No | Yes |
|---|---|---|---|
| **High** | 13 | 1 | 1 |
| **Medium/Low** | 6 | 6 | 0 |
| **Very High** | 10 | 0 | 10 |




To test the statistical significance of our null hypothesis we must calculate how probable a sample that extreme would be shown again i.e. find the p-value of the test. In this case p-value=2.551*10-5, which is a tiny value very close to zero. Thus, we reject the null hypothesis in 99% level of confidence, and we conclude that the factor HDI and IRON LOAD MONITORING are heavily related to each other.

## HEALTH EXPENDITURE- IRON LOAD MONITORING

One final test we can conduct regarding the financial situation around iron load monitoring, is about the health expenditure of every country. We are going to examine the differences in the average of health expenditure percentages of the three different levels of the factor 'IRON LOAD MONITORING'. The test is called Analysis of Variance, and it can be applied with the F-statistics. After the analysis in R, we have the following results:

- The category 'NO' of Iron Load Monitoring has on average 1.2356 lower health expenditure percentage than the category 'EXISTS'
- The category 'YES' of Iron Load Monitoring has on average 1.9807 higher health expenditure percentage than the category 'EXISTS'
- The category 'YES' of Iron Load Monitoring has on average 3.2343 higher health expenditure percentage than the category 'NO'.
- For the null hypothesis: 'There are no statistical differences between the means of the levels ('yes', 'exists', 'no') of the factor Iron Load Monitoring' we found the p-value of the F-statistics equal to: 0.02556. So we reject the null hypothesis in a 95% confidence level, but with some reservations. Thus, we conclude that there are differences between those three categories
- Using Tukey's Multiple Comparison on means, a 95% family wise confidence level for the three categories' differences are:
- YES-NO: [0.31,6.15]

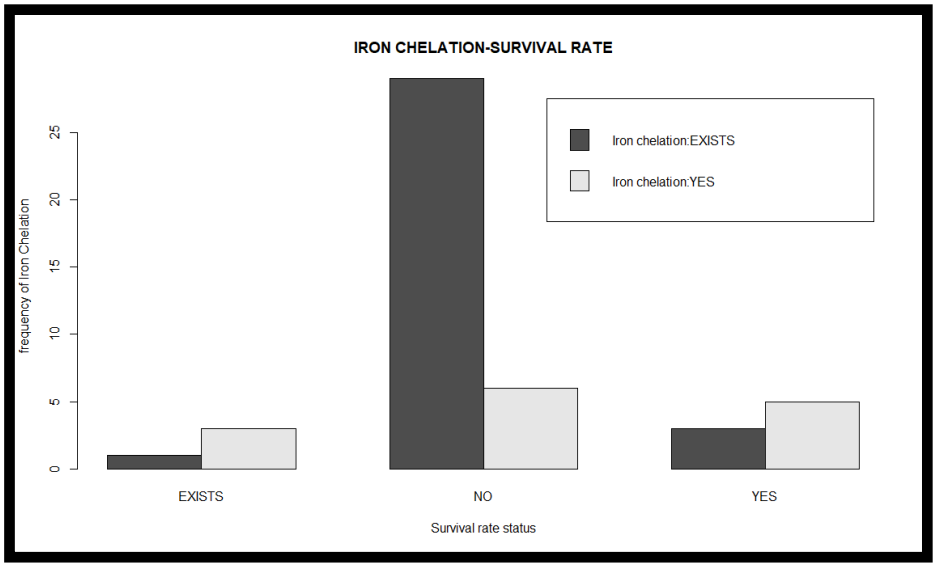
- YES-EXISTS: [-0.19,4.16]
- NO-EXISTS: [-1.25,3,75]
- Note1: The countries Yemen, Laos and Afghanistan have been excluded from the test because of their unknown status.
- Note2: Palestine has been excluded from the test because of no value given
- Note3: USA removed because of the extreme value of Health Expenditure which could cause problems in the used model.
- Note4: We assumed that the sample from the health expenditure for every country follows a normal distribution.

A critical chapter in the availability and the effectiveness of iron overload control is iron chelation. In this stage of our statistical tests, we are going to examine the same relationships of our variables but this time with the factor 'IRON CHELATION'. Now we only have two available levels instead of the three of 'IRON LOAD MONITORING' and those are the categories 'YES' and 'EXISTS'.

## IRON CHELATION-SURVIVAL RATE

Once again, our null hypothesis is that the two variables are independent with each other, i.e. iron chelation provided in any country is not involved or has an impact in the patients' survival rate. The table and graph provide us with an idea:

| Survival Rate | 'Exists' | 'No' | 'Yes' |
|---|---|---|---|
| **Iron Chelation Provided** | | | |
| **'Exists'** | 1 | 29 | 3 |
| **'Yes'** | 3 | 6 | 5 |



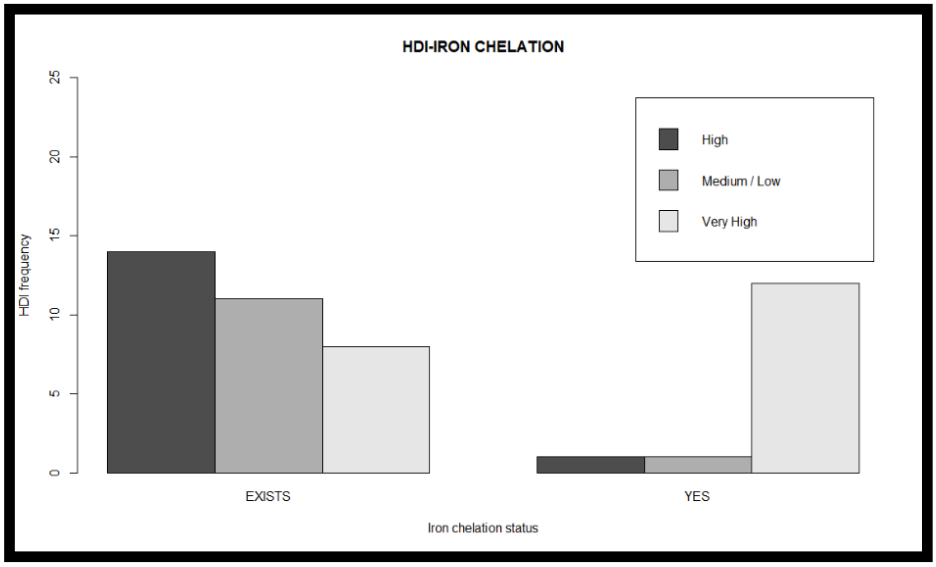

Performing the Chi-Squared test we have a p-value=0.0048, which means we reject again the null hypothesis in a 95% level of confidence. A situation like that is very unlikely to be occurred if we had accepted the null hypothesis, therefore we must assume that there is a form of relation between the variables 'Iron chelation' and 'Survival Rate'. It is understandable that patients where in their country have an Iron Chelation which

'EXISTS' have a much higher probability of having 'NO' in their survival rate status than the patients whose country has 'YES' in iron chelation provided.

## HDI-IRON CHELATION

Repeating the same steps and making the same assumptions, we test the relationship between HDI and Iron Chelation:

| HDI Level/Iron Chelation | Exists | Yes |
|---|---|---|
| **High** | 14 | 1 |
| **Medium/Low** | 11 | 1 |
| **Bery High** | 8 | 12 |




The null hypothesis of the chi-squared test is as usual the same: 'Factors HDI and Iron Chelation are independent'. The p-value of the test is 0.0005 which is very small. So we tend to reject the null hypothesis in a 99% level of confidence and accept the alternative hypothesis: 'Factors HDI and Iron Chelation are not independent variables'. From the graph we can observe that countries with high and medium - low HDI are more likely to have 'EXIST' in their iron chelation status, while most of the countries with very high HDI have a 'YES' status in their iron chelation situation.

*Note: The countries Yemen, Laos and Afghanistan have been excluded from the test because of their unknown status.*

## HEALTH EXPENDITURE-IRON CHELATION

Given the fact that the health expenditure percentage of every country is normally distributed, we can also examine the relationship between Iron Chelation and health Expenditure. More precisely, we are going to analyse the variance of the two different levels of Iron Chelation and come to a conclusion about their health expenditure means. The results of the statistical analysis and the F-statistics are the following:

- The countries from the category 'YES' of Iron Chelation have on average a 2.0480 higher percentage than the countries from the category 'EXIST'
- For the null hypothesis: 'There are no statistical differences between the means of the levels ('yes', 'exists') of the factor Iron Chelation' we found the p-value of the F-statistics equal to: 0.01468. So we reject the null hypothesis in a 95% confidence but interestingly, we do not reject the null hypothesis in a 99% level of confidence. We must point out that our decision about the level of confidence reflects the acceptance or not of the null hypothesis, and that shows that there are not huge statistical differences between the means of the levels of Iron Chelation
- Using Tukey's Multiple Comparison on means, a 95% family wise confidence level for the two categories' differences is 'YES'-'EXIST': [0.4236-3.6723]
- Note1: The countries Yemen, Laos and Afghanistan have been excluded from the test because of their unknown status.
- Note2: Palestine has been excluded from the test because of no value given
- Note3: USA removed because of the extreme value of Health Expenditure which could cause problems in the used model.