11. DISEASE BURDEN OF TRANSFUSION DEPENDENT THALASSAEMIA
TIF'S PERSPECTIVE

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INTRODUCTION

As defined by most relevant bodies, "disease burden" is the impact of a health problem as measured by financial cost, mortality, morbidity, or other indicators. It is commonly measured by calculating the combination of years of life lost due to premature mortality and equivalent 'healthy' years of life loss due to disability. In general, it is the impact of living with illness and injury and dying prematurely.

This implies a systematic collection, analysis and interpretation of population health data, which in many situations is just not done and accurate data are not available. Rather patchy information is derived from publications of small aliquots of patients usually from academic centres. This is particularly true if the disease is relatively rare. The requirements for data collection include accurate diagnosis, classification of subgroups of disease, patient numbers, complication rates and especially mortality figures. In addition, the impact on quality of life and family economics must be considered.

Disease entities which are present from birth, require lifelong treatment and collect multi-organ complications as the patient grows in years as well as resulting in premature death, are particularly difficult to report with accurate information. Another factor which complicates data collection and comparison between countries and regions is the significant differences in quality of care and availability of adequate treatment modalities to manage all patients with equity. WHO defines quality of care (QoC) as the provision of healthcare services that improve desired health outcomes for individuals and populations through effective, efficient, and safe means [1]

It may be asked further on whom this 'burden' is, it can be the patient, the family, society, the health service or the Ministry of Finance, but in fact all are affected. These concerns are addressed by the Global Burden of Disease Study, which is important to know and understand since at central provider level, many decisions are based on its results which remain the guide for health policy makers in all countries.

THE GLOBAL BURDEN OF DISEASE STUDY (OR GBD PROJECT)

This study was initiated in the early 1990s by the World Bank, because of concerns that health services around the world were not effectively dealing with the health challenges. Major issues causing premature mortality and the disability consequent to disease, were not being met because of inappropriate allocation of resources, especially in the developing world. Planning should be based on both the prevalence of a given disease or risk factor and the relative harm it causes. In the World Development Report 1993 by the World Bank [2] the following issues were raised concerning the health systems (see box below):

- **Misallocation of Funds: investing in health interventions of low cost-effectiveness. The example given is surgery for most cancers, as compared to the treatment of common diseases such as tuberculosis.**
- **Inequity: spending disproportionately to the affluent so that the poor lack quality care.**
- **Inefficiency: wasting money, for example on brand names as opposed to generic drugs, poor supervision of staff and underutilization of hospital beds.**
- **Exploding costs: for example, a rapidly growing demand for costly tests and procedures.**
- **Governments are urged to pursue economic growth policies that will benefit the poor**
- **Finance and implement a package of public health interventions to deal with the substantial externalities surrounding infectious disease control, prevention of AIDS, environmental pollution, and behaviours (such as drunk driving) that put others at risk.**

However, in this report we see no reference to congenital or hereditary disease, which require lifelong investment and affect poor and rich alike. Even the 'The World Summit for Children' these conditions are not mentioned. This has led policy makers to not include the m in their priorities.

These sensible housekeeping concerns were then given practical measures by the Global Burden of Disease project (GBD) and supported by the WHO. Indicators were developed quantifying the contribution of disease and public health concerns. Indicators include the disability-adjusted life years (DALY), which is the number of years of healthy life lost due to death and illness. These indicators aid health services to prioritise by identifying disadvantaged groups and targeting health interventions [3]. They are all valid points for good health planning but at the same time are based on economy and 'appropriate' use of funds, aiming to reduce waste. These are important considerations, especially when resources are limited, and they support the maximum benefit on a population level. When it comes down to the needs of the individual with a rare disease, then the ethics of this approach become debatable. Should the rights of the individual be sacrificed to the benefit of the total or should the system consider how best to serve all members of the society. A cancer patient who needs surgery in this model would be deprived because it is not a cost-effective intervention. But if such a person can afford a private investment, then surgery can be made available even if this increases inequality. Health as a human right of all cannot be satisfied and inequalities will continue because the limited resources must be allocated to benefit the majority.

The issue we as TIF raise is not that we believe the World Bank or the WHO or the GBD project are wrong approaches, but that in their effort to get the best out of limited resources, they have reduced health to a series of indices that are used by administrations to prioritise health but often forget the person. In addition, the indices used are based on inadequate information and can be often misleading. The objective is to find solutions for congenital and chronic conditions which may be rare and so not given priority in service provision. Experience, even with the inaccuracies and approximations available to this global review, is that resources to adequately address the needs such patients are not allocated, leading to suffering and early death when in fact treatment can lead to the growth of productive citizens. In this respect resources, including economic resources are wasted more so than if and adequate investment was offered to raise tax-paying citizens as encountered in some countries.

The GBD continues as an independent project with the support of the WHO and funds from the Bill Gates Foundation. It has adopted measures quantified in terms of quality-adjusted life years (QALYs) or disability-adjusted life years (DALYs) [4]. Both of these metrics quantify the number of years lost due to disability (YLDs), sometimes also known as years lost due to disease or years lived with disability/disease. One DALY can be thought of as one year of healthy life lost, and the overall disease burden can be thought of as a measure of the gap between current health status and the ideal health status (where the individual lives to old age free from disease and disability). A cost-effective policy or intervention is measured by the ratio of cost to health benefits or DALYs gained.

Cost effectiveness according to the 1993 report is difficult to estimate, since costs vary between countries and outcome measures are difficult to estimate in complex multi-organ diseases in which morbidity is often difficult to monitor, and survival is variable.

THE BURDEN OF β-THALASSAEMIA

Morbidity in β-thalassaemia is due the effects of the primary condition - anaemia, ineffective erythropoiesis with expansion of haemopoietic tissue, organomegaly, poor growth and fragile bones. These are partially, rarely totally, corrected by blood transfusion. Then, starting from childhood, tissue damage starts due to the toxicity of unbound iron. This tissue damage increases with age leading to organ dysfunction in heart, endocrines and liver mainly. The degree to which these effects are present in individual patients will depend on availability, individual tailoring and adherence to iron chelation, so that in a population of patients a spectrum of morbidity is encountered. The level of morbidity will also determine the quality of life but also the mortality rate in a given population.

The extent of morbidity or the complication rates, measured by various parameters, is a reflection of the quality of clinical management as well as patient adherence. Patient adherence is often episodic, with periods when tissue damage alternates with periods when intensified iron chelation partially rescues the vital organs. Over time there is a cumulative effect, with increasing organ dysfunction and so disability becomes established to varying degrees. Effective management by the conventional clinical tools available today will minimise these catastrophic effects. The clinical interventions required to prevent and manage these complications are complex and expensive, requiring clinical expertise and organisation which in turn mean adequate investment at central government level. Many countries are reluctant to make this investment to the extent required, deciding that there are other priorities for the limited resources available. The result is that many patients, are treated sub-optimally; in fact, the majority of the global thalassaemia population is included. Sub-optimal treatment is self-defeating since it allows complications to increase and premature death to be the final outcome, increasing instead of decreasing the burden of thalassaemia.

All the measures proposed, whether years of potential life lost (YPLL) or DALYs, must rely on data very difficult to come by [5]. As recorded in this Global Review of Thalassaemia Services, very few centres treating patients keep registries and very few countries keep a national registry of patients even to know patient numbers, let alone to record morbidity and mortality data. Classifying haemoglobin disorders according to these measures and comparing their public health importance to other diseases is therefore, largely based on calculations or even guesswork. Better data collection should become a goal and should be promoted in all countries. At the same time, there is a need to better understand how the term 'burden' is applied to conditions that manifests at birth, progress throughout life with increasing organ involvement but yet with an appropriate therapeutic

approach such as applying conventional treatment, can result in long survival with a good quality of life. The number of data items that need to be collected and appropriately recorded to add up to a meaningful concept of the term 'burden' in thalassaemia is demonstrated in a series of recent published attempts to estimate burden [6, 7].

Disease burden in β-thalassaemia is a complex concept which needs several parameters to adequately define:

1. The total number of patients – including the total needing treatment and those needing partial treatment
2. The age distribution of these patients, since the needs of each age group are different. This demonstrates both the degree to which prevention of affected births is effective but also the effectiveness of clinical services provided and contributed to reduction in mortality.
3. Complication rates – these vary from population to population according to timely interventions and quality of care
4. The needs in the treatment modalities: Blood transfusion, iron chelation, monitoring and treating complications (mainly but not confined to allo-immunisation, heart disorders, liver disease, endocrine conditions, renal complications etc.)
5. Loss of productivity – can this be expressed in terms of DALYs? DALYs is a summary measure that combines mortality and morbidity measures, assessing non-fatal outcomes.
6. The degree of social support in place, including the degree financial coverage for treatment and reduction, if possible elimination, of out of pocket expenses.
7. The cost of all these parameters is essential to assess, since economic burden will indeed determine resource allocation. However, costs alone are an incomplete measure since they fail to capture pain and suffering that impact on the quality of life of the patients themselves and importantly their families.
8. Quality of life elements (pain, discomfort, anxiety/depression, effect on daily activities)

Quality of life and functionality status, mental and emotional effects of patients and the repercussion on the family and social environment have to be incorporated in the equation.

Measures that only consider one or two of these aspects, will not portray the whole spectrum or describe the real burden. Reliance on a single measure can be very misleading where any chronic disease is concerned and the effect on public health and individual wellbeing.

There is no challenge to the philosophy of a disease classification which utilises the prevalence of a disease along with the outcome – both morbidity and mortality.

TIF, as a humanitarian organization, cannot adopt an isolated economic model. A more analytical and critical look at the impact of thalassaemia on patients and on society is required demonstrate the obvious inequalities across the world and use any proposed tools to promote health policies which reduce inequalities. We need to use our burden of disease measures to show what can be done by quality care and provide policy makers with tools to measure their own achievements or deficiencies. Monitoring progress cannot rely on costs alone, which may lead health authorities to adopt prevention measures alone without increasing support to patients.

An issue that makes comprehensive assessments even more important is the advent of newly approved treatments which may also be curative. Affordability is a major obstacle increasing the inequalities, allowing

the wealthy to become transfusion free while the majority continue on inadequate conventional therapy, thereby increasing disease burden.

The parameters of disease burden described above are developed separately in each chapter of this review. The classification of anaemias in the recent GBD report, where in 2019 haemoglobinopathies are mentioned in the 17th position of the 0-9 age group in terms of DALYs, but not in any other age group [8]. Indeed, thalassaemia is a lethal disease of childhood in most parts of the world even though the privileged now survive to the sixth decade or more. This 'positioning' is based on disability weights which for thalassaemia were found to be 0.501 (0.403-0.600) in 2016 and 0.485 (0.425-0.545) in 2019, the difference presumably being due to reduced mortality [9]. It is recognized that haemoglobinopathies are a significant source of death and disability. {Disability weights represent the magnitude of health loss associated with specific health outcomes and are used to calculate years lived with disability (YLD) for these outcomes in a given population. The weights are measured on a scale from 0 to 1, where 0 equals a state of full health and 1 equals death}.

THE TIF EXPERIENCE OF MORTALITY AND MORBIDITY OF β-THALASSAEMIA

From the incomplete data in TIF's possession, there is a global population of over 800000 patients with β-thalassaemia and almost 60,000 new cases are being added each year. The global prevalence could be significantly higher acknowledging the absence of effective prevention in most countries. However, one may understand that an almost equal number to those born annually, dies at an early age due to suboptimal care. Non-Transfusion Dependent Thalassaemias may have a better life expectancy [10, 11].

RESULTS CONCERNING THE BURDEN OF DISEASE ACCORDING TO WHO REGIONS

East Mediterranean Region Haemoglobinopathy Status

Introduction

The East Mediterranean region of WHO includes all Arab speaking nations with the exception of Algeria; it also includes Iran, Pakistan and Afghanistan. The total population is over 740 million inhabitants. In this large group of countries there is great diversity in economic and social development, which is reflected also in the quality and availability of services for haemoglobin disorders. One unifying element is that in all countries of the region Islam is the prominent religion, which is accompanied by similar cultural attitudes that may affect issues like prevention. Another common practice in all these states is the high rate of cousin marriage which has an effect on the birth incidence of inherited disorders such as thalassaemia.

Another characteristic, especially of the Arab nations is the high prevalence of both thalassaemia and sickle cell genes. This results in increased incidence of beta thalassaemia, homozygous sickle cell anaemia and HbS/beta thalassaemia patients, increasing the burden of these disorders on patients, families and the health system.

In this report we attempt to describe the current situation of haemoglobinopathy services in the region in relation to the health systems and quality of services as affected by economic and political factors. The huge

diversity concerning economic development, the high level of displaced populations and the armed conflicts which affect many areas of the region make haemoglobin disorders a public health issue of great concern. In the midst of pressing problems, patients who need lifelong complex services are often forgotten or sacrificed to other priorities, resulting in poor outcomes.

Socio-economic development

- In 5 countries more than 25% of the population is living below the international poverty line, i.e. 1.90$ / person/ day as defined by the World Bank (current IPL is 2.15$/person/day, affecting 9.2% of the world's population)
- There is generally a low investment in health

Table 1. Socioeconomic and Health Investment Indicators in the EMR

Country	HDI rank	WB rank	HE/cap WHO data	HE/%GDP WHO data	UHC index
Afghanistan	0.478 low	LIC	81$	15.5%	41/100
Bahrain	0.875 VH	HIC	1110$	4.72%	76/100
Djibouti	0.509 low	LMIC	63$	2.01%	44/100
Egypt	0.731 high	LMIC	151$	4.36%	70/100
Iran	0.774 high	UMIC	573$	5.34%	74/100
Iraq	0.686 med	UMIC	202$	5.08%	59/100
Jordan	0.72 high	LMIC	299$	7.5%	65/100
Kuwait	0.831VH	HIC	1533$	6.31%	78/100
Lebanon	0.706 high	LMIC	994$	7.95%	73/100
Libya	0.718 high	UMIC	381$	3.89%	62/100
Morocco	0.683 med	LMIC	187$	5.99%	69/100
Oman	0.816VH	HIC	845$	5.33%	70/100
Pakistan	0.544 low	LMIC	36$	2.95%	45/100
Palestine	0.715 high	UMIC		•	•
Qatar	0.855 VH	HIC	2188$	4.18%	76/100
Saudi Arabia	0.875 VH	HIC	1211$	5.54%	74/100
Somalia	Not rated	LIC	•	•	27/100
Sudan	0.508 low	LIC	23$	3.02%	44/100
Syria	0.577 med	LIC	89$	3.05%	64/100
Tunisia	0.731 high	LMIC	223$	6.34%	67/100
UAE	0.911 VH	HIC	2192$	5.67%	82/100
Yemen	0.455 low	LIC	64$	4.25%	42/100

- Pure economic criteria do not always reflect service development. For example, Iraq and Palestine are classified as upper middle-income countries but political and social disturbances over the years have not allowed them to fulfil their potential despite having given priority to services for haemoglobin disorders.
- The Human Development Index (HDI) is a statistical composite index of life expectancy, education (expected years of schooling of children at school-entry age and mean years of schooling of the adult population), and per capita income indicators. It expresses human development beyond purely economic criteria and is a better reflection of the ability of countries to deal with health issues especially where complex services are required. The under 5 mortality rate, in the absence of

thalassaemia mortality data and since untreated patients will contribute to this indicator, reflects the HDI index: those countries with a low HDI score are exactly those with an under 5 mortality rate of more than 30/1000 livebirths. On the other hand, those with an under 5 mortality of <10/1000 are those with a very high HDI score.

- UHC service coverage index combines 14 tracer indicators of service coverage into a single summary measure, as a measure of SDG Indicator 3.8.1. Coverage of essential health services, defined as the average coverage of essential services based on tracer interventions that include reproductive, maternal, newborn and child health, infectious diseases, non-communicable diseases and service capacity and access, among the general and the most disadvantaged population. The indicator is an index reported on a unitless scale of 0 to 100, which is computed as the geometric mean of 14 tracer indicators of health service coverage. The tracer indicators are as follows, organized by four components of service coverage: 1. Reproductive, maternal, newborn and child health 2. Infectious diseases 3. Noncommunicable diseases 4. Service capacity and access. Examples of a satisfactory UHC index are 81/100 for Cyprus, 85/100 for France, 77/100 for Greece, and 88/100 for UK. Concerning the services to thalassaemia patients, it seems that countries with UCH index >71 provide free and good quality services (Bahrain, Iran, Kuwait, Lebanon, Qatar and UAE), those with an index between 60-70 seem to have developing services (Egypt, Oman, Jordan, Morocco, Syria and Tunisia) while those whose index is 40-50 have poor services and patients have to rely on family resources to obtain the needful (Afghanistan, Iraq, Pakistan, Sudan and Yemen representing 51.4% of the region's population). Djibouti, Somalia and Libya are relatively low incidence areas and are left out of this equation. The correlation of services and family spending for services with the UHC index needs further investigation.

- The EMR is a populous region with over 740 million inhabitants. Yet health spending is restricted. Taking the health expenditure per capita as an indicator only 5/21 countries actually spend more than 1000$/capita (serving 7.3% of the region's population); another 7/21 countries spend 200-1999$/cap (22.5% of the region's population; 9/21 countries spend <199$/cap and these host 70.2% of the region's population.

- Currently many thalassaemia patients are hoping to survive amid protracted emergencies in Syria, Afghanistan, Yemen and Palestine (Gaza mainly). This includes natural disasters such as earthquakes affecting NW Syria and floods in Libya.

- According to a UNICEF report (2020) 22.5 percent of children in the general population under 5 years of age were stunted, 9.2 percent wasted, and 9.9 percent were overweight. The Arab region also ranked second for adult obesity in the world in 2019, with 27 percent of the adult population obese. https://www.unicef.org/mena/reports/enhancing-resilience-food-systems-arab-states Basic health and nutrition issues are of general concern but also reflect on the health of haemoglobinopathy patients.

- Migrations and refugees:

Jordan: 4/10 people living in Jordan are migrants (https://www.iom.int/countries/jordan). 658000 are Syrian registered in the country, but a total of 1.3 million are estimated with those living outside the camps (UNHCR https://www.unicef.org/jordan). 85% of these live below the poverty line. Possible 185 thalassaemia patients among them. In addition, there are 2 million registered Palestinian refugees. Of these 370000 (18%) are hosted in 10 recognised camps. Also 67000 Iraqis, 15000 Yemenis, 6000 Sudanese. There are a possible 450 thalassaemia patients from this group [12].

Lebanon: hosts 1.6 million refugees mostly from Syria. Almost 90% are in extreme poverty.

Internally displaced persons: there are 12.6 million internally displaced people (IDPs) in the MENA countries.

Yemen: In this country of prolonged civil conflict, 78% of the population is living below the poverty line, making life even more precarious for the 90,700 refugee and asylum-seekers and 4.5 million displaced Yemenis

North-west Syria: where 2.7 million people were already displaced, and 4.1 million people are reliant on humanitarian aid.

Table 2. Overall health status in the region

Country	IMR/1000 livebirths Unicef 2020	Under 5 mortality/1000 livebirths	Life expectancy	Healthy life expectancy at birth HALE
Afghanistan	44.97	58	64.23	53.9
Bahrain	5.97	6.8	80.69	65.9
Djibouti	47.18	55.9	63.71	58.0
Egypt	16.65	19.5	70.81	63.0
Iran	11.14	12.9	76.97	66.3
Iraq	21.32	25.2	72.05	62.7
Jordan	12.92	15.0	75.02	67.6
Kuwait	7.58	8.9	80.45	70.1
Lebanon	5.97	7.0	76.07	66.0
Libya	9.53	11.1	73.25	65.2
Morocco	16.02	18.7	75.20	63.7
Oman	6.45	11.0	78.97	64.7
Pakistan	54.15	65.2	67.34	56.9
Palestine	14.2		74.28	
Qatar	4.93	5.8	81.73	67.1
Saudi Arabia	5.99	7.0	78.10	64.0
Somalia		114.6	57.35	49.7
Sudan	39.92	56.6	66.10	59.9
Syria	18.45	22.4	72.45	62.9
Tunisia	14.29	16.6	76.94	66.9
UAE	5.62	6.6	80.46	66.0
Yemen	45.71	59.6	64.52	57.5

Table 3. Available services

Country	Doctors /1000 pop	Density of nurses per 1000 people	MRI density per million population	VNRD as % of total donations	National haemovigilance program
Afghanistan	0.254	0.4	0.1	40.5%	no
Bahrain	0.92	2.5	2.3	99.5%	No
Djibouti	0.2	0.7	No data	No data	No data
Egypt	0.45	1.9	No data	14.3%	no
Iran	1.58	2.1	3.8	100%	yes
Iraq	0.71	2.4	1.63	No data	No
Jordan	2.56	3.3	3.92	50%	Yes

Country	Doctors /1000 pop	Density of nurses per 1000 people	MRI density per million population	VNRD as % of total donations	National haemovigilance program
Kuwait,	2.29	7.4	5.3	70%	no
Lebanon,	3.2	1.7	8.3	No data	no
Libya	1.9	6.5	7.0	No data	No
Morocco,	0.73	1.4	0.7	75%	yes
Oman,	1.99	3.9	4.4	100%	no
Pakistan,	0.98	0.5	0.22	10.5%	yes
Palestine,	No data	No data	5.5	No data	No data
Qatar,	2.49	7.2	11.2	100%	No data
Saudi Arabia	2.76	5.8	3.0	40%	yes
Somalia,	0.02	0.1	No data	35%	No
Sudan,	0.28	0.8	0.32	17%	no
Syria	1.46	1.5	No data	No data	No data
Tunisia	1.22	2.5	0.54	34%	yes
U A E	2.88	5.7	10.6	93.5%	yes
Yemen.	0.2	0.8	1.15	41%	no

- Data on blood transfusion is from the WHO Global Status Report on Blood Safety and availability 2016 (most data from 2013 reports). These figures may have improved since then; but for patients who have all their lives dependency on transfusions the indication is of long-term deficiencies in quantity and quality of blood.
- MRI density / million inhabitants: 1 magnet/million is regarded as the minimum adequacy. This means that Afghanistan, Morocco, Pakistan, Sudan and Tunisia have no possibility to serve thalassaemia iron measurements, while Iraq, and Yemen will also have difficulties to provide machine time.
- Whole blood processed into components in this region is 65% of donated blood, compared to 99% in Europe.

Table 4. Epidemiology of haemoglobin disorders

Country	β-thal carriers	HbS carriers	Expected β-thal patient births/1000	Expected SCD births/1000	Known β-thal patients	Known SCD patients
Afghanistan	3.8 (Delacour 2013)	0	0.361	0	16500	0
Bahrain	2.9	13.8	0.210	6.0	21	600
Djibouti	0	?				
Egypt	5.3	0.3	0.702	0.082	9258	1166
Iran	4	1	0.4	0.225	20777	2000

Country	β-thal carriers	HbS carriers	Expected β-thal patient births/1000	Expected SCD births/1000	Known β-thal patients	Known SCD patients
Iraq	4.8	0.7	0.576	0.18	19955	6075
Jordan[13]	3.5	1.5	0.306	0.319	1450	216
Kuwait	2.12	6	0.112	0.274	475	600
Lebanon	2.3	1.8	0.132	0.288	375	387
Libya	1.5	2	0.056	0.250	?	?
Morocco	1.67	1.76	0.07	0.224	500	?
Oman (Al Riyami 2001)	2.2	5.8	0.121	1.479	591	8000
Pakistan	6	0.25	0.900	0.077	50000	?
Palestine	4	1.25	0.401	0.288	864	131
Qatar	3	5	0.225	1.375	163	354
Saudi Arabia	2.37	4.24	0.14	0.951	8919	26000
Somalia	0	rare				
Sudan	3.9	2.4	0.380	0.612	665	?
Syria	5	0.5	0.625	0.131	7700	1200
Tunisia	2.21	1.9	0.122	0.3	742	1526
UAE	3	1.1	0.225	0.175	2000	?
Yemen	4.4	2.2	0.484	0.605	800	11000

Because of the scarcity of national registers and the often-small sample surveys, epidemiological data for the region is incomplete. However, even inaccurate data on carrier frequency, still indicate that the region is rich in the prevalence of both thalassaemia and SCD. TIF contacts in each country have reported the numbers of patients and for β-thalassaemia the number exceeds 140000, while sickle cell patients are at least 60000 but with data missing for several populations of the region. The numbers alone are indicative of a high burden of disease, which is increased by inadequate case management in many locations leading to an increase in complications and premature death.

In the EMR, Iran has one of the best records of thalassaemia management and this is reflected in the age distribution of patients. In an analysis of 1831 patients in Northern Iran [14] (about 10% of the Iranian thalassaemia population), the mean age of patients was 30 ± 9.7 years (76% TDT). This can be compared to a report from neighbouring Iraq where 65% of patients were <18 years and 35% > 18-35 years (in contrast, in Italy 68% were aged ≥35 years and 11% were aged ≤18 years).

One factor increasing the prevalence of haemoglobin and other hereditary conditions in the EMR is the customary practice of cousin marriage in all countries of the region. This is expressed as the inbreeding

coefficient >0·0156 (inbreeding coefficient measures the proportion of loci where the offspring of consanguineous marriage is predicted to receive identical gene copies from both parents).

Country notes, indicating latest burden of disease and outcomes:

Afghanistan: the political upheavals have not allowed investment and policies to address the needs of TDT patients. There is lack of information and epidemiological data crucial to policy, services and interventions. Because of low UHC index, patients of low economic status cannot afford basic treatment, and often neglect seeking treatment. Child Foundation (an international NGO, active mainly in Iran) funds the only free thalassemia paediatric clinic in Afghanistan, which treats nearly 200 patients who need blood transfusions and other treatments. The clinic is part of Mazar-e Sharif Hospital. Most of thalassemia patients have limited access to regular and safe blood transfusions. (Qaderi et al 2021)15. Around 300 new affected births per year are expected and the figure of 16500 for existing patients was quoted by an NGO LSOA (Life Saving Organisation of Afghanistan), active in the care of thalassaemia patients in 2012 (certainly out of date but no new information is available). There is no prevention programme.

Bahrain: this is mainly a sickle cell prevalence country with a haemoglobinopathy programme going back to 1984. This includes a prevention programme based on obligatory premarital screening; in a recent analysis (Bahram S 2023)16 67% of at-risk couples decided to proceed with their marriage; there is a positive attitude toward IVF with PGD by 60% of at-risk couples. Concerning patient care it is noted that in a recent survey of caregivers, 14.8% reported catastrophic health expenditure and other practical difficulties in providing care for sickle cell patients, including dissatisfaction with hospital facilities, and insufficient healthcare services. This in a country with high HDI and long-term service development. However, in a survey of families' catastrophic health expenditure occurred in 14.8% of caregivers (Al Saif K 2022)17. In addition, the survey revealed dissatisfaction with hospital facilities, and insufficient healthcare services. These are suggestive that quality of care and patient satisfaction are not simply a matter of economics. Patient centred care requires staff education as well as organisation of the patient journey.

Egypt: From a sample of 200 patients with beta-thalassemia major (mean age 24.6840± 5.30761), attending one clinic, 48% had a ferritin level >3500 ng/mL with a total of 72.5% above 2500 ng/Ml. According to BMI measurements 23.5% were underweight and 9.5% overweight. There is need to pay attention to iron overload in Egypt reference centres (Ibrahim AS 2023)18 as the effect will be an increasing complication rate and a threat to life. In another study involving 30 young thalassaemia patients (ages 14.77±2.45), LIC was 13.40 (8.86–25.00) mg Fe/g dw, while the median (IQR) cardiac T2* was 18.7 (2.1–17.1) ms. The β-TM patients in this small study had no clinical heart disease with a mean EF% and FS% of 65.7 ± 8.41 and 36.63 ± 6.47, respectively, yet the longitudinal systolic strain values by STE were significantly lower compared to standard control values which might reflect an early LV dysfunction. In this study also iron overload is evident (Tantawy et al 2022)19.

In a survey of thalassaemia patients aged from 2-12 years (mean 11.34), 9.17% already had hypothyroidism, 7.5% had disturbances of glucose homeostasis (not diabetes), 6.66% had hypoparathyroidism, and 66.7% were regarded as malnourished based on Z- scores of BMI. These results may seem similar to those of other countries, but the age group of patients is much younger; this indicates poor management, which is confirmed by a very low pretransfusion haemoglobin (6.82g/dl mean, 7.5 median) and a high serum ferritin (mean 3631) [20]

These reports from reference centres in the country, are indicative of an as yet reduced patient care system with an increasing disease burden as they survive to adulthood. Furthermore, economic difficulties on a national level did not allow the purchase of chelating agents during several months of 2024; this is bound to increase the disease burden of the 10000 or so thalassaemia patients living in Egypt and results will be obvious during the coming years, even if the deficit is corrected.

A premarital screening program was initiated this year and has already reached almost one million individuals (Dr Mona Hamdy personal communication). From the first 250000 cases, 1.8% are β-thalassaemia carriers and 0.45% are sickle cell carriers, result much lower than those reported from surveys over past years.

Iran (Islamic Rep. of): Iran is also a country with a high burden of β-thalassaemia. Over the years services have developed and experienced gained in both disease prevention and management. Centres of expertise have developed in main urban centres where the condition is most prevalent.

Survival and other outcome indicators reflect the quality of care in this country. However, published figures may not represent the total thalassaemia population in a country. In an analysis of 1831 patients in Northern Iran (about 10% of the Iranian thalassaemia population), the mean age of patients was 30 ± 9.7 years (76% TDT) [14]:

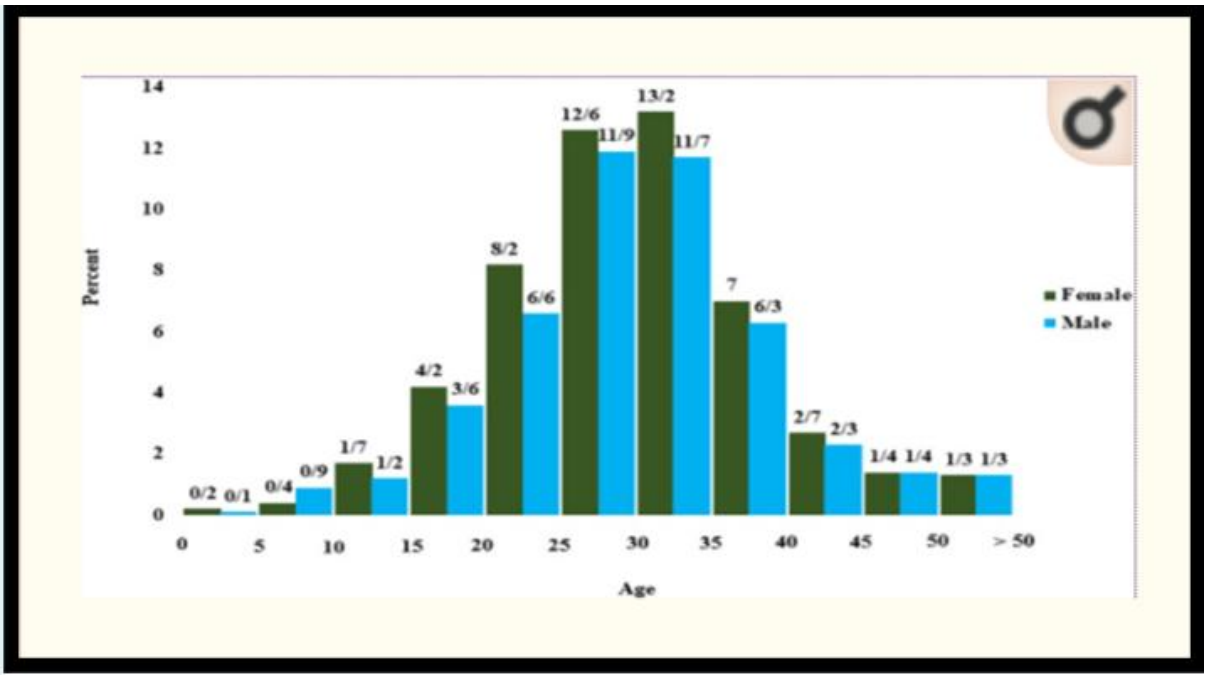

Figure 1. Distribution of 1385 transfusion-dependent patients by age and gender, Mazandaran Province, 2016

In this group cardiac iron was measured by MRI was similar to that found in reference countries. However, liver iron was much higher in that only 14.6% had an LIC <3. In another major centre, reviewing endocrine complications in 2019 [21], hypogonadism and bone disease were reported much higher than in reference countries, while diabetes and hypothyroidism were much the same.

In a much larger cohort [22] of 5491 patients from various parts of the country, the mean age was only 23.8 ± 11.3 years (71.7% TDT).

In another study from Iran, features of QoL correlated to the patients' laboratory findings, such as liver function and fasting blood sugar, as well as education, indicating that quality of care and outcomes of treatment play a significant role in estimating the quality of life and the burden of disease [23] .

In 2016 [24] the annual cost to treat each patient with major thalassaemia was estimated to be 8,321.8$ according to World Bank data GDP/capita in 2017 was 5,520.3$. Average family income would be less, and so universal health coverage supports patients, even though access to some services (such as MRI) is limited. The cost of preventing the birth of any major thalassemia patient through screening was calculated to be US$32 624. The lifetime treatment cost of any thalassemia major patient was US$136 532. Iran has attempted to

reduce birth incidence while upgrading patient care despite an economic embargo which is limiting its ability to import medications.

Iraq: The total number of patients in Iraq from reports communicated by the national Thalassaemia Committee, based on reports from the various treatment centres in the country there are around 17624 thalassaemia patients, of which 8611 are thalassaemia major. In addition, there are 7800 patients suffering from sickle cell syndromes. Programming at central level for thalassaemia services is under way and patients receive support for their treatment.

A cohort of 150 patients from Dohuk are reported [25]. This is a young cohort representing about half of the attendees, so they present with low ratios for organic complications like heart disease and diabetes. The high and the high positivity rate for HCV (35.3%), are danger signals for this group if management is not upgraded soon. These results are representative of many patient outcomes in which services meet with obstacles in their development, either economic or political. In this study published in 2020, the following findings are summarised:

- The median age of the enrolled patients was 13 years (range: 1–35 years), and only 2.0% were 30 years or older. In Iraq the bulk of β-TM patients are children or adolescents. This confirms an older report from a peripheral unit where the higher percentage of patients were at age < 10 y. (47.2%) [26]
- The mean pre-transfusion haemoglobin was 8.6±1.0 g/dL, and it was maintained ≥ 9.0 g/dL in 38.7% of patients
- Thalassaemic faces were noticeable in around half of the patients (50.7%)
- The median serum ferritin was 2762 µg/L, with 53.3% of the patients having serum ferritin in excess or equal to 2500 µg/L.

This is evidence of suboptimal management, which may be worse in other parts of the country, confirming other studies which point to an uneven level of care.

In a survey of 242 TDT patients, from Sulaymaniyah (northeastern Iraq) [27], 83 patients were TDT, and the rest 159 NTDT. The mean age was 17 ± 10.2 years, with a range of (1.4–54 years). Of the TDT patients 65% were <18 years and 35% > 18-35 years, the following complications were listed:

- Bone disease 75.9%, Growth retardation 44.4% (in those <18years), hypothyroidism 13.4% (in those >18years), Diabetes 6% (in those >18 years), Pulmonary hypertension 7.2% (in those >18 years).
- In the same study 159 cases of NDTD patients were studied with reduced incidence of bone deformities, osteoporosis, growth retardation and diabetes.
- There was an increased incidence hypothyroidism (16.8%) and pulmonary hypertension (11.3%) including isolated cases of thrombosis, leg ulcers and extra-medullary haemopoiesis.
- Serum ferritin was <1000µ/l in 31.3% of the TDT group and in 76.6% of the NTDT (32% of these were regularly transfused). These results indicate a good level of care in this region of Iraq [.]

A more recent report of the Arab Thalassaemia Forum (unpublished) the following emerged:

- Pre-transfusion haemoglobin is <7g/dl in 35% of patients, 7-9g/dl in 50%, and only in 15% of patients is it kept over 10g/dl.
- 47% of patients experience various transfusion reactions.
- 1% are infected by transfusion transmitted infections (TTI).

- MRI for iron measurements is not available.
- Complications recorded are in the heart (30%), hypoparathyroidism (13%) and osteoporosis (14%).
- Poor compliance to iron chelation is witnessed generally.
- Peak age of patients is between 16-25 years.
- Secondary education in patients over the age of 16 years is completed by 6.6% and university by 2.8%.
- Causes of death are due to infections (38%), cardiac complications (74.5%) and severe anaemia (4.2%).

The conclusion is of a country that has central planning for thalassaemia services, including prevention, with financial patient support and progress towards universal health coverage (UHC). However, services have not reached an equitable level either in patient care or disease prevention (without prevention 1132 new affected patients are calculated to be born annually). The country is paying the price of successive conflicts and political turmoil. Nevertheless, the existence of national planning and an expert national advisory committee encourages progress in Iraq so disease burden should reduce in the coming years.

Jordan: Despite governmental attentional to thalassaemia over many years. caregivers in Jordan experience financial burden associated with regular hospitalization and unpaid leave for employee mothers [28] and the need for psychosocial support is emphasised. These remarks are in keeping with the countries UHC index and other indicators. Furthermore, 4/10 people living in Jordan are migrants https://www.iom.int/countries/jordan. 1.3 million are refugees from Syria, while there are 2 million registered Palestinian refugees and others from Iraq, Yemen and the Sudan. Some 81% live in urban areas outside of refugee camps, and 85% of these live below the poverty line. 82% of these refugees were able to access health services while the rest were unable due to inability mostly to afford fees and increasing health cost. This is bound to affect thalassaemia patients. [UNHCR Socio-economic situation of refugees in Jordan Q2 2023.pdf]

According to the National registry in 2017 there were 1450 thalassaemia patients in the kingdom. [29]. According to the estimated carrier rate (2-4% mean 3.5%) then there may be 76 new affected births each year if no prevention. So, a further 500 new cases may have been added in the last 7 years, even though ongoing premarital may have reduced this (no reports on the effectiveness of prevention have been recently published)

The average annual cost was estimated to be 2,674 JOD (3773.7$) for a single thalassemia Jordanian insured patient and 4,627 JOD (6529.8$) for un-insured, while the non-Jordanian patient' annual cost was estimated 4,751 JOD (6704.8$) if insured and 6,651 JOD (9386.2$) if un-insured [30]. The Jordanian Ministry of Health (MOH) is the sole facility responsible for treating these patients from the pre-marital program until required medications regardless of their nationality. This imposes an extra burden to the Jordanian health budget as the flow of refugees from Syria and Palestine continues. Such population movements make prevention also difficult to implement efficiently. A mandatory National Premarital Thalassemia Screening Program was implemented in Jordan in 2004, however, results in terms of affected births prevented are not known.

Lebanon: Another Middle East country with a long history of thalassaemia control. The average age of a cohort of 228 thalassaemia patients treated at the Chronic Care Centre in Beirut is 32.1 years [31]. This alone is indicative of improved patient care in this country. 54.4% were employed and university level was reached by 26.3% subjects, 7.9% reached high school level, and 32.5% have a level less than high school. The existence of a national reference centre in the country has contributes to better outcomes despite political and economic difficulties. Despite this effort Lebanon is also host to 1.5 million refugees from Syria most of whom have to rely on out-of-pocket spending even for primary care services. Medicine and health are amongst the top five reasons for a family to resort to debt, according to a UNHCR report [Health access and utilization survey among refugees in Lebanon – 2022 UNHCR 2023]. The fate of most patients with chronic disorders like the haemoglobin disorders is not known. A minority of thalassaemia patients 138, was catered for by a clinic in the

Bekaa Valley created by the Medicines sans Frontier, which catered for children up to the age of 14 years. In this charity service a treatment protocol was followed, maintaining a pre-transfusion haemoglobin of 9.24g/dl on average and an average serum ferritin level of 2659ng/dl (range 424- 6020ng/dl). Over a period of 5 years and having access to the three chelating agents the clinic was able to maintain monitoring parameters to safe levels. MRI T2* was also possible for 19 patients. This outcome in a relatively resource poor setting, is a blessing for this minority of patients (Issa L et al Abstract 2023 TIF International Conference). The plight of the migrant and refugee populations in the Middle East is a major concern.

As in Jordan the ongoing prevention programme is likely to be hampered by the influx of refugees and the disease burden is likely to increase.

Morocco: Local experts suggest that that there are 1100 thalassaemia patients mean age 16 years, and up to 5000 SCD patients, but there is no national registry to confirm these figures. Concerning patient care, 95% are treated in 8 public university run hospitals. Each of these centres reports yearly to the Ministry and so patient numbers are regarded as accurate by the Ministry. Treatment is free. However, access to chelating agents is very difficult but the Ministry clams no shortages, rather poor prescribing by the doctors.

A virtual meeting between The National Ministry of Health, local experts, TIF and representatives of the Arab Forum took place on the 22nd of September 2022. The result of the meeting was expressed in a Memorandum of Understanding between TIF and The Ministry of Health, which expresses their joint desire to collaborate in the areas of prevention and control of haemoglobin disorders, through strengthening the professional capacities of medical and paramedical personnel from the ministry of health in this area. The MoU recommended the creation of a joint multidisciplinary expert advisory committee, to make suggestions on prevention, public awareness, preparation of national treatment guidelines and the organization of various activities, including Conferences, Workshops, Forums etc. The lack of prevention is likely to continue increasing disease burden along with the increasing complication rates in affected patient population.

Oman: a recent analysis of liver function and iron load parameters is revealing of current trends in patient care: in this study of 91 patients, the median age (IQR) of the subjects was 33 (9) years, and BMI was 23.8 (6.1) kg/m2. "Despite regular chelation and blood transfusions, there was a significant iron overload with rising SF levels and LIC measurements by MRI. The median SF levels rose from 1309 at the start of chelation to 1881 ng/mL, which was statistically significant. There was also a comparable and statistically significant rise in the LIC from a median level of 10.2 to 14.2 g/dry wt. of liver. However, with sustained patient education and compliance monitoring, it was encouraging to see the results of sustained chelation efforts, with the median LIC decreasing significantly to 7 g/dry wt. at the last follow-up [32]. These results do not differ significantly from those of advanced centres of Europe and so there is an accepted good level of care at least in one University reference centre in the country. In another recent study of 187 patients with β-TM with a median follow-up of 24.9 years, those born after 1980 had a lower risk of death (P = 0.005), hypogonadism (P = < 0.0001), and cardiac complications (P = 0.004), while overall complication rates were similar to advanced centres [33]. State support and universal coverage help in achieving these good results. Family support has also contributed greatly to the quality of life of thalassaemia patients [34]

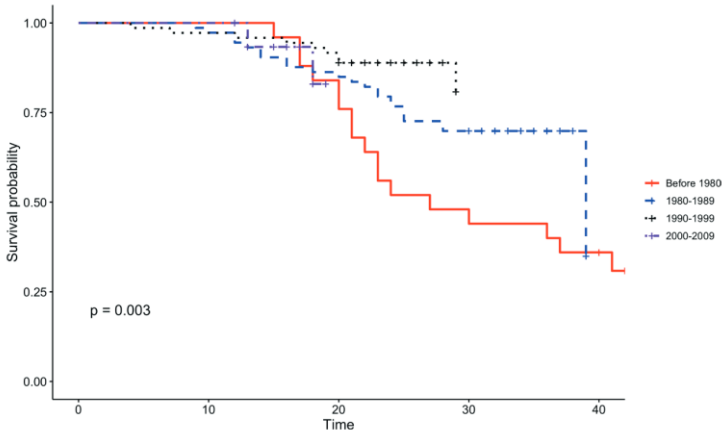

Figure 2. Overall Survival according to the birth cohort

These are acceptable results and coupled with the fact that there is ongoing prevention the disease burden is likely to improve over the years. In one report 71.5% took a premarital screening test before marriage, even though the test is not compulsory and is offered on voluntary basis [35]. In this same study 23.3% cancelled engagement upon positive screening results, while 13% of participants continued with marriage for either emotional or family reasons.

Pakistan: This is a low HDI country with a high burden of thalassaemia, and a challenge to service provision. A study of 21 parents of children with thalassemia a low level of education but also knowledge only three (14.28%) parents declared that they knew that they carried a genetic trait, indicating also poor counselling. Challenges, physical, socio-emotional, financial, and familial were detected in this small group [36]. Despite poor resources, in the country significant work has been done to improve the thalassemia status of the country; this includes the establishment of reforms to private philanthropic organizations which offer services to the majority of patients [37]. However, there are no standard management protocols exist; prevention programmes have been initiated in most provinces [38] (Khaliq S 2022).

Patients and families are not adequately supported by the healthcare system. In a recent study of 100 thalassaemia patients and their families, the total expense incurred on treatment by the end of the month was PKR. 5000–10,000 (USD31-62) in a government run hospital, while in the private sector the total expense incurred on treatment by the end of the month was around PKR 80,000 (USD500). Around 37% families have an average monthly income of PkRs25000 (USD150) only, and as a result they sold their livelihoods to satisfy medical expenses, while 31% compromised on their children's education expenses and 23% curtailed the health expenses of their other children. [39]. Apart from the out-of-pocket expenses which often exceed income Caregiver lack of knowledge leads to delayed diagnosis but also poor outcomes. To further add burden there is social stigma to deal with and poor response to prevention because of ignorance and high consanguinity rate, which maintain the birth of around 5-6000 new cases each year [Baqar M, Ahmed JM, Asim M, et al. Experiences of family caregivers of children living with thalassaemia-major in Karachi: a phenomenological study. BMJ Public Health 2024;2:e001359. doi:10.1136/]bmjph-2024-001359].

Such a system of poor support is coupled with poor clinical service and so increasing complication rates and early mortality. In this setting charity organisations have been formed to support patients by developing their own clinical services. The quality of these independent services is variable but may also be of good standard. The result is an uneven level of patient care and outcomes. A saving grace comes from an expanding prevention programme which was initiated in the Punjab and is currently expanding in the other provinces. However, national figures on prevention are not yet available and despite efforts the bulk of the population is not reached [40]. This lack of adequate investment means the burden of thalassaemia is likely to increase in the coming years.

Palestine: These are self-governing territories under constant political and economic pressure and the danger of armed conflict (which materialised in 2023-24). A recent quality of life study indicated poor scores in all domains in 104 patients in the West Bank and Gaza [41]. This is a reflection of both social conditions and clinical services in a country offering the best possible services under the circumstances, having given priority to haemoglobin disorders. In a 2021 study of 309 patients with b-thalassemia the average age was 23.4 ± 10.4 years, which is comparable to many countries outside the developed world. However, the pre-transfusion Hb level was 8.4 ± 1.4 g/dl, and 73.1% had iron overload with serum ferritin (SF) levels ≥ 1,000 µg/L (mean ± SD = 3,175.8 ± 3,378.8µg/L, ranging 75.5–17,450.0). MRI was not available to measure iron in heart and liver [42]. These are incomplete data, yet they reflect a population of patients who will have increased complications in later life and confirms the findings of poor quality of life referred to in the first study. In the 2nd quarter of 2023 Gaza became a war zone and the fate of the over 300 thalassaemia patients are yet to be known since communication was lost. TIF is aware that medications have reached the patient population only sporadically, blood transfusion is a problem for many since the needs of casualties are given priority. In addition to deteriorating patient care, war casualties have been reported. At least 27 patients have reached Egypt, but their fate is also in doubt. Both blood supply and iron chelation are in doubt in this war zone which is currently expanding.

Qatar: this is a high-income country and if income was the only factor, it is expected that patient care would be of high quality. In a study of 2018 LIC was assessed by hepatic R2 MRI, an indication of the availability of this technology. However, 35% of patients (young patients' age mean: 21.7 years; range 9-35 years) were found to have an LIC ≥ 15 mg/g/dw and high serum ferritin (4,488 ± 2,779µg/L); this is a reflection of unmet needs even in a high-income setting [43].

Saudi Arabia: a high-income country with a high burden of haemoglobin disorders especially SCD. Issues concerning the adequacy of services can be identified. Blood supply for example depends to a great extent on public awareness as well as on organisation of blood drives; it is an issue of community involvement. In a 2021 study from the eastern provinces indicated that 158 patients for a three-year period, 14,508 units of packed red cell units were ordered, and 9,530 units were received that is, 34% of demanded units were not supplied [44]. This inevitably will impact Hb levels in these patients and so long-term outcomes. Despite issues like these, the Kingdom is adopting policies for 'Health Sector transformation through Model of Care strategies', which include the development and implementation of dedicated blood disorder programs (Dr Hatoon Ezzat personal communication). The premarital screening program established in 2004 has now screened over 5.5 million partners. This program was supported by an educational program for counsellors. The screening revealed that 1.38% are β-thalassaemia carriers and 4.25% are sickle cell carriers. The at-risk marriages have reduced from 3% in 2004 to 85% in 2020. The program includes a newborn screening program (mainly for SCD and other variants, including alpha thalassaemia), A registry of Inherited Blood disorders (IHBD) has been created which has comprehensive data on 23481 patients aiming to reach 65000 by the end of 2024. This is a model program which can be imitated by other countries of the region.

Syria: this country has been subject to prolonged conflict which has disrupted services and prevented development, severely affecting the prognosis of thalassaemia patients. The prevalence of the condition is significant with approximately 5% of the population carrying the beta thalassemia gene. The National Thalassemia Program in Syria was established in 1997, aiming to optimize both patient care and prevention. The Syrian conflict, since its eruption in 2011, had particularly detrimental effects on thalassemia patients, especially those who were displaced. From March 2019, a total of 4,677 patients have been registered to receive chronic blood transfusions in the areas under Syrian government control. However, all services have suffered, and this includes the loss of trained medical and nursing staff. In the city of Homs before the conflict the median age of patients was 14 years whereas in recent years during the conflict the median age is 10 years; economic sanctions imposed the conflict disrupted the supply of medications, and a significant percentage (15.1%) of the patients had not received any chelation for six years, spanning from 2012 to 2018, due to their being trapped in

the armed conflict areas. The median SF concentrations of the patients significantly increased from 3274 ng/ml in 2009 to 4672 ng/ml in 2019 (P < 0 0001). Iron overload and poor outcomes are to be expected in this country [45]

United Arab Emirates: High HDI country with long standing services aiming to serve thalassaemia patients as well as disease prevention. In a study of 137 TDT (median age of 12 years (range 2-49 yrs), severe iron load in the liver (LIC) was noted in 16.1% (≥15 mg/g dw) and normal/mild LIC in 62% (<2-7 mg/g dw). T2* of the heart was normal in 83.9% (>20ms) with 6.9% severe [46]. These results are improved compared to other countries of the region, especially compared to the results of Qatar with a similar age range of patients.

One important issue is that 88.50% of the population are expatriates; the majority of these are from India and Pakistan while there is a sizable proportion from Egypt. These are ethnic groups rich in thalassaemia genes. In recent study [47] of 255 thalassaemia patients, 65.5% were non-UAE nationals; 73.3% were in the > 18 years age group while 90.6% had thalassaemia major. The mean total annual direct medical cost per patient was AED 131,156 (95% CI: 124,735 –137,578) =307963.89 USD, of which ICT was the most expensive component, followed by blood transfusions. The median (IQR) household annual income was 96,000 AEDs (26136.57 USD). These high costs reflect the wealth of the country For Emiratis there is full coverage while for ex-patriates the extent of coverage is determined by the employee's salary and designation.

Conclusions

The countries of the region have considerable variability in economic and social development. However, as far as services for haemoglobin disorders are concerned, even high HDI countries are reporting results which need improvement, based on indicators such as iron overload. The large refugee population in the region further complicates the prioritisation of haemoglobin disorders. Despite some countries being in the high resource group the overall picture of the region requires attention and policies which may favour these chronic patients. In the high resource states mainly of the Arab peninsular, there is compulsory health insurance for the large migrant population.

WHO South-East Asia Region (SEAR)

Introduction

The WHO South-East Asia Region is home to over 2 billion people, a quarter of the world's population. 11 Member States - Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand, Timor-Leste. WHO has country offices in all 11 Member States. The WHO South-East Asia Regional office in based in New Delhi India.

With the Region prone to natural disasters, disease outbreaks and health risks of climate change, one of WHO's key priority is to strengthen emergency risk management for sustainable development. Promoting universal health coverage – health for all - and building robust health systems are key priorities. The Region has eight flagship priority programmes, aligned to WHO's global triple billion goals and the UN Sustainable Development Goals:

1. Maternal and Child Health: to accelerate reduction of maternal, neonatal and under five mortalities.
2. Eliminate Measles and Rubella by 2023.

3. Universal Health Coverage: Continue progressing towards Universal Health Coverage with focus on human resources for health and essential medicines.
4. Neglected Tropical Diseases
5. Noncommunicable Diseases: Prevent and control noncommunicable diseases through multisectoral policies and plans, with focus on "best buys".
6. Antimicrobial Resistance: Further strengthen national capacity building for preventing and combating Antimicrobial Resistance.
7. Health Emergencies: Scale-up capacity development in emergency risk management in countries.
8. Ending Tuberculosis: Accelerate efforts to End TB by 2030.

WHO Collaborating centres: As of January 31, 2022, there are 105 active WHO Collaborating Centres across 8 member states of WHO South-East Asia Region. These include:

- 2 on blood safety and Blood Transfusion Services in National Blood transfusion Service Sri Lanka, Colombo. Thai Red Cross Society, Bangkok
- 1 for Strengthening Ethics in Biomedical and Health Research at the Indian Council of Medical Research, Bangaluru
- 2 for reproductive health, including Birth defect and stillbirth surveillance and a newborn-birth defects (NBBD) Database. Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, and the Indian Council of Medical Research (ICMR), Mumbai. Siriraj Reproductive Health Research Centre, Bangkok and Chulalongkorn University, Bangkok
- 1 for community-based activities in the area of maternal, newborn, child and adolescent health at the Mahatma Gandhi Institute of Medical Sciences, Sewagram, Wardha
- 1 for NCD prevention and control, through the identification and collation of policies, tools, and best practices and research studies on NCDs, enhancing the skills and competencies of doctors, nurses and health workers. At the All-India Institute of Medical Sciences (AIIMS), New Delhi

Policies promoted by the Regional Office:

Blood Donation (based on World Blood Donor Day 2023 speech by RD): In the South-East Asia (SEA) Region, around 19.4 million units of blood are collected, which constitutes around 0.94% of the region's population donating blood. Ideally, any country's requirement for safe blood can be met easily if 1 to 3 percent of the total population donates regularly. Of the eleven member states, only three have achieved 100% voluntary non remunerated donations (VNRDs) while the rest of the member states are striving to achieve 100% VNRDs (average of 82% VNRDs in SEA Region). 100% of donated blood is tested for transfusion-transmitted diseases.

Universal coverage: Between 2010 and 2019, the Region increased its UHC service coverage index from 47 to 61. Between 2000 and 2017, the Region reduced the number of households impoverished or further impoverished from out-of-pocket spending on health from 30% to 6%. In 2017, around 299 million people in the

Region faced catastrophic health spending, and an estimated 117 million people in the Region were pushed or further pushed below the purchasing power parity poverty line of US$ 1.90 a day. An estimated 40% of health budgets in low- and middle-income countries are spent on medicines, with much of the cost borne out-of-pocket by patients.

Manpower development: Since 2014, the density of doctors, nurses and midwives in the Region has improved by over 30% – a tremendous achievement.

World Birth Defects Day: Globally, an estimated 8 million newborns are born with a birth defect every year. Nine out of every ten children born with a serious birth defect are in low- and middle-income countries. The most common severe birth defects are heart defects, neural tube defects and Down syndrome. In the WHO South-East Asia Region, birth defects are the third most common cause of child mortality, and the fourth most common cause of neonatal mortality, accounting for 12% of all neonatal deaths. Between 2010 and 2019, birth defects increased as a proportion of child mortality in the Region, from 6.2% to 9.2%, and in four countries, birth defects now contribute to more than 20% of under-five mortality. In 2019, birth defects contributed to at least 117 000 deaths in the Region, equal to around 22% of the global total. All Member States have initiated hospital-based birth defect surveillance and are implementing national action plans to prevent and manage birth defects. Six Member States – Bangladesh, Bhutan, India, Maldives, Myanmar and Nepal – continue to support a WHO-developed online database to better track birth defects. To date, the database has recorded more than 4.7 million births in the Region, including about 51 000 infants born with birth defects. The Region has several priorities:

- First, improving the coverage and quality of preventive interventions such as rubella immunization, quality antenatal care
- Second, enhancing health system capacities to detect, treat and care for birth defects, with a focus on adapting new WHO guidance on universal screening of newborns for hearing impairment and eye abnormalities
- Third, sustaining and expanding surveillance and improving data systems, with a focus on strengthening not just coverage and quality, but analysis and application.
- Fourth, increasing support for parents and caregivers for early childhood development and to improve disability care.

"Every child has the right to survive and thrive, with full access to quality and comprehensive health and social services. On World Birth Defects Day, WHO reaffirms its commitment to support all countries of the Region to urgently strengthen health systems to prevent, detect, manage and care for birth defects, for every child, everywhere." RD speech

Patient Safety: Since 2015 the WHO South-East Asia Region has made targeted efforts to reduce unsafe medication practices and errors, with a focus on addressing counterfeit and substandard products, and enhancing patient safety and reporting systems. This is in line with the Region's Strategy on Patient Safety 2016–2025. Most countries of the Region now have in place national patient safety and/or quality strategies that are aligned with the new Global Patient Safety Action Plan 2021–2030. The Plan aims to advance policies, strategies and actions to eliminate all sources of avoidable risk and harm to patients and health workers.

Child health in the South-East Asia Region: Member States in the Region have demonstrated significant progress in reducing newborn and child mortality over the last two decades and the Region achieved the MDG4 target of two-third reduction in under-five mortality in 2016. The progress has continued during the SDG phase and by 2019 five countries in the Region achieved the 2030 target of under-five and newborn mortality and the Region as a whole is likely to reach the 2030 target for under-five mortality but may narrowly miss the newborn mortality target. In the South-East Asia Region, around 52% of under-five mortality is contributed by deaths during the neonatal period. The most common causes of under-five mortality in the Region is the complications of prematurity followed by pneumonia and diarrhoea. Commonest causes of neonatal mortality are prematurity, birth asphyxia and neonatal infections. However, the coverage of evidence-based interventions remains low and uneven in several Member States. There is a large disparity in child health by wealth status, residence (rural-urban), mother's education level and social status, not only in mortality but also in the coverage of interventions.

Noncommunicable diseases in the South-East Asia: Noncommunicable diseases (NCDs), principally cardiovascular diseases, cancer, diabetes and chronic respiratory diseases, impose a major and growing burden on health and development in the South-East Asia Region. In the region, 62% of all deaths are due to NCDs accounting for 9 million persons. Of particular concern is the high proportion of premature mortality from NCDs (deaths before 70 years of age).

Research: is indispensable for resolving public health challenges. Research for health spans 5 generic areas of activity:

- measuring the magnitude and distribution of the health problem
- understanding the diverse causes or the determinants of the problem, whether they are due to biological, behavioural, social or environmental factors
- developing solutions or interventions that will help to prevent or mitigate the problem
- implementing or delivering solutions through policies and programmes; and
- evaluating the impact of these solutions on the level and distribution of the problem.

A new "Research and Innovation Unit" has been established in January 2022 within the Healthier Population and Non-Communicable Diseases (HPN) Department. Vision: Achieving the best possible public health outcomes and health equity in South-East Asia Region powered by the latest in science, innovation and evidence. Regional strategy on research for health 2018-2022.

Table 5. Socio-economic development

Country	HDI rank	World Bank rank	HE/cap in USD WB data	HE as % GDP WB data	UHC index WB data
Bangladesh	0.661 med	LMI	50.66	2.63%	52
Bhutan	0.666 med	LMI	133.7	4.37%	60
India,	0.633 med	LMI	56.63	2.96%	63
Indonesia	0.705 high	UMI	132.96	3.41%	55
Maldives	0.747 high	UMI	825.57	11.35%	61
Myanmar	0.585 low	LMI	72.11	4.62%	52
Nepal	0.602 low	LMI	58.31	5.17%	54
Sri Lanka	0.782 high	LMI	151.06	4.07%	67
Thailand	0.800 v high	UMI	305.09	4.36%	82
Timor Leste	0.607 low	LMI	120.87	9.85%	62

Comments

This group of countries are generally in the 'developing' category with only Thailand, Maldives and Indonesia gaining the upper middle-income category. This difference is less obvious when the Human Development Index is considered, since Thailand and the Maldives reflect better social development but Indonesia lags with the other members of the group and Sri Lanka ranked higher. Overall, as far as health service support is concerned the table provides evidence that the Maldives and Timor Leste are spending more on health. In general, however, with the exception of Thailand no country in the region offers secure universal coverage to all its citizen as reflected in the UHC index (defined in the section for EMR countries). The level of coverage and healthcare development that is derived from the table suggests that thalassaemia patients and their complex demands on the health system, may not be adequately supported in the countries of the region, while Thailand and the Maldives being more likely to offer the necessary services.

The Democratic Republic of North Korea is not included in this discussion both because thalassaemia is very rare in the Korean peninsula but also because economic and other data are not available.

This generally poor health development is reflected in the overall health indicators of the populations of these counties:

Table 6. Health Indicators and Healthcare Support in Selected South and Southeast Asian Countries

Country	IMR/1000 livebirths	Under-5 mortality/1000 livebirths	Life expectancy	Healthy life expectancy at birth HALE
Bangladesh	29.58	29.1	73.98	64.3
Bhutan	23.18	27.6	72.49	64.3
India	27.0	32.6	72.03	60.3
Indonesia	19.31	23.0	71.01	62.8
Maldives	5.27	7.6	81.07	70
Myanmar	35.05	43.7	67.46	60.9
Nepal	23.59	28.2	70.78	61.3
Sri Lanka	5.92	6.9	76.8	67.0
Thailand	6.36	8.7	79.91	68.3
Timor Leste	32.93	42.3	69.31	60.9

In this respect also the Maldives, Sri Lanka and Thailand stand out with indices which approach those of developed and resource rich nations. They indicate more organised and effective health services and stand out as being categorised as high HDI countries. In contrast the rest indicate a poor performance even though improving compared to past years. It is also a reflection of the large populations with often diverse cultures and divisions into tribal groups. This picture is reflected in the achievements concerning thalassaemia.

Table 7. Available services

Country	Doctors/1000 population	Density of nurses/1000 population	MRI density/ million population	VNRD as % of total donations*	Nat haemovigilance program
Bangladesh	0.7	0.5	0.49	22%	YES est 2018
Bhutan	0.5	2.1	1.33	80%	Yes 2016-7
India,	0.7	1.7	0.21	76%	Yes 2012
Indonesia	0.6	4.0	NA	91%	Yes
Maldives	2.1	4.7	2.9	36%	No
Myanmar	0.7	1.1	0.24	99%	Not only in central est
Nepal	0.9	3.3	NA	83%	Yes
Sri Lanka	1.2	2.5	0.42	100%	Yes 2009
Thailand	0.9	3.2	NA	100%	Yes 2001
Timor Leste	0.8	1.7	NA	18-20%	No

** Voluntary non-remunerated blood donations to ensure blood safety in the WHO South-East Asia Region to support universal health coverage ISBN Number: 978-92-9021-044-3 © World Health Organization 2023*

The indicators used are derived from the needs of thalassaemia patients. Adequate overall manpower is inadequate in all of the countries; in contrast the UK and Cyprus have 3.2 doctors/1000. Only the Maldives approaches this figure and so he possibility of devoted doctors for haemoglobin disorders is limited in all the region. Likewise, the possibility for MRI monitoring of iron load is limited (compare with Cyprus MRI density of 14/million and Greece of 29/million).

Blood safety is improving in the region with the exception of Bangladesh, the Maldives and Timor Leste. For the rest there remains the question whether good practices are even throughout the country – especially in India.

Table 8. Prevalence and Burden of Thalassaemia and HbE Disorders in Selected South and Southeast Asian Countries

Country	β- thal carriers	HbE carriers	Expected β-thal births/1000	Expected HbE/β- thal births/1000	Estimated β- thal patients	Estimated NTDT patients
Bangladesh	3.5%	10.2%	0.31	1.7	12000	30-40000
Bhutan	0.7%	4%	0	0.01	NA	NA
India	3.9%	1%	0.38	0.2	150000	NA
Indonesia	5%	6%	0.63	1.5	10974	NA
Maldives	18%	0.9%	8.16	0.81	633	NA
Myanmar	0.5%	26%	0.1	0.65	NA	4079
Nepal	4%	4.4%	0.4	0.88	600	NA
Sri Lanka	2.2%	0.5%	0.12	0.06	2000	NA
Thailand	2.9%	24.6%	0.21	3.57	2070	96390
Timor Leste	5%	6%	0.63	1.5%	NA	NA

In addition, 4 countries of the region have a significant number of sickle cell carriers:

- India has 3% AS carriers which lead to 0.82/1000 births of SCD syndromes with over 125000 patients
- Maldives has AS 0.13% which leads to 0.12/1000 births and 14 known patients
- Sri Lanka has 0.15% AS which leads to 0.12/1000 births and 51 known patients
- In Nepal AS is said to be 5% but this is confined to one geographical area but could lead to 1.63/1000 affected births. Total patients are not known

The whole region has a major prevalence of haemoglobin disorders and yet because of poor resources and uneven development of services, thalassaemia services are not given priority in health planning. This is reflected in the policies of the regional WHO office which hardly mentions haemoglobin disorders (see the outline of polices in the introduction to this section). However, much progress in specific issues such as increasing health coverage, blood adequacy and safety and creating reference centres in certain locations which are an example for more development. Patient support groups are gaining ground, but prevention programs are very limited in the region.

Bangladesh: this is a country of over 160 million people and with many health issues to consider, including water-borne diseases, essential nutrition and improved water sanitation and hygiene. There is no national registry, but the carrier rate indicates a high prevalence, and the estimate is of over 50000 affected patients. According to a study by Khan et al over 10.0% of the patients suffer from Hb E/b-thal and many are NTDT, while 4.0% have b-thal major [48] . To quote a recent description of the situation "Facilities for blood transfusion are not present in all the district hospitals. Furthermore, blood transfusion is also a costly procedure for the patients to afford, frequently due to the lack availability. Chelating agents are also very expensive due to low supply" [49] []. The treatment is not free and so the patients from weaker economically families are undertreated.

The burden of disease in this country is huge while families are not supported adequately to deal effectively with the children's medical needs. Families affected by beta-thalassemia encounter significant financial burden due to the high cost of treatment [50].

Currently, most infants are neither diagnosed nor treated and probably die in early infancy from the consequences of anaemia. Organised treatment is only available at the thalassaemia clinics in Dhaka and in Chittagong. There are national guidelines since 2019 but not implemented by the majority of treating physicians. Blood is not filtered and often whole blood is given. Voluntary donation is inadequate. All three iron chelators are available but not free of charge; indeed, patients pay for many services including laboratory tests and MRI. Alternative medications aiming to reduce transfusion burden are often used, including thalidomide, and hydroxyurea. The result is that iron load is high and co-morbidities increased. Indeed, blood transfusion is also a costly procedure for the patients to afford. Moreover, the costs of treatment, even when discounted, are beyond the means of the large majority of families, so that only 1% of the thalassaemia population benefit from reasonable management [49]

These findings are similar to a report from a TIF delegation visit in 2019 [Report of a delegation visit to Bangladesh, supported by Thalassaemia International Federation, the Ministry of Health and Bangladesh Thalassaemia Samity. Telfer P, Petrou M et al 2019]. The team also emphasized the wide variation in prevalence across the country:

Table 9. Regional Variation in Thalassaemia and HbE Carrier Frequencies in Bangladesh

Division	Number tested	Het b-thal	AE	EE	% het b thal	% AE	% EE
Barisal	77	2	4	2	2.6	5.2	2.6
Chittagong	260	17	20	1	6.5	7.7	0.4
Dhaka	475	12	39	4	2.5	8.2	0.8
Khulna	159	2	8	0	1.3	5.0	0.0
Rajshahi	338	14	44	0	4.1	13.0	0.0
Rangpur	116	5	31	7	4.3	26.7	6.0
Sylhet	14	1	1	0	7.1	7.1	0.0
% of Total Tested	1439	53	147	14	3.7	10.2	1.0

These carrier frequencies are challenged by a recent survey of 1000 university student from 3 districts, using capillary electrophoresis and molecular studies; the findings were 1.7% for β-thalassaemia carriers and 5.8% of HbE carriers [Khan MA et al. A pilot study- thalassemia screening program in Bangladesh TIF Int Conference Abstract 2023]

Other findings of the TIF delegation were the confirmation that all of the patients were inadequately chelated, and transfusions for those with thalassaemia major are generally insufficient, and pre-transfusion Hb is generally 6-8 g/dl. These basic findings indicate that there is need for more effort with the health authorities, despite other pressing health issues, to improve quality of care. The needs were also demonstrated by a study on the Health-Related Quality of life which concluded that "This study found an association between lower income, blood transfusion, disease severity, comorbidities, and medical expenses and the deterioration of HRQoL among the patients". The conclusion is that "National action plans are required to guarantee the holistic welfare of thalassemia patients" [51]

Bhutan: a small mountain country, with a population less than 800000 people, has a low prevalence of β-thalassaemia genes and HbE. On the other hand, α-thalassaemia is more common. However, clinically important mutations are rare, and little is known about services.

India: Because its large population (now over 1.4 billion) and high prevalence of thalassaemia and sickle cell genes India bears a large burden of the global haemoglobinopathy population. The estimate is of 100,000 thalassaemia patients [52]. Every year 0.5/1000 livebirths will be added suffering from beta thalassaemia and HbE/ beta thalassaemia (around 15000 new affected births/ year).

The distribution of these genes is heterogeneous both geographically and among tribal and linguistic groups. In a recent review of the literature the β-thalassaemia carrier rate in the general population amounted to 3.74% (95% CI 2.52-4.97) but higher in the tribal groups [53]

Universal Health Coverage is not yet fully implemented in India even though the government introduced the Ayushman Bharat Yojana scheme to bring the healthcare services within the reach of the community. Healthcare out-of-pocket expenditure is estimated at around 62.6 per cent of total health expenditure so haemoglobinopathy cannot be free of health-related expenses. If the entire present cohort of 150,000 thalassaemia patients was receiving adequate care, the annual cost would be USD448 million, and with an added cohort of 125,000 cases over a decade by 2026, the annual cost of care is predicted to escalate to USD820 million [54].

Even though government hospitals cover the cost of treatment of thalassaemia this is does not satisfy all needs and patients supplement by out-of-pocket expenses. There is support from NGOs, but again not all needs are satisfied. In a recent estimate of cost for treating children younger than 12 years in Mumbai, the cost was found to be US$ 981 per patient per year. Direct costs contributed to 94% of the cost of illness with chelation therapy (23%) and blood investigations (21%) being major contributors. Even at subsidized rates, the financial burden to the families from lower socioeconomic strata is considerable [55]. Such financial issues result in undertreatment but also psychological stress in both patients and families [56]. Overall, the quality of life (QoL) of patients (children in a current study) significantly correlates with their carers' CarerQoL, mother's educational level, parent's working status, as well as quality care [57].

Quality of care is variable across India, with some academic mainly centres offering near optimal care, even though at a cost, while the majority of patients receive substandard treatment. This is reflected in outcomes. One example is the rate of transfusion transmitted infections which in turn reflect quality of blood banking: 39.9% of regularly transfused children were found to have TTIs with hepatitis C being the most common (34.5%), followed by hepatitis B (4.5%) and human immunodeficiency virus (1.8%); this was found to be related to the per capita monthly family income as well as the blood transfusion frequency [58]. In another study of 328 β-TM children attending the thalassemia day care unit of a medical college 48.2% were malnourished with a mean body mass index of 13.9 kg/m2; this was related to socio-economic factors such as caste and mothers' education (compare with 7.8 % of children in the USA by Fung et al 2010) [59]. It is noteworthy that most reported results involve children with thalassaemia indicating the overall age distribution of patients in India. In contrast a report to TIF from expert patients in India (Varesh and Anubha March 2021) involving 740 patients across several states, indicate an improving survival:

Table 10. Age Distribution of Thalassaemia Patients in India (Report from Expert Patients, 2021)

Age group	% of patients
<10 years	25%
10-20	30%
20-30	25%
30-40	15%
>50 years	4%

This indicates that 44% are young adults, even though in this cohort there may be a selection of treating centres from academic units. The overall picture of undertreatment of the majority is not negated, hope however for improvement of patient care is present. According to a recent report a National Policy has been proposed for the management and prevention of hemoglobinopathies that will embark on a comprehensive program, providing adequate care and augmenting the existing public health care services. It will also include training, genetic counselling and easier access to preventive options and a National Registry.

The overall picture of clinical services for thalassaemia patients in India is one of gradual improvement but the journey has not yet reached its goal. In a recent presentation by the Haemoglobinopathies subcommittee of the Indian Paediatric Haematology Group [60], it was stated 68 centres across India participated in the survey with 11660 patients, and the findings in summary are that MRI T2* is offered in half of these; leukodepleted packed red cells are offered in 84% but filters are purchased by the patient in 41% of centres. In addition, one third reported difficulty in 'arranging blood donors'. Concerning patient outcomes, they reported growth retardation in 60% of patients, 75% have iron overload, 37% have psychosocial issues and multidisciplinary care was available in 62% of centres.

In a review of the literature concerning quality of life in thalassaemia patients of india it was clear that children experience a low QoL, and it was concluded that there is need to increase parental and family awareness, to promote the use of support groups, psychosocial counselling, and emotional support [61]. However, improving the level of medical care and offering comprehensive financial coverage will go a long way to reducing the burden of both the patient, the family and the state. Another suggestion is establishing a robust public-private

partnership, along with training healthcare providers, private and government doctors in urban and rural areas, strengthening the blood bank, and supporting the management of b-TM [62].

Indonesia: Indonesia has a relatively high incidence of thalassemia, with approximately 3-10% people being carriers. According to national data there are over 11000 patients under treatment. The country introduced a universal health coverage scheme in 2014 and these patients are included to benefit from free treatment of both blood transfusion and iron chelation. However, adjuvants necessary for quality care such as MRI and multidisciplinary care are not available across this large territory to all patients. The age distribution of patients in this country is not known. In fact, the vast geographical area over which patients are scattered and the variable quality of services in each region make it impossible to generalize. Reference centres for thalassaemia management are mainly in Jakarta, and so it may be expected that these centres represent the best possible care that is offered in the country. One state of art centre is located in the Cipto Mangunkusumo Hospital [63]. In this unit both children and adults are treated, and all treatment has in recent years been fully supported by national health coverage. Patients are regularly monitored, and MRI is available. In a 2018 report from this hospital of MRI results on liver and heart iron the measurements on 546 patients are analysed, 56.4% under the age of 18 years and 43.6% over 18 years. For the purpose of this report and for comparison with other adult populations it was chosen to reproduce the findings of the over-18-year population: heart iron deposition was found within normal range (>20ms) in 82.7% of adults which is comparable to countries like Italy Cyprus and Greece while liver iron concentration was within normal rage in only 13.4% of the patients. Despite these results, the key message here is that patient care can achieve good results in any country, provided that the services are supported by universal coverage.

In a group of young adults from a unit in Java (mean age, 21.5 ± 7.2 years), 15-53 years, the mean hemoglobin before blood transfusion was 7.2 ± 1.7 g/dL and mean serum ferritin was 4414.5± 3165.2 ng/mL. [64]. These results are evidence of undertreatment, and organ complications are expected. Similar results are reported from a reference centre in Jakarta on a group of 30 patients with ages ranging from 13-41 years. The mean Serum Ferritin was 9,019.3ng/ml (SD3,889.4) in patients with a cardiac T2* <20ms and 4,118.4 (SD2,373.6) in those with a T2* >20ms [65]. Similar findings are still being reported from Indonesian hospitals [66, 67]. The reasons given include the availability of iron chelators which is uncertain in some rural areas and poor adherence to iron chelation therapy and maintaining pretransfusion haemoglobin to acceptable levels [68]. These findings confirm that quality improvement is needed, and international guidelines adopted.

Deferiprone had a lower mean annual cost of USD 3581 than deferasirox, which had a cost of USD 6004. This has been considered and deferiprone was the most common iron chelator used (86.7%). Detailed medical and non-medical costs have yet to be calculated so the national health insurance can budget adequately for all patients in the country [69].

The Maldives: The Maldives is an island nation with a population currently estimated at over 500,000 people located in the Indian Ocean. It consists of 1900 islands, of which 200 are inhabited. It has the world's highest concentration of carriers at 16-18% of the population [70, 71] Screening over the years of 110,504 individuals indicated a β-thalassemia carrier frequency of 16.2% [72]

The latest report is of 666 patients registered which amounts to around 1 for every 800 inhabitants. This a considerable burden of disease and has led to the recognition of thalassaemia as a major public health issue by the Ministry of Health. This has led to long standing programs of raising awareness, screening and patient care. There is one reference centre where the majority of patients receive routine treatment freely provided by the state. Despite this optimum care is still to be achieved. In a recent survey about 46% of patients have a serum ferritin below 2500ng/ml while the rest are above that level (the mean ferritin was 3,339.6 µg/l). The mean

haemoglobin level was 8.35 (SD 0.95) while 42% of subjects had a haemoglobin level of 9 gm%. 55.7%) claimed they were always compliant to chelation, while the rest claimed to be compliant sometimes. [73] MRI assessment of iron overload is still unavailable despite efforts. There is an increasing economic development which hopefully will assist in offering optimal care in the coming years. All treatment is offered free of charge since universal coverage is available.

Ongoing prevention for many years is partially successful in reducing birth incidence hindered partly because of the difficulty of raising awareness and reaching remote islands.

Myanmar: this is a country with a very low prevalence of β-thalassaemia, the overall carrier rate being only 0.5% while HbE is 26%. Only one province, Kayin, reports a high β-thalassaemia carrier rate of 8.9% but the population is only 1.5 million compared to the 54 million of the whole country. The reported 4000 patients are mostly NTDT. According to a report from the Yangon Children Hospital, the levels of hemoglobin (Hb) appear to be very low and patient management poor [74]. Blood transfusion is provided free of charge since 2014. Since most (70%) of patients are NTDT, only 18% of patients in Yangon have a serum ferritin level >2000ng/dl. HCV positivity is 12.6%. However, universal coverage has not yet been applied, and so family contribution is necessary.

Nepal: in this country both sickle cell genes and thalassaemia genes are frequent. Sickle cell is more concentrated towards western part of Nepal and especially in Tharu ethnic population. In contrast, the distribution of β-thalassemia is found throughout the country and among all ethnic groups of population [75]. Most known β-thalassemia patients are treated at the Children's Hospital in Katmandu. The challenges in managing chronic conditions like beta-thalassemia in remote rural areas, where healthcare access and awareness are limited, mean that many patients are left untreated or seriously undertreated [76].

All basic treatment is provided free by government funds. In a recent publication the medical charts of 54 thalassemia major patients registered at the Civil Service Hospital were retrospectively analysed: The median age of the patients was 17 years (3–34 years); 71% of patients failed to maintain haemoglobin above 9.5 gm% primarily because of the unavailability of red blood cells; the mean serum ferritin was 4486.12 ng/mL (range 469–9585 ng/mL). Overall, 80% [77] of patients reported interrupted use of iron-chelating agents because of frequent shortages of medicines; 93% of patients were found to have stunted growth; overall, 7.6% had cardiac complications, and 5.5% had hypothyroidism; 54.1% of females of reproductive age had primary amenorrhea. The average cost of thalassemia care was 70,000 NRS (~533 USD) in paediatric patients and 250,000 NRS (~1906 USD) in adult patients per annum. This includes the cost of blood transfusion, commute to the transfusion centre, and iron-chelating agents [77]. There is no prevention program and the fate of patients outside Katmandu is unknown. Much work has yet to be done in Nepal to improve the services but at least government interest has been aroused. Similar results are reported in a survey from a peripheral hospital [78]. The healthcare services of Nepal as well as the medical community have increased their interest in thalassaemia in recent years and if this continues progress towards reducing disease burden will also increase even though prevention is still at limited.

Sri Lanka: The majority of patients have β-thalassemia and a minority (16%) HbE/ β-thalassemia. In one review 61% of patients had low pretransfusion haemoglobin levels (< 9.0 g/dL) despite receiving high transfusion volumes (> 200 mL/kg/year) [79].

Sri Lanka does not have a regular national registry, but in a recent report data was collected from most if not all treatment centres [80]; data on 1774 patients from 23 centers were collected. 1219 patients (68.7%) had homozygous β-thalassaemia, 360 patients (20.3%) had hemoglobin E β-thalassaemia, and 50 patients (2%) had sickle β-thalassaemia. Patients with thalassaemia major, with mean age of 13.2 (SD 7.6) years (range 5 months—44years) were significantly younger than those with HbE β-thalassaemia [mean age 21.5 (SD 12.9) years, range 6 months to 60 years; p<0.0001]. This is a typically young, undertreated population of patients with a mean serum ferritin level of 2383.

According to a report from the patient support association in 2019, the government spends over Rs. 800,000/- (about 2400 USD) per child annually, "who will invariably die at a young age".

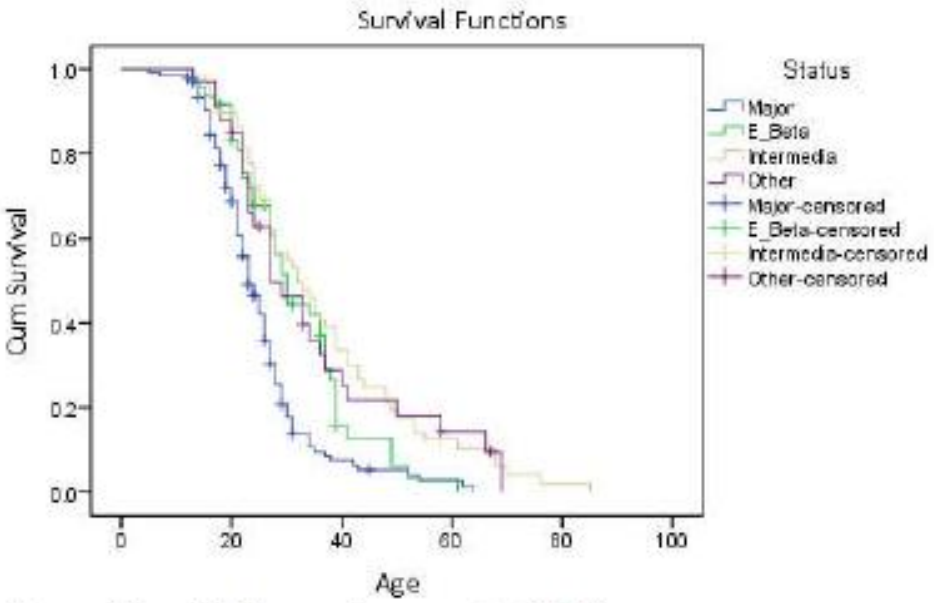

Figure 3. Survival Functions of Thalassaemia Patients in Sri Lanka by Disease Subtype (Hemals Thalassaemia Care Center, 2017)

A sharp decline in survival after the age of 30yrs is seen especially in β-thalassaemia major. [81]]. The overall survival of patients of β-TM is still not on a par with that of the Mediterranean countries [82.]. In contrast median survival in HbE/ β-thalassaemia patients was 49 years [83].

In Sri Lanka, the Ministry of Health started a thalassaemia screening programme for school children and young adults in 2005. The program is voluntary and based on the 'Safe Marriages' concept, so community awareness is of vital importance if birth incidence is too affected. One of the most fundamental issues with the thalassemia screening program is that it has operated without central control: individual hospitals conduct their own screening programs not collated by the Ministry of Health and annual births showed no clear reduction until 2012 [84, 80]. Prenatal diagnosis is available but is a limited service confined to academic centres [85].

A cost of illness study was published in 2020, which discussed the cost of treating children (< 18 years) in 2017. The total annual direct hospital cost was $US 2092 per patient year. With added household costs were $US 206 (total societal burden of $US 2807 per patient year). Despite support relatively low levels of household income resulted in about 1 in 4 households experiencing catastrophic costs (> 10% of total income). [86].

Sri Lanka has a medical community and an infrastructure of services that could result in excellent outcomes. Poor central support to service development and quality as well as family support, does not help to achieve the standards that the country is capable of.

Thailand: A country with constant development, which has recently moved to high HDI category. It is characterised by a large, affected population by haemoglobinopathy patients with a very large majority being HbE/ β-thalassaemia. In addition, there is a high prevalence of alpha-thalassemia (20-30%) and variants like Hb Constant Spring (1-8%). The burden of disease in terms of patient numbers was summarized by Prof Suthat Fucharoen in 2019 during a SEATAF conference:

Table 11. Estimated Burden of Haemoglobinopathy in Thailand: At-Risk Couples, Affected Births, and Living Patients (Prof. Suthat Fucharoen, SEATAF Conference, 2019)

Conditions	Couples at risk/year	Affected births/year	Living patients
Homozygous β-thal	828	207	2070
HbE/ β-thal	12852	3213	96390
Hb Bart's hydrops fetalis	3332	833	0
HbH disease	22400	5600	336000
Total	**39412**	**9853**	**434460**

There is a long tradition of research and service development which have made Thailand a reference country for the whole SE Asia. Despite this case management is uneven across the country and so patient data variable. In a multi-centre study, including peripheral centres, conducted between 2015 and 2017, the mean hemoglobin level was 7.1 ± 1.3 g/dl in patients with TDT and 7.7 ± 1.2 g/dl in patients with NTDT. The mean serum ferritin was 2,250 ± 2,313 ng/ml in patients with TDT, and 1,483 ± 1,530 ng/ml in patients with NTDT. The patients were selected to be over 18 years, and the mean ages were similar between the TDT and NTDT groups, 27.8 years vs. 29 years. Examples of complications in this group include extramedullary hematopoiesis, detected in 12.5% of TDT patients and only 4.9% of NTDT patients, indicating possible undertransfusion [87]. In a more recent cohort from Chiang Mai, including 209 TM and 279 HbE/ β-thal patients, predominant causes of mortality were infection-related (36.9%) and cardiac complications (27.7%). The mean age of these patients was 13 years, and a main predictor of poor outcome was iron overload identified as serum ferritin >3000ng/ml, affecting 16.4% of this cohort [88]. Hospital admissions were also mainly due to iron overload with infections being the second cause [89]

For patient care national guidelines have been prepared, based on TIF's Guidelines for the Clinical Management of Thalassaemia, but modified to be a realistic reflection of local circumstances.

The cost of treatment as estimated in 2010 [90] is as follows:

- for ages 1-10 years – 2900 Euros/year
- for ages 11-20 years – 5000 euros/year
- for ages 21-30 years – 7230 euros/year

The health system of Thailand is divided into three schemes, reaching all of the 68.4 million population (2018):

- The Universal Coverage Scheme (USC), this is the largest scheme covering 48.8 million people.
- Civil Servant Medical Benefit Scheme (CSMBS) covering 4.97 million people
- The Social Security Scheme (SSS) covering 14.47 million people
- Under these schemes all thalassaemia patients are supported for full treatment. Haematopoietic Stem Cell Transplantation (HSCT) is still out-of-pocket, with a projection for full support by 2020.

The cost to manage patients with TDT, living 10 to 30 years, is approximately 39,393 to 20,000 USD/patient covering regular blood transfusions and iron chelation [91] . A cost-benefit analysis of an 8-year prevention programme in Chiang Mai province (north Thailand), involving 21975 pregnant women and their husbands and which resulted in the prevention of 80 affected births, cost 93,667 USD. This included screening and pre-natal diagnosis. For the same period the cost of treatment was 6,756,401USD. This means that the benefit vs cost is 72:1.

Both treatment and prevention are reimbursed under the universal coverage insurance scheme. Since 2002, Thailand's entire population of 63 million has been entitled to a comprehensive health benefit package [92].

A national prevention program was initiated in 1997. This includes antenatal screening in the first trimester of pregnancy and the availability of prenatal diagnosis all free of charge [93]. Aborting the foetus with thalassemia diseases was not well-accepted. Other challenges affecting prevention include the fact that medical personnel do not inform about PND availability, laboratory errors are another preventable issue and approximately 50% of pregnant women attend ante-natal clinics late in pregnancy. However, this is a well-studied population with sensitised authorities and a reduced burden is expected.

Timor Leste: little is known about thalassaemia in this country. It is assumed that it has the same pattern of disease as Indonesia of which it was once a province. However, there is no published information on services and TIF has no member associations in the country.

Comments: This WHO region hosts one of the largest thalassaemia populations in the world. It consists of LMIC mainly countries, with large geographical areas and complex population structures with tribal groups, linguistic subgroups and a variety of religions and cultures. National programs are scarce and quality of care very variable, ranging from a few centres of excellence to many centres unable to meet the real needs of patients. Much work has to be done at national level which depends on raising awareness and advocacy both by professionals and support associations. This is an area where TIF activities should constant and almost daily.

WHO West Pacific Region (WPR)

Introduction

The Western Pacific Region is home to almost 1.9 billion people across 37 countries and areas. Headquartered in Manila, Philippines. It includes countries big (such as China, with 1.4 billion people) and small (such as Niue, home to just 1000 people).

There are 15 country offices across the Region: 11 WHO representative offices and 4 country liaison offices. Together with the Regional Office, the 15 country offices support 37 countries and areas. Of interest to TIF because of significant presence of thalassaemia: Australia, Brunei Darussalam, Cambodia, China, Hong Kong, Laos, Macao, Malaysia, Papua New Guinea, Philippines, Singapore and Vietnam. However, there are other member states with reported thalassaemia syndromes but no real data. From TIF database there are around 4000 new births per year affected by beta thalassaemia syndromes and a minimum of 40000 living patients (excluding China)

The region is characterised by unprecedented economic growth, while migration and urbanization in the region have created opportunities for better lives.

For health development training programmes and supporting the building of comprehensive local health services have been the main policies. While recognizing that communicable diseases remains a significant public health issue, the increased prevalence of noncommunicable diseases, coupled with ageing populations throughout the Region, means there needs to be a greater emphasis on preventive and health promotion activities, even as communicable diseases continued to require considerable resources.

Three main priorities have emerged for the regional office as the issues reflecting the Western Pacific's unique economic, social and environmental context:

1. Health security, including antimicrobial resistance
2. NCDs and ageing (mainly heart disease, stroke, cancer, diabetes and chronic respiratory diseases, responsible for 86% of deaths in the Western Pacific Region)
3. Climate change and the environment.

Projects and services promoted to address these issues:

1. Communications for Health (C4H): On 20–21 April 2023, the World Health Organization (WHO) Regional Office for the Western Pacific convened the Member States Consultation on the Draft Regional Action Framework on Communication for Health (C4H). C4H is a tool for health to help Individuals, health workers, policymakers and government leaders make decisions every day that affect people's health. Evidence-based, strategic communications – that is, using communication principles and processes to target a particular audience for a specific purpose, based on known audience needs and preferences for tackling complex health challenges. Whether it be promoting health-protective behaviours, increasing vaccination rates, reducing stigma around mental health, or advocating for inclusive health policies, strategic communication can play an important role. Communication is, in itself, a public health intervention: it is a technical field backed by theory and evidence {can we get them to add thalassaemia awareness?}

2. Behavioural and social sciences for better health: investigating the cognitive, social, and environmental drivers and barriers that influence health-related behaviours. Applying behavioural and social sciences requires a multidisciplinary approach and the adoption of theory, methods, research, practical tools and techniques drawn from psychology, sociology, anthropology, communications, marketing, economics, systems thinking and design thinking, among others. Behavioural and social sciences evidence can contribute to and complement other public health efforts that focus on the non-medical factors that influence health outcomes. WHO includes behavioural and social sciences in its work in different ways and across a variety of issues.

3. Essential Medicines and Health Technologies: The Essential Medicines and Health Technologies (EMT) unit supports Member States to improve access to essential, high-quality, safe, effective and affordable medicines and health products.

4. Health Policy and Financing: The Health Policy and Financing (HPF) unit provides technical assistance to Member States to develop robust health financing systems across the core functions of revenue collection, pooling and purchasing. HPF also supports countries to develop coherent and realistic health legislation, policies, strategies and plans, with strong links between national and operational levels, and to monitor their implementation.

5. Equity and Social Determinants: The Equity and Social Determinants (ESD) unit collaborates with Member States and other stakeholder groups to advance the Sustainable Development Goals by addressing the underlying social determinants of health. ESD supports countries to develop and implement health policies and programmes that enhance health equity, integrate pro-poor, gender-responsive, and human rights-based approaches. WHO Western Pacific Regional Office supports Member States in developing and implementing their national health policies, strategies and plans by:

- Engaging in technical collaboration to build national capacity for equity-focused policy and programme design, data collection and analysis, and multisectoral and multistakeholder collaboration.
- Fostering country-led regional peer learning and cooperation.

6. Noncommunicable Diseases: Noncommunicable diseases (NCDs), principally cardiovascular diseases, cancer, diabetes and chronic respiratory diseases, are the leading causes of death and disability in the Western Pacific Region. The WHO Western Pacific Region NCD and health promotion programme supports Member States to implement global and regional actions plans to prevent and control NCDs by:

- Raising the priority accorded to NCDs through international cooperation and advocacy
- Strengthening national capacity to accelerate country responses
- Reducing modifiable risk factors through the creation of health-promoting environments
- Strengthening health systems to address prevention and control of NCDs through people-centred primary health care and universal health coverage
- Promoting national capacity for high-quality research and development; and
- Monitoring trends, determinants and progress to achieve global, regional and national targets through evidence-based interventions.

7. The Health Information and Intelligence (HII) unit: supports Member States to strengthen health information systems, promote the adoption and scale-up of digital health and the utilization of integrated health information for decision-making.

8. The Innovation and Research (INR) unit: aims to define WHO's meaningful contribution to better leverage innovation for health. This is accomplished by taking the process of iterative development from the stimulation and identification of innovation to its adaptation and scale-up, including financial, systems, technological and social innovation. Public health innovation refers to the development of a new process, policy, product or program that increase quality, impact and efficiency. Going beyond mere ideation and piloting, to implementation at national level.

9. The Universal Health Coverage (UHC) unit: supports Member States' efforts to transform health systems on their UHC journey with tailored strategies informed by new ways of working, best practices, tools and strategic direction. This is accomplished by:

- Convening the Technical Advisory Group on Universal Health Coverage in the Western Pacific Region (UHC TAG) and providing technical support
- Identifying areas of synergies with UHC for possible collaborative efforts through the Technical Advisory Group Alliance, a coordination mechanism engaging all TAGs in the Western Pacific Region to collectively work towards achieving the For the Future vision
- Sharing best practices and knowledge to advance UHC with health system transformation in countries.
- These policies and strategies promoted by the regional office can be tools for the development of thalassaemia services since the burden of thalassaemia is high in this region.

Table 12. Socio-economic development

Country	HDI rank	WB rank	HE/cap WB data	HE/%GDP WB data	UHC index
Australia	0.951	High	5901.11	10.56	87
Brunei	0.829	High	650.48	2.39	78
Cambodia	0.593	LMIC	115.76	7.51	58
China	0.768	UMIC	583.43	5.59	81
Hong Kong	0.952	High	NA	NA	NA
Laos	0.607	LMIC	68.29	2.69	52
Malaysia	0.803	UMIC	418.66	4.12	76
Papua New Guinea	0.558	LMIC	63.93	2.53	30
Philippines	0.699	LMIC	193.79	5.61	58
Singapore	0.939	High	3537.0	6.05	89
Vietnam	0.703	LMIC	166.23	4.68	68

The countries of this region vary from the richest to the poorest. This is reflected in the health expenditure which varies from 6000 USD TO 60 USD. Some countries even those in the LMIC category are making an effort to improve by devoting a higher percentage of the GDP to health while a few countries do not seem to be addressing the health needs of their population. Universal health coverage seems to be characteristic of the wealthy countries, demonstrated by the fact that Low HDI countries also have the lowest UHC Index. It can be predicted that quality of services will suffer in these same settings.

Hong Kong is a special administrative region in China with a much higher HDI level than mainland China. We will deal with it as a separate entity even though politically it is part of PRC. The population of 7.4 million benefits from a more advance healthcare system with different outcomes. Likewise, Taiwan, a country of 23 million is not recognised as an independent country and so is not listed in any WHO region. However, it has a high economic development and the HDI is estimated at 0.93 in 2023. A national health insurance system was introduced in Taiwan in 1995, mandatory for all citizens. Health expenditures is 6.4% of GDP. As for Hong Kong we will refer to Taiwan separately since both are high prevalence countries which have developed services for thalassaemia.

Table 13. Overall health status in the region

Country	IMR/1000 livebirths	Under 5 mortality/1000 livebirths	Life expectancy	Healthy life expectancy at birth
Australia	2.96	3.7	83.73	70.19
Brunei	10.26	11.5	74.54	65.6
Cambodia	21	25.7	71.46	61.5
China	5	7.3	78.79	68.5
Hong Kong	1.17	1.97	85.83	NA
Laos	34	44.1	69.27	60.5
Malaysia	6.49	8.6	76.42	65.7
Papua New Guinea	32.81	43.9	66.12	57.1
Philippines	22.14	26.4	72.3	62.0
Singapore	1.54	2.2	84.27	73.6
Vietnam	14.42	20.9	74.74	65.3
Taiwan	3.9	4.1	79.84	NA

These basic health indicators are related to HDI and wealth of the countries. The same is true of the various services.

Table 14. Available services

Country	Doctors/1000 population	Nurses/1000 population	MRI density per million	VNRD as % of total donations	National haemovigilance program
Australia	4.1	13.1	14.71	100	yes
Brunei	1.61	5.9	2.39	100	No
Cambodia	0.2	1.0	0.07	100	no
China	2.2	3.1	NA	Almost 100	no
Hong Kong	1.3	8.2	NA	100 shortages	yes
Laos	0.4	1.2	0	70	no
Malaysia	2.3	3.5	2.89	99.9	
Papua New Guinea	0.1	0.5	0	NA	no
Philippines	0.8	5.4	0.3	41%	no
Singapore	2.5	6.2	7.76	100	yes
Vietnam	0.8	1.4	NA	40% of needs	no
Taiwan	1.6	4.6	NA	100	yes

- Manpower is an important contributor to quality of health services. If the general manpower in doctors and nurses is insufficient for the whole service, then it is probable that thalassaemia clinics will not have adequate staffing. In this region Cambodia, Laos, Papua New Guinea, the Philippines and Vietnam having less than one doctor per 1000 of the population. The same countries with the exception of the Philippines are lacking in nurses.

- The possibility of MRI measurements of iron in heart and liver seems possible only in Australia, Brunei, Malaysia and Singapore. Very large patient populations of this region cannot benefit.

- Adequacy and safety of blood are also deficient with the exception of the 4 countries with the least number of patients (Australia, Hong Kong Singapore and Taiwan). To make matters worse, many patients have to pay for blood since many countries do support all patients with universal coverage; In a report from southern China patients need to pay 260.6$/ month for blood while the monthly family income is 198.5$ (x1.3 more than the monthly income) to which serious shortages in donated blood must also be added. This adds to the burden of disease and takes away wellbeing quality of life and survival. [Chen S, Liu Y, Yin X, Lu Q, Du X, Huang R, Jia Y, Wang X, Xi X. Transfusion burden and willingness to pay for temporary alleviation of anemia status in transfusion-dependent beta-thalassemia patients in China. BMC Health Serv Res. 2024 Oct 10;24(1):1215. doi: 10.1186/s12913-024-11547-2]

Country	β-thal carriers	HbE carriers	Expected β-thal patient births/1000	Expected HbE/β-thal births/1000	Known β-thal patients	Known HbE/ β-thal patients
Australia	0.4	0.4	0.004	0.008	332	•
Brunei	2	3.7	0.1	0.37	179	•
Cambodia	0.2	34.4	0.001	3.44		•
China	0.66%	•	0.334	•	•	•
Hong Kong	3.05	0.33	0.233	0.05	382	•
Laos	2.6	30	0.169	3.9	275	•
Malaysia	2.9	2.6	0.21	0.377	4906	3861
Papua New Guinea	5	NA	0.625	NA	•	•
Philippines	1.2	0.4	0.036	0.024	600	•
Singapore	1.6	1.7	0.064	0.136	258	•
Vietnam	1.63	3.5	0.066	0.285	20000	•
Taiwan	1.1	•	•	•	454	•

- In this table the number of patients represents only the last reported numbers reported to TIF by local collaborators and can only be an approximation. Apart from Vietnam and Malaysia most countries of the region report small numbers. However China is expected to have a large affected population but because of a lack of registry and each region having a separate policy, even an approximation is not possible; based on carrier frequency of β-thalassaemia in the southern provinces the expected affected births are around 2000 (1966) – this could mean almost 30000 patient living up to the age of 15 years, without considering HbE (low frequency) and alpha thalassaemia (high frequency).
- In the reported patient numbers, the total given does not differentiate TDT and NTDT except in Malaysia which maintains a national registry.

Country summaries

Australia: this is a country of immigrants in which about 12% of the population has ancestors from thalassaemia prevalent countries. The number of known patients is over 300 but since there is no national registry this may be a minimal number. Australia is a high-ranking economy and in medical services it is characterized by a very strong infrastructure and an active contribution to medical research. In this research thalassaemia is well represented. The level of clinical care for thalassaemia may be regarded as being on par with European reference centres and so outcomes can be a measure of comparison with the other countries. In one study of iron loading and its control, it was found that mean serum ferritin in TDT patients was 1686ng/ml and 1230 in NTDT patients with only 10% exhibiting cardiac sideroris by MRI T2* measurements; on the other hand, hepatic iron load was high (LIC by R2 Ferriscan) in 48% of all thalassaemia patients and 33% of TDT patients [94]. This experience indicates chelation practices which are indicative of reference centre outcomes in most countries. In a more recent survey of adult women with TDT and age range from 18 years to over 50 years, 63.3% had a serum Ferritin<1,000 ng/ml and the complication rate was similar to that of western countries reference centres; Hypogonadism 33.3%, Diabetes mellitus 15.0%, Hypothyroidism 21.7% etc. [95]. For prevention carrier screening tests are available and free with a referral from many GP clinics, screening is voluntary, but it is not certain that community understanding is enough to bring most couples to the counselling clinic. Prenatal diagnosis and preimplantation genetic testing are available.

In summary the burden of disease is reduced by good clinical services but there is a question whether birth incidence is affected by the current level of preventive services.

Brunei Darussalam: a Sultanate of 452,524 (2023 est) people located on the island of Borneo. Most of the population is of Maly origin with some indigenous people and a Chinese minority. It is an oil rich country with a booming economy. Thalassaemia and HbE are carried by about 5-6% of the population and 200 patients are reported to be under treatment [96]. Of these patients 55 are on regular transfusions according to a newspaper report from the main treatment hospital (Women and Children Centre of Raja Isteri Pengiran Anak Saleha (RIPAS) Hospital). Concerning the level of care and the outcomes of patients little is known because of no published data and also there is no patient association linked to TIF. Voluntary screening is available and awareness promoting events organized by the Women and Children services take place annually.

Cambodia: in this country β-thalassaemia is carried by only 0.2% of the population; however, HbE is carried by 34.4% so that thalassaemia syndromes are frequent, with about 130 new cases per year. There are large regional differences in the frequency of thalassaemia genes; for example, in one region (Preah Vihear) the carrier rate of HbE is 55.9%. In addition, there is a prevalence of non-deletional as well as deletional alpha thalassaemia. [97]. A large proportion of these patients are likely to have NTDT, but severity is expected to be variable and morbidity to increase with age. Packed red cells (PRCs) are available at most referral hospitals (provincial

hospitals). Oral iron chelators [deferiprone (DFP) and deferasirox (DFX)] are only available from a private pharmaceutical company [98]. In the National Pediatric Hospital, Phnom Penh, there are about 450 children registered as hemoglobinopathy (2018) of which 150 are severe cases (115 β- Thal, 45 α- Thal/HbH disease). A National guideline for the Clinical Management of Patients with Thalassemia in Cambodia has been developed and published by Ministry of Health in 2011. This is not generally known or practiced outside the National Pediatric Hospital. Oral Deferiprone (GPO-L1, product of Thailand) is available in the private pharmacies, and so it is of very limited use. It is not on the list of essential medicine of the Ministry of Health. The other chelating agents are not available in the country (information from Dr Try Lytheang, Department of Paediatric Hemato – Immunology, National Paediatric Hospital, Phnom Penh 2019). These facts and the absence of health insurance coverage means that the majority of patients do not benefit from adequate medical care and so disease burden is expected to increase with age and early death is a common outcome.

China: this is a country with a huge population (estimated in 2023 to be 1,425,671,352 people) and a large geographical territory. Thalassaemia and other haemoglobin disorders are highly prevalent only in the territories south of the Yangtze River. Migration flows are expected to carry the genes to the northern territories but there are currently no data as to the extent of epidemiological change. The nationwide prevalence of β-thalassaemia is 0.66% in mainland China [99]. Current knowledge of epidemiology is summarised in the table below:

Table 15. Epidemiology of thalassaemia and haemoglobin disorders in Southern China

	Fujian	Guangxi	Guangdong	Guizhou	Hainan	Hong Kong	Sichuan	Yunnan
α thal carriers	3.17%	14.95%	8.53%	9.76%	12.69%	5%	1.66%	?
β thal carriers	1.32%	6.78%	4.53%	4.9%	2.09%	3.05%	3.2%	3.7%
HbE carriers	0	0.42%	0.1%	0	0	0.33%	0	1.6
Expected β thal/1000	0.044	1.15	0.513	0.03	0.109	0.233	0.256	0.342
Expected β /HbE/1000	0	0.142	0.023	0	0	0.05	0	0.296
Total β thal births	18	803	552	17	132	16	202	224
Total β /HbE births	0	99	24	0	0	3	0	194
Total α thal hydrops	18-20	902	182	17	13	19	1-2	94

In these 8 provinces almost 2000 new patients are added every year who are homozygote β- thalassaemia to which are added 320 with HbE/ β-thalassaemia. The births of significant syndromes of α-thalassaemia are not known but since non-deletional forms exist the burden of disease increases even more. In addition, there are expected to be several thousand cases of hydrops fetalis in these provinces (3,325 was reported as the annual incidence in Guangxi). To this burden the relatively rare cases of thalassaemia found in the northern provinces must also be added. The contribution of northern Chinese populations may be greater than expected since in a recent study of 974 pregnant women in the north around 3% were diagnosed as β- thalassaemia carriers [100]. The total number of living patients across China is not known, but a recent publication estimates that about 300,000 people in China have thalassaemia major or intermedia requiring medical intervention, even though 15000 are currently being treated [101].

The level of care is variable since there are centres of excellence mainly in university hospitals, but poor care is witnessed (from TIF visits) in rural and small urban settings. In a report to TIF from the China Thalassemia Association 2011, it was stated that Thalassemia patients are facing poverty, discrimination, employment and insurance problems. Inequalities were found to be associated with low education, and residence. Progress is of course ongoing and there is now nation-wide availability of partial or full insurance for prenatal genetic testing, RBC-transfusions, iron-chelating drugs and haematopoietic cell transplants, even though regional differences remain. Even so more than half of patients do not receive needed transfusions because of supply shortages [101]. There is also need for improvement in the prevention practices

The undiscounted lifetime direct medical cost for a patient with β-thalassaemia major was estimated to be $518,871 (95% CI: $293,524-$744,217), 75.6% of which was due to the cost of iron chelation therapy; the annual direct medical cost, direct non-medical cost, and indirect cost per adult patient with β-thalassaemia major at 56 kg were $13,478, $2,542, and $4,000, respectively [102]. The gross national income per capita in China is forecast to amount to €11.87k in 2023.

These facts indicate that the burden of disease is still high both in economic terms and in medical outcomes. Hong Kong is a special case with a much highly developed economy (the GDP per capita in Hong Kong is expected to reach 44931.00 USD by the end of 2023) and more organized and uniform health services (e.g. IMR <2/1000). The 350-400 patients under treatment are expected to have better outcomes even though recent data are not available.

Prevention programs exist now in all the high prevalence provinces but are most organized in Guangxi and Guangdong. Premarital screening and prenatal diagnosis (PND) for the prevention of thalassaemic foetuses are available [103]. In these provinces significant reduction of birth incidence has been achieved.

Laos: a country of 7.5 million in which HbE is the predominant variant with much less β- thalassaemia. The predominant clinical syndrome is expected to be NTDT. Health services are generally 'poor' in this low resource country as evidenced by a high IMR and under-5 mortality. This is reflected in thalassaemia services in which patient care is indeed limited: treatment is only available in the capital city of Vientiane. The level of blood transfusion seems adequate and bedside filtration of packed red cells is offered. However, for iron chelation Deferiprone only is offered. Patient care is suboptimal on this evidence. Prevention has started and there is a screening service in Laos which consists of Premarital screening (Opportunistic), Preconception screening (Opportunistic) and Antenatal Screening which is mandatory. According to the National Strategy of Maternal and Child Health, screening for thalassaemia along with anaemia in general, is included in the list for obstetric services to follow. The intention is to reach ANC attendance 100% by 2025 (at present 60% coverage only). There is a laboratory screening algorithm for ante-natal clinic screening. Amniocentesis is available in the capital Vientiane, along with a guideline for safe termination of pregnancy. Molecular diagnosis is available in the capital. In the provinces however, there is limitation of human resources [unpublished information from Dr. Alongkone Phengsavanh, Dept of OBGYN, and Dr. Sourideth Sengchanh, Dept of Paediatrics, University of Health Sciences 2019} [104]].

Malaysia: Malaysia has maintained a thalassaemia patient register for many years. The most recent report is published in 2020 [105], on 8681 patients. The majority of the patients were in the group of 5.0–24.9 years of age (5146/7984 patients, 64.45%), and the largest number of patients were aged between 10.0 and 14.9 years (1394, 17.46%). However, this large cohort includes a spectrum of severity, including HbE/β- thalassaemia, thalassaemia major, intermedia and HbH disease. For thalassaemia major the peak age group is 10.0–14.9 years (Fig.). For HbE/β-thalassaemia, the peak age group is 15-20 years. As seen in the age distribution curve, this is a young patient population. This is an indication that much improvement is required across the treatment centres in Malaysia to improve outcomes by conventional treatment, which is also evidenced by the distribution of patients according to the level of ferritin.

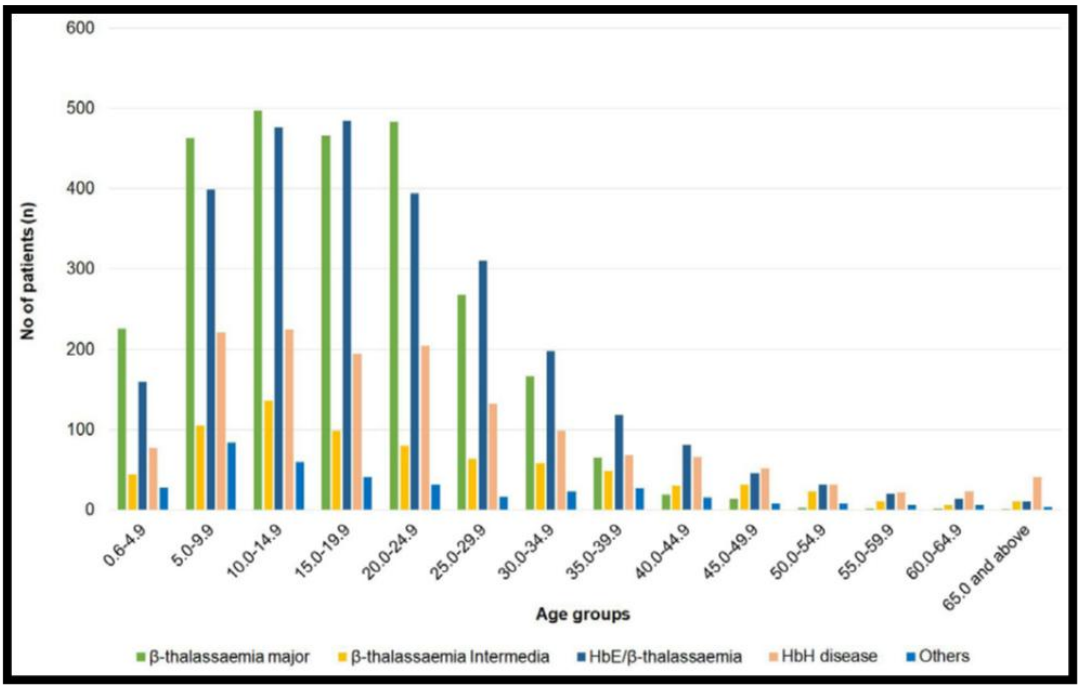

Figure 4. Age Distribution of Thalassaemia Patients in Malaysia

In economic terms the lifetime cost for a TDT patient has been calculated to be US$ 561,208, with chelation cost accounting for 56.9 % of the total cost followed by blood transfusion cost, 13.1%. including the family healthcare expenditure, then lifetime cost is estimated to be 606,665 USD. [106]. The survival probability at 45 years of age, has risen from 65% in 2007 to 85% in 2017. Public universal healthcare is accessible to all legal residents of Malaysia, funded by the government, to provide low-cost universal and comprehensive services.

In assessing burden of thalassaemia, it essential to review results from provinces where many patients are treated. In a 2024 report from Sarawak, patients aged 10 years and above (median 21 years), 34.8% patients had mean serum ferritin 2500ng/ml and above, and 66.6% had liver iron concentration (LIC) ≥7mg/g. These are indications that burden of disease will increase rather than decrease over time [107].

As in many countries issues such as adherence and psychosocial support must also be considered if improved outcomes and a reduced morbidity burden is to be expected. In a recent study amongst adolescents with TDT only 51.4% had good adherence [108].

In a 2023 TIF patient' survey on service quality 10 responses were received all in the Malay language, representing 0.125% of the total Malay patient population. The average age of this group was 31.7 years (range 21-48); this may indicate an adult or at least a growing, as opposed to a child population. Only 3 patients are employed full time, while 5 are looking for work; this may reflect employer prejudice towards chronic disease. 5 patients had less than high school education, with 3 having completed secondary and 2 tertiary educations. 7 patients are single and 3 married. Pre-transfusion Hb is below 9g/dl in 9/10 patients, a fact which must be confirmed since this is below guidelines. Chelating agents are available, with no interruptions in supply. Ferritin levels are measured every 3 months in only half of the respondents while the other half are tested every 6 months. 2 patients did not know their ferritin level while 3 were below 1000ng/ml, and 3 >4000ng/ml. Cardiac T2* is measured annually in 9/10 patients but measurements are far below the performance experienced in reference countries: only 2/10 have T2* >20ms while 3 patients did not answer (presumably are not aware of their result). Liver iron is measured by MRI in 9/10 patients, while one did not respond. 2 patients reported LIC <7 mg/kg dw while 3 did not know their result. Despite universal health coverage 3 patient stated that they pay

for blood transfusion! Concerning the offer of multidisciplinary care none of the patients responded to the question. This is a very small sample of the total patient population, but the indications are of a service that is still in need of improvement along with increasing knowledge and community awareness.

In November 2016 the prevention policy was reviewed by launching a nationwide screening of 16-year-old students complemented by a cascade screening of high-risk families. The reduction in birth incidence has not been significant so far partly because only about 28% of at-risk couples accept both prenatal testing and pregnancy termination [information from Dr Mohammed Hishamshah 2018], but also knowledge of thalassaemia among unmarried individuals is found to be low [109].

Papua New Guinea: little is known about this country and TIF has only been able to communicate with one doctor and one parent. The north coastal region of the country is where malaria is hyperendemic and where most thalassaemia genes are found. In a 2006 study it was found that the frequency of the alpha thalassaemia genotype in pregnant mothers was 0.61[110].

In a study of 21 patients and their families in 2021, they were transfused at very low Hb levels, and "no child was receiving chelating agents, and most had clinical evidence of iron overload. There were important impacts of thalassemia on quality of life, including very poor school attendance and some aspects of children's self-perception. Families faced significant burdens and made genuine sacrifices to care for their children".[111]. In fact, this report is referring to just blood transfusion and no other attempt to treat a situation reminiscent of the 1960s in most countries. If an old study is found to be true, then 5% of the population of this country could be carriers of beta thalassaemia, then almost 100 new affected children can be expected to be born every year. If this is also true, then most will be dying without a diagnosis during childhood.

Philippines: Limited population studies of Filipinos in Hawaii and Taiwan found gene carrier frequencies of 9.1% and 6.8%, respectively [112, 113]. Another Taiwan study showed a showed a showed a β-thalassaemia carrier frequency of 0.9% in Filipinos [114]. This confirms Mutolsky's findings of the 1960s [115].

Haemoglobin disorders are now included in the national newborn screening program [116]. The alpha thalassaemia syndromes especially HbH disease are predominant, while β-thalassaemia is rare.

Being a rare disease in a low resource country means that it has not been given priority in health policy. Inclusion in the NBS program is one step taken as is the creation of a national registry, which however has never been completed: in 2019 60 β-Thalassaemia cases and HbE/beta thalassaemia 15 cases. Knowledge concerning thalassaemia is very limited among health professionals, according to a report from Dr Maria Liza T. Naranjo, M.D, National Children's Hospital, Manila, in 2019 (SEATHAF meeting. There is a health insurance system (PHILHEALTH), which covers blood transfusion (USD 52.33 per day) as outpatient care, maximum of 22 days/ year and hospital admissions (USD 133.00), maximum of 44 days/ year. Iron chelation is not supported but this is in the pipeline. Blood donation is 41% from volunteers, 44% from replacement donations (usually by family members, and 15% from paid donors. Pre-transfusion Hb can fall to 3-4g/dl (at accost of 28-105 USD) in many parts of the country. Leukodepleted, packed red cells are not always available, and the cost rises to 34-166 USD. There is no NAT testing. Monitoring of iron overload is by serum ferritin and MRI T2* (private) at a cost of USD 285.71. All three iron chelating agents are available in the country but totally at the patient's expense (Dr Marites B. Estrella 2019). Many patients still die at 9-15 years, although there are many survivors up to around 30 years. With these facts disease burden is made high by the lack of support to families, increasing complications and premature death.[117].

Singapore: in contrast to its neighbours Singapore is a very high-income country with developed health services and adequate insurance coverage for its citizens. The population (5.92 million est for 2023) is multi-ethnic, but the Chinese is the predominant element (76%), with Malays 15.4%, Indians making up 7.4%. In a molecular study of cord blood specimens, the carrier frequency for alpha-thalassemia mutations was about 6.4% in the Chinese, 4.8% in Malays, and 5.2% in Indians. Only alpha deletions were observed in the Chinese.

The carrier frequency for beta-thalassemia mutations was 2.7% in the Chinese, 6.3% in Malays, and 0.7% in Indians [118.]. There is a significant patient population which is offered treatment according to guidelines. However, results according to a recent report indicate that iron chelation could be better: liver iron loading was the most common transfusion-related complication and occurred in 79% of patients. Cardiac iron loading (T2* Technology is available at a cost of US$270) was noted in 28.3% and endocrine complications were present in 34.2%. Liver iron loading was significantly associated with higher mean ferritin level. The cohort of older thalassaemia patients aged 31-50 experienced significantly higher rates of cardiac iron loading, endocrine complications and lower TranQOL scores compared to younger age cohorts. [119]

A National Program for Thalassaemia Screening was initiated in 1992, at the KK Women's and Children's Hospital. This programme registers all thalassaemia carriers, provides free counselling and subsidized screening of 15USD (spouse & first-degree relatives). In this programme the pick- up rate is 4.5% for all carriers: this is broken down to 0.9% beta thalassaemia, 3% alpha thalassaemia, and 0.55% HbE carriers. Genetic counselling is provided to at-risk couples with informed choice for prenatal diagnosis. [Information unpublished from Law Hai Yang, Deputy Director National Thalassaemia Registry, KK Women's and Children's Hospital 2018]

Patient numbers are: Beta thalassaemia major 102 (64 Chinese), Intermedia 17 (14 Chinese), HbE/beta thalassaemia 139 (98 Malays), HbH Disease 699 (582 Chinese), other haemoglobinopathies 477 (272 Chinese).

Vietnam: α-Thalassemia is particularly prevalent in Vietnam, with a reported prevalence rate of 51.5%. Carriers of β-thalassaemia are overall only 1.63% and HbE 3.5%. A newer study of 10112 of first-time pregnant women and their husbands, indicates alpha thalassemia is 10.73%, the carrier rate of beta thalassemia is 2.24%, and 0.29% (29 patients) of patients carry both alpha thalassemia and beta-thalassemia gene mutations [120]. The different findings may be due to regional differences. In a similar study from south Vietnam (Ho Chi Minh City), 7.82% carriers of α-thalassemia (α-thal), 5.31% carriers of β-thalassemia (β-thal), and 0.63% concurrent α-/β-thal carriers were found, the differences again may be regional [121]. Also, from South Vietnam 6.2% of women were found to be carriers of β-thalassemia [122].

Patient numbers are not known but local experts estimate about 20000 with clinically significant syndromes (from discussions with doctors at the National Institute of Haematology and Blood Transfusion NIHBT, Hanoi). These patients are from different ethnic communities and geographical regions of the country; the majority are those of the Kinh ethnicity but there are also 54 other ethnic or tribal groups. [123]. The disease is present in all regions of Vietnam but is more prevalent among mountainous ethnic minorities. The level of care varies considerably but is regarded as improved in the main urban centres of Hanoi and Ho Chi Minh City. Low pre-transfusion haemoglobin level (62.1 ± 1.7 g/dl) has been reported in the past and is still the reality in some regions, with some patients not chelated [124]. A study of 288 health-insured paediatric patients (mean age of10.4 (±11.3) years), found that the average annual economic burden of Thalassemia treatment was approximately USD 426.7(±294.0), in a region in which the average income was 158.7 USD/month. The treatment was costly for low-income patients as it cost nearly a quarter of an adult's annual income in the region. Health coverage is not complete (UHC index 68) and so out of pocket expenses are required. This reduces the possibility of optimal care considerably and so increases the burden of disease in terms of increased morbidity and mortality [125].

Of the patients treated at the NIHBT, 16.6% are under the age of 6 years, 27.4% 6-15 years, 27.7% 16-30 years and 28.3% are over the age of 30 years. 49.1% have HbE/thalassaemia, 27.7% beta thalassaemia, 16.1% HbH disease and 7.2% HbH Hb Constant Spring. Health insurance reimburses 100%, 95% or 80% of diagnosis and treatment, while the country is moving toward the implementation of universal health coverage. Blood donation is voluntary unpaid (100%). DFO is provided only for in-patients and DFP and DFX for outpatients. [presented by Dr Ha Nguyen Thi Thu, of the NIHBT thalassaemia clinic SEATHAF 2018].

To prevent thalassemia, in 2021, the Prime Minister approved the National Target Programme, part of which is the prevention of thalassemia in ethnic minority and mountainous areas. The objective is to reduce the number

of children born with thalassemia and gradually improve the quality of life of children born with thalassemia. This is achieved through screening and counselling aa part of the pre-marital health check but also screening women in pregnancy. [https://baonghean.vn/phong-chong-benh-tan-mau-bam-sinh-tai-vung-dong-bao-dan-toc-thieu-so-va-mien-nui-post260634.html]. Prenatal diagnosis (PND) and (PGD) are offered in collaboration with the obstetric hospitals in Hanoi.

The picture is of fairly rapid development in this large country and hope for the coming years.

Taiwan: this is a high income, high HDI country with a high prevalence of thalassaemia syndromes. It has a single-payer National Health Insurance Program since 1995. There is a registry for catastrophic illness database which includes patients who suffer from major diseases and are granted exemption from co-payment.

In Taiwan, patients with TM primarily are treated with RBC transfusion and iron chelation, including leukocyte-depleted RBCs to maintain pretransfusion haemoglobin level greater than 10 g/dl. Iron chelation therapy includes DFO, oral deferiprone and oral deferasirox, tailored to individual needs. In a study of 2011, the median age of TDT patients was 17.2 years (range, 0.1–48.0 years), with 58.1% patients being younger than 20 years and 41.9% older than 20 years. The mortality rate fell from 2.9% in 2007 to 0.7% in 2011. The complication rates have a rate and pattern similar to those of reference countries [126]. In a more recent study of 2984 patients with beta-thalassemia, the mean (SD) age was 37.8 (23.7) years, which again is indicative of survival analogous to that of reference countries [127].

A National Thalassemia Major Prevention Program has been in place since 1993. A study conducted in 2012 indicated a 91% reduction in the incidence of thalassemia major compared to the period between 1986 and 1995 in Southern Taiwan. Consideration must be given to the impact of interracial marriage, since global migration and international marriage has affected the distribution of hemoglobinopathies in Taiwan. A more comprehensive prenatal screening for new immigrants with a longer follow-up is warranted. [128].

As far as disease burden goes, Taiwan appears to report results analogous to reference countries such as Italy.

Comments

As in other WHO regions, the thalassaemias take second place in the interest expressed by governments and even the regional office. The relation between quality of service remains a function of healthy economy and prevalence rate. Middle level economies with high prevalence, including Malaysia and China are promoting policies which are expected to give results in the near future while other countries have yet to adopt such policies or offer needed support to families and patients.

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WHO European region (EUR)

The countries of this region can be divided into those in which the haemoglobinopathy genes are prevalent in the indigenous populations (mainly the Mediterranean coast) and into those where these genes are rare but are being introduced by migration flows in the recent decades.

- Countries with a carrier rate for β-thalassaemia, >2%: Albania, Azerbaijan, Bulgaria, Cyprus, North Macedonia, Greece, Italy, Malta, Tajikistan, Turkey, Uzbekistan
- Countries with a carrier rate for β-thalassaemia 1-1.99%: Armenia, Bosnia, Georgia, Kazakhstan, Kyrgyzstan, Montenegro, Portugal, Romania, Serbia, Spain, Turkmenistan

- Countries with a carrier rate for β-thalassaemia <1% in the indigenous population: Austria, Belgium, Croatia, Denmark, France, Germany, Ireland, Netherlands, Russian Federation, Sweden, Switzerland, United Kingdom

Table 16. High prevalence countries

Country	% β-thal carriers	% HbS carriers	Expected β-thal patient births/1000	Expected SCD births/1000	Known/est β-thal patients	Known/est SCD patients
Albania	5.0	1.4	0.625	0.399	356	174
Azerbaijan	3.71	0.8	0.344	0.164	1350	200
Bulgaria	2.5	0	0.156	0	270	0
Cyprus	14	0.27	4.9	0.191	659	56
North Macedonia	2.6	0	0.169	0	25	0
Greece	8.1	0.6	1.64	0.252	3241	1080
Italy	4.3	2.1	0.462	0.562	7102	2280
Malta	3.0	0	0.255	0	21	0
Tajikistan	5.0	0	0.625	0	NA	NA
Turkey	2.2	0.44	0.121	0.053	5500	4300
Uzbekistan	3.0	0	0.225	0	250	0
Total					18774	8090

- These countries, like other European countries also have been accepting immigrants from the Middle East and Africa. The effect of these migrations is not mirrored in the table, since it is a changing picture each year. The table reflects only the indigenous population. In general migrations are introducing more SCD than β-thalassaemia.
- The estimate of affected births is not calculated since in the countries with the highest carrier prevalence, effective prevention programs, developed and running for several decades, have significantly affected birth incidence.
- Cyprus, Greece, Italy and Turkey have developed services both for prevention and patient care, within systems of socio-economic coverage; this means catering for both financial and psychosocial needs of patients. Tukey being a large country with areas with les development and having the major migration/refugee issues, has regional deficiencies in patient care, which however authorities are trying to address.
- In the rest of this group of countries services provided do not satisfy all needs to the same extent. This increases the burden of disease and results in poor outcomes for patients.

Albania: this is a country with just under 3 million people. Both β-thalassaemia and SCD are prevalent with treatment centres being concentrated in 2 locations, the Mother Tereza Hospital in Tirana and the General hospital of Lushnjë. Published literature is scarce but according to the latest report (2022) from collaborators in the country the following information is provided:

- Patient numbers are: 291 thalassaemia major (180 Tirana, 110 Lushnje, 1 Fier) and 290 sickle cell syndromes (190 Lushnje, 5 Fier, 95 Tirana) with 7 new births in Tirana in 3 years. There are no known HbH cases [According to a report in 2022]

- Blood transfusion: Shortages are seasonal in July /August. However, there is also a chronic shortage since donations in Albania are 12/1000 inhabitants. Safety is now assured since the national Transfusion service is now well equipped and is centralised since 2010.
- Iron chelation – all 3 chelators are available and free of charge.
- MRI is still not available
- Multidisciplinary care: Works well in Lushnje with the hospital service. In Tirana patients have to be referred by the family physician to specialists; this is usually not proactive monitoring but referral once a complication is suspected
- Prevention: no national program. If premarital couples are informed by their GP they go to private lab. 2nd affected child prevention is practiced

These practices are not conducive to optimal care and good outcomes.

Azerbaijan: Azerbaijan is a country of high prevalence for beta thalassaemia. With the carrier rate of 4%-8.6%, β-thalassemia is one of the most prevalent hereditary disorders in the country {129}. There are almost 2000 patients with haemoglobin disorders under treatment in the country, or around 1 per 5000 of the population, amounting to a significant public health burden. All patients in the country are treated in one centre in Baku, the Republican Thalassaemia Centre and investigated and provided with blood for transfusion again by one centre, the Institute of Haematology and Transfusion Medicine. This means that clinical and scientific expertise are concentrated and gained for the benefit of patients.

- There is considerable support for this centre from the Heydar Aliyev Foundation, making the services sustainable and allowing development. There is also support from the Azerbaijan Thalassaemia Association, headed by a group of well-informed patients.
- There is universal health coverage under a compulsory health insurance system since 2021 and not out of pocket expenses for patients.

With these advantages there has been progress over several years. A prevention program of premarital screening is mandated by law since 2015; there is also genetic counselling of at-risk couples and the offer of prenatal diagnosis. Since 2015 over 500000 people have been tested of which 3.7% have been found to carriers of beta thalassaemia.

Deficiencies in the quality of care are expressed by patients which must be given consideration:

- Reactions to blood transfusion are frequent. There is no haemovigilance programme and so these reactions may not be reported. It was confirmed, for example that 20-25% of the patients have been infected by HCV (in the Azeri population of blood donors, around 5% are carriers of this virus).
- There are periodic interruptions in supplies of chelating agents, especially of desferrioxamine. Measurement of cardiac and liver iron by MRI is still not available and so those that can afford it travel to other countries, mainly Turkey, for their annual tests.
- Vaccinations and post-splenectomy prophylaxis do not seem to be offered.
- The element of multi-disciplinary care, with monitoring by cardiologists or endocrinologists at least is not offered.

It is clear that despite progress, there are still gaps in the provision of optimal care in this country in which resources are limited (GDP/cap = 7736.7usd and 5.9% of the population lives below the national poverty line in 2021)

Bulgaria: Bulgaria has a carrier frequency of 2.4% overall, but carriers are mostly in specific regions, along the Black Sea coast and the south. New affected births each year are estimated at 11 while the latest estimate for the prevalence is around 300 patients. If however, we consider an average of 6% carriers in the coasted areas where the population is around 1 million, then the homozygote's birth rate in these regions goes up to 0.9/1000 which means that 9 babies may be born is these regions alone. There is need to create a national patient register for thalassaemia, which will help greatly in describing the true picture and identify patients living in low prevalence areas of the country. Bulgaria's health system is based on a compulsory social health insurance scheme, with a single purchaser - the National Health Insurance Fund (NHIF), despite this some are uninsured and so out-of-pocket health spending is often necessary. To what extent this affects thalassaemia patients is uncertain. In general, all basic treatment is offered free of charge, including monitoring with MRI techniques for all patients, according to guidelines. There is a growing adult patient population, whose iron status is improving over the years [130].

Prevention is not centrally organized and there is limited or no recorded effect on birth incidence, and there is limited use of prenatal diagnosis.

Cyprus: this was one of the first countries to respond to the high burden of β-thalassaemia, dating from the early 1970s. Carrier rates were estimated at 15-17% in the 1960s even though over the years the rate seems to have fallen to 12-14% [131, 132]. The approach in Cyprus was comprehensive from the beginning, combining prevention, based mainly on premarital screening and improving patient management according to the evolution of evidence based clinical guidelines.

From a recent analysis of the Cyprus thalassaemia registry (care of Dr S. Christou 2020) the following age distribution is obtained for patients with β-thalassaemia major: The mean age of patients 42.3 years, (median 44 years), with a gradual reduction due to patient loss in the 6th decade.

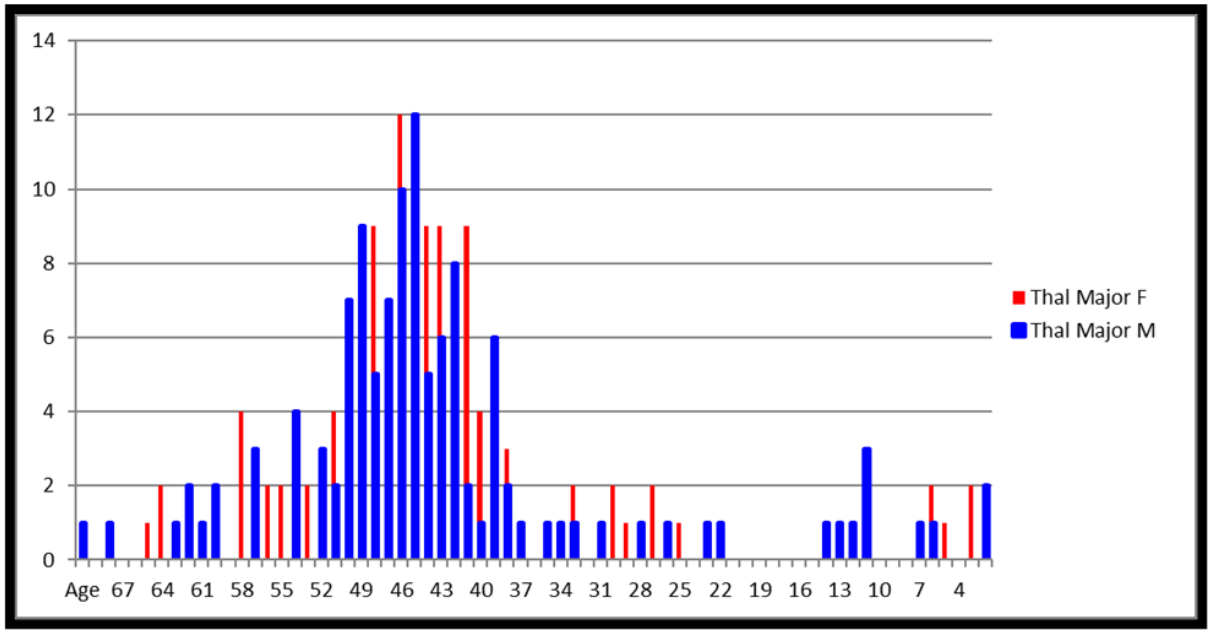

Figure 5. Age distribution of β-thalassaemia major patients in Cyprus

In the recently published data, 538 TDT patients were studied over a total of 19,083 patient years. Median age at 30/12/18 was 40.9 yrs, IQR 38.0- 47.6 [133]. Overall, the mortality was 5.0 per 1000 patient years follow up. The causes of death are shown to be shifting away from cardiac deaths to, liver, infectious causes and

malignancy deaths. In a more detailed analysis of the same cohort, which almost all of the TDT patients in Cyprus, 80.4% of individuals survive to 50 years of age. The effect of genotype on survival and complication rates is analysed in ref 132, indicating that delays in transfusion and iron chelation due to milder genotype has resulted in more severe long-term outcomes.

Concerning the complications of TDT the figures reported by the treatment centres of Cyprus, are comparable to the reported results from Greece and Italy, and seem, at national level to be the best at this time. 48.9% have a serum ferritin level <1000ng/ml, 85.4% have a cardiac T2* >20ms and 51% an LIC <3 mg/g dw (73.5%< 7 mg/g dw). At the same time almost 30% have completed tertiary education and 74% are working full time, while around 50% are married or cohabiting [134]. These results are indicative of strong support from the health authorities and the community.

The adult population of thalassaemia patients are active in various professions and the reduction in new births, demonstrate the reduction in 'burden' that conventional therapy allows.

North Macedonia: From past surveys, the average incidence of beta-thalassemia (thal) trait is 2.6% [135]. This is a small country of 2 million people, with few reported patients – only 25 last reported to TIF.

The HDI is currently 0.784 – high ranking but still below its neighbours. There is a compulsory insurance-based health system, with near universal coverage. There have been reports from patients of low pre-transfusion Hb but detailed information on patient outcomes is not available. No prevention program is active.

Greece: The National Registry for Haemoglobinopathies in Greece (NRHG) was established in 2009. In 2012 the first review of the registry was published and in 2019 the analysis of the period 2010 to 2015 was published [136]. The total number of registered patients in this report is 4032, 2099 (52.06%), of these are categorized as TDT; 873 (21.65%) are NTDT patients; 1032 (25.6%) patients had sickle cell anaemia (SCA) or S/β-thalassaemia. The total number of alive patients per age group during this period is provided in Figure 6 below:

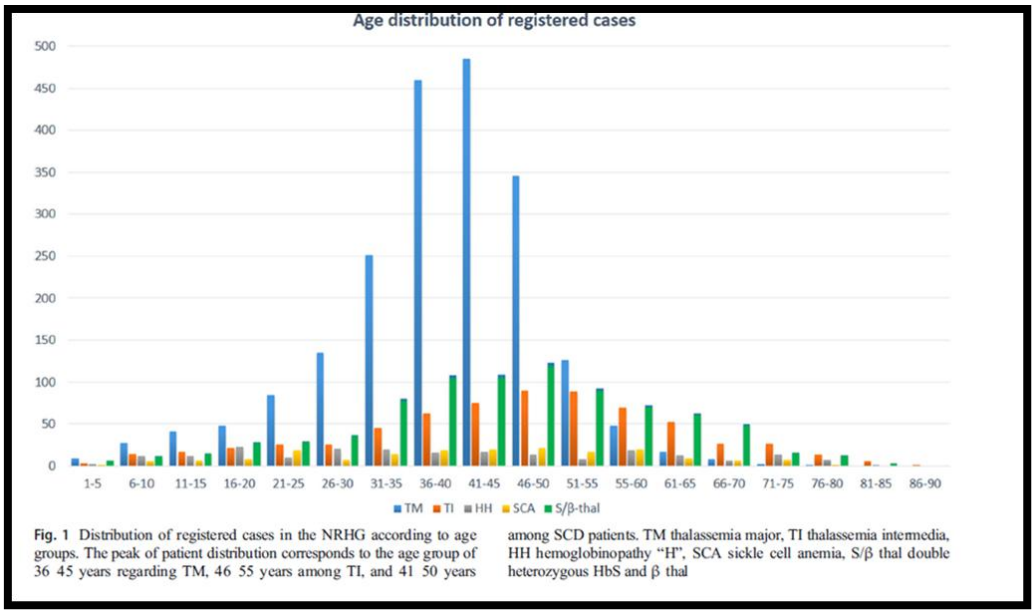

Fig. 1 Distribution of registered cases in the NRHG according to age groups. The peak of patient distribution corresponds to the age group of 36 45 years regarding TM, 46 55 years among TI, and 41 50 years among SCD patients. TM thalassemia major, TI thalassemia intermedia, HH hemoglobinopathy "H", SCA sickle cell anemia, S/β thal double heterozygous HbS and β thal

Figure 6. Age distribution of registered cases

The peak of patient distribution corresponds to the age group of 36–45 years among TM patients, 46–55 years among TI cases, and 41–50 years among sickle cell disease (SCD). These results are comparable to those of Italy, UK and Cyprus. In a study of 201 eligible adult patients [median (interquartile range, IQR) age 45.7 (40.2–50.5) years; 75.6% > 40 years old; the average pre-transfusion haemoglobin, median (IQR), was 9.9 (9.4–10.3) g/dL; the average serum ferritin, median (IQR), was 549.3 (287.2–1034.8) μg/L, with 70% having ferritin <1000 μg/L; MRI LIC, median (IQR), 2.2 (1.3–4.8) mg Fe/g dw; myocardial T2*, was Normal (>20 ms) in 90.5% and mild (≥14 to ≤20 ms) in2.5% [137].

Despite good outcomes barriers to access health care among beta-thalassaemia patients receiving transfusions still persist, especially for those who live far from transfusion centres and have lower incomes [138]

In a multicentric study of TDT patients in Greece the participants' mean age was 39 ± 9 years (range:18–68). Almost half of the study population were married (46%) and had offspring (42%). Most participants had a higher educational level (77%), and 59% were employed. Only 7% of the participants had an abnormal heart MRI T2*, whereas 39% of the participants had an abnormal liver MRI T2*. Health related quality of life was assessed, and it was noted that despite good medical care adult TDT patients exhibit significantly lower HRQoL compared to the general Greek population. Employed TDT patients exhibited both significantly and clinically higher quality of life scores. The relevance to burden of disease is that employment, allowed by good clinical care enhances quality of life and wellbeing [139].

Italy: Italian health services have a long tradition of development of both prevention and patient management with good survival and morbidity outcomes. The best known are the series of publications by Borgna-Pignatti over the years [140]. Here we refer to the latest presentation, which is based on the WebThal database [141]. The cohort in this study represents 3,986 thalassaemia patients treated at 36 centres in Italy, which treat over 50% of the total number of patients in the country. For patients with thalassaemia major, 68% were aged ≥35 years and 11% were aged ≤18 years. Patients with thalassaemia intermedia were slightly older:

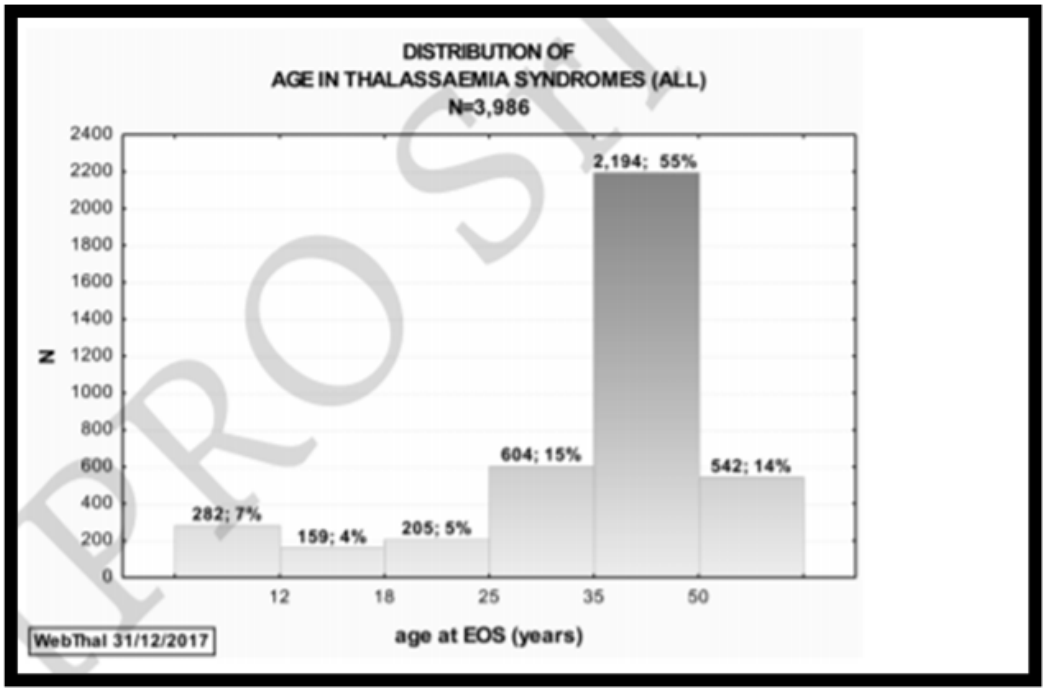

Figure 7. Distribution of age of patients with thalassaemia syndromes at 36 treatment centres in Italy

This age distribution bears witness to the successful provision of conventional treatment in Italy and compares well with Cyprus and Greece. This also holds true where the complication rates are concerned. It also demonstrates the limitations of conventional treatment in allowing for a 'normal' lifespan to all patients, even under the best conditions.

A second registry exists covering 182 centres and 1873 TDT patients [142]. An interesting observation from this registry was that centres which treated 30-80 patients show a higher percentage of appropriately monitored patients compared to centres with fewer patients, supporting the need for reference centres.

A recent study of a longitudinal cohort of 709 transfusion-dependent β-thalassemia major patients (51.1% males) born between 1970 and 1997 and followed through 2020 at seven major centres in Italy, showed an overall survival probability at 30 years being 93.3% (95%CI: 88.6-98.3) in the youngest birth cohort (1985-1997). Concluding that survival in patients with β-thalassemia major continues to improve with adequate access to care, best practice sharing, continued research, and collaboration between centres [143]. Older patients are more likely to develop multiple disease-related morbidities, including osteoporosis, endocrine disorders, liver disease, renal dysfunction, and cancer. Research into clinical outcomes of the older generation of thalassaemia patients, which is increasing in numbers, is needed [144]. In an analysis of 214 TDT patients from Italy, the mean was 46.7years; this compared to most of the patients of the world is a very satisfying record and evidence of the good application of conventional therapy. Yet the mortality rate is still much higher than matched controls; this same group of patients had a healthcare resource utilization which increases with age (e.g. out-patient service rates). So the burden of TDT must be seen in this light as demanding more and more services, and not simply as an improving outcome [Udeze C, Dovizio M, Veronesi C, Esposti LD, Li N, Dang TXMP, Forni GL. Mortality, Clinical Complications, and Healthcare Resource Utilization Associated with Managing Transfusion-Dependent β-Thalassemia and Sickle Cell Disease with Recurrent Vaso-occlusive Crises in Italy. Pharmacoecon Open. 2024 Oct 28. doi: 10.1007/s41669-024-00532-4.]

Italy is one of the few countries in which near optimal care is offered to patients free from out-of-pocket expenses and through good clinical care and reduction of new affected births has reduced the burden of disease. However, immigration of both refugee and economic migrations is altering the epidemiology of haemoglobin disorders and especially increasing sickle cell disease prevalence [145]

Malta: a small but developed country with a very high HDI (0.918). Only 29 patients are followed with the predominance of a mild β++ mutation (IVS1-6). No published data on patient outcomes and there is no prevention program.

Turkey: a large Mediterranean country with a variable gene frequency of β- thalassaemia across its territory. It is reported that there are 5500 known patients but in one study of treatment centres, and considering missing data, infrequent care for NTD β-thalassemia patients, and other errors, there may be as many as 8000 patients both TDT and NTDT [146]. This same study estimated that the total annual direct medical care cost was approximately USD 95,491,900 in Turkey, with TD β-thalassemia patients accounting for USD 58,347,900 (61.1%), and concludes that the costs reported were likely underestimated. This is a considerable burden for this upper middle income country which also has a large refugee population from neighbouring Syria, which also has a high frequency of thalassaemia. Services to thalassaemia patients, including refugees is under Universal Healthcare Insurance. However, there is a parallel private healthcare option and some out of pocket expenses are required.

In 2012 the Turkish Society of Pediatric Hematology set up a National Registry for Hemoglobinopathies. A recent review of the registry produced an age distribution as follows:

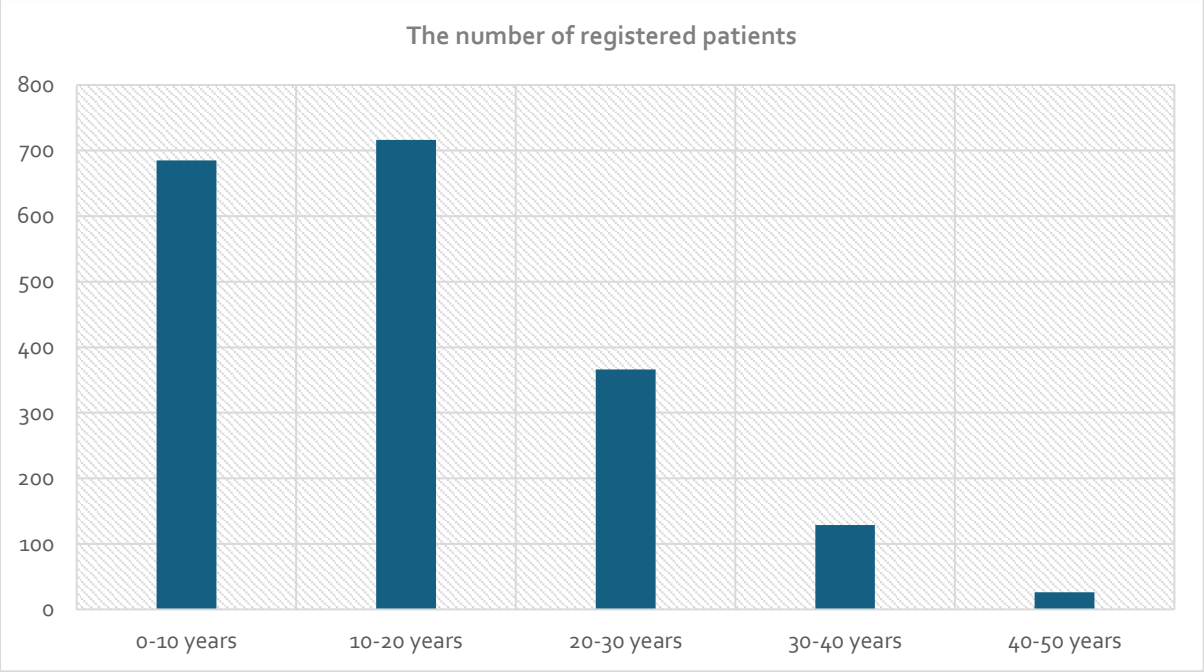

Figure 8. Age distribution of β-thalassaemia patients in Turkey

This is a relatively young patient population, which is due to the variable quality of services in a large country and to a large refugee population. [147].

A hemoglobinopathy control program has been implemented since 2003 and has reduced the annual affected births in recent years.

Countries with a carrier rate for β-thalassaemia <2%:

Of these countries Romania, Spain and Portugal have patient populations which have drawn attention of health authorities while little is known about the countries of central Asia (the 'stans').

Romania: β-Thalassemia is uncommon in the Romanian population, with an uneven distribution across the country. Carrier rate is estimated at 1% and there are 200-300 affected patients. Most patients are treated at the "National Institute of Transfusion Hematology") every 2-6 weeks, and every 3 months biochemical values and virus infection markers are monitored. However, there is no proactive multidisciplinary follow up and no MRI assessment of iron overload.

Only 5 new cases expected every year in a country with a population 20 million. This makes this condition a rare disease in this country. There is no screening program, but prenatal diagnosis is possible [148].

Spain: Thalassaemia is a rare disease in Spain. In an update of the Spanish registry of haemoglobinopathies (REHem-AR), published in 2024, there were 187 recorded cases of β-Thalassemia, 115 (54%) TDT and 72 NTDT and 27 had HbH disease. This is a significant increase on the recorded cases of the 2020 report [149]; there are also 1317 SCD patients on the registry. The geographical distribution across the country is very heterogeneous with a prevalence ranging from 0.1% to 5% [150]. The sickle cell genes are much more common and increasing because of migrations mainly from Africa.

Portugal: like Spain there are very few β-Thalassemia patients (around 40) but almost 1000 SCD patients, also enhanced by migrations

Low prevalence European countries:

This group are mainly Northern European countries in which migrations have introduced haemoglobinopathy genes, mostly in the 20th and 21st centuries. The main host countries are UK, France, the Netherlands, Germany and the Nordic countries. No country is exempt from these migrations and Italy, Greece, Cyprus, Turkey are also adding to their disease burden, especially of the sickle cell syndromes. [151].

Of the host countries the UK and France have historically the oldest permanent populations which originated from high prevalence areas due to their colonial history. For this reason, policies to address the haemoglobinopathy burden were developed.

Table 17. Prevalence of β-Thalassemia and Sickle Cell Disease in Low Prevalence European Countries

Country	Known β-Thalassemia patients	β-Thalassemia patients/100,000	Known SCD patients	SCD patients/ 100,000
United Kingdom	1790	2.6	12913	19
Netherlands	350	1.98	2000	11.3
Germany	600	0.72	5000	6
France	800	1.23	32400	50
Denmark	83	1.4	236	3.98
Sweden	140	1.3	584	5.5

In considering the figures in the table it is noted that they based on estimates since apart from the UK and France other countries do not have a registry (under development in Germany), so figures are estimates from local experts; in addition, figures may be changing from year to year because migrations continue, and also new affected births are not controlled. In the UK a program of ante-natal clinic screening has been ongoing for many years; this is supported by counselling and prenatal diagnosis services.

The UK Haemoglobinopathy Registry (https://nssg.oxford-haematology.org.uk/red-cell/documents/patient-information/nhr-patient-information-leaflet.pdf Annual Data Report 2020/21 last accessed 07/09/2024) provided the data for the numbers of patients and for the age distribution of thalassaemia patients. The younger patients are due to the difficulty of reaching all affected families in a multi-cultural society as well as new migrations. The older age groups are the result of optimal clinical management in reference centres even though many immigrant families reside in areas where clinics may see less than 5 patients.

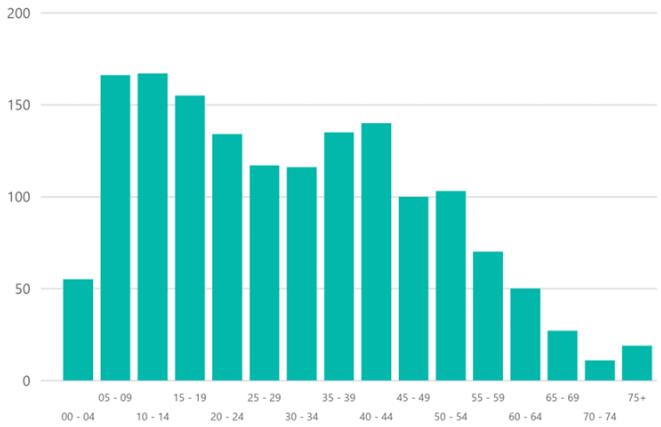

Figure 9. Thalassaemia patients in the UK by age group (copied from the Annual data Report 2020-2021).

The 10-year crude mortality rate is 6.2% for the UK thalassaemia patients. If compared to the age/sex adjusted death rate in the general population, which is 1.2%, this suggests that even in a country offering optimum conventional care a 'normal' life span is not supported. Similar conclusions arise from a 2024 study of 237 TDT patients with a mortality of 1.19 per 100 person years, compared to 0.2/100 in controls. Like the Italian patient population morbidity and service usage increases with age [Udeze C, Ly NF, Ingleby FC, Fleming SD, Conner SC, Howard J, Li N, Shah F. Clinical Burden and Healthcare Resource Utilization Associated With Managing Transfusion-dependent β-Thalassemia in England. Clin Ther. 2024 Nov 1:S0149-2918(24)00287-X. doi: 10.1016/j.clinthera.2024.09.024.]

These programs in Europe include newborn screening which are designed for identification of sickle cell patients.

A national thalassaemia registry is ongoing in **France** with similar results [152]. As in the UK, the strong health service infrastructure allows for optimal care in reference centres but in regions of the country where patient density is particularly low the lack of clinical experience leads to a reduction in service quality. For example, the result of the national registry presented in 2019 indicated the of 666 patients (441 with TM) the median age was 23 years. Only 50-60% of patients had had an MRI iron measurement [153]. These reports are confirmed by a 2024 report which indicates that patients with TDT in France experience significant clinical complications, elevated mortality, and substantial healthcare resource utilization [Baldwin J, Udeze C, Li N, Boulmerka L, Dahal L, Pesce G, Quignot N, Jiang H, Galactéros F. Clinical burden and healthcare resource utilization associated with managing transfusion-dependent β-thalassemia in France. Curr Med Res Opin. 2024 Aug;40(8):1289-1295. doi: 10.1080/03007995.2024.2368197.]

In **Germany** an SCD registry has been established with an estimated number of at least 2000 patients [154]. Also, newborn screening is ongoing [155]. However, thalassaemia is regarded as a rare disease and there is no registry yet. As a rare disease requiring complex clinical protocols, the level of patient care is heterogeneous, and patient reports indicate that many are undertransfused (Hb 7-8g/dl). This indicates a major need in the Northern European setting where a rare disease policy is yet to be applied and a hub and spoke arrangement to support patients from reference centres has not been applied.

Similarly, **Sweden** and **Denmark** are countries with a very robust healthcare infrastructure but where thalassaemia is rare. Quality improvement programs are ongoing through professional groups such as the Nordic Forum for haemoglobin disorders.

The general agreement is that the burden of these diseases is increasing in Europe and so policy makers and professionals are alerted to plan for services which will favour the best patient outcomes.

WHO American Region (PAH)

Epidemiology

In the American continent thalassaemia is are rare condition while sickle cell disease is much more common. TIF has active members in 5 countries with a thalassaemia prevalence: Argentina, Brazil, Canada, Trinidad and Tobago, and USA. There are contacts with individual patients from Mexico, Cuba, Venezuela and Surinam.

Table 18. Estimated Prevalence of β-Thalassemia and Sickle Cell Disease in Select Countries of the Americas and Health Indicators

Country	β-thalassaemia carrier rate	Estimated number of patients b-thal	Sickle cell disease carrier rate	Estimated SCD patients
Argentina	1.35% 0.8% in 4000 donors [156]	No data	0.7%	No data
Uruguay	0.41% [157]	No data	0.76% (2.22% in Afro descendants)	No data
Jamaica	1% [159]	No data	9.8% (neonatal screening) [158]	No data
Brazil	0.25%-3% maximum in Sao Paolo [162]	382 TM+ 280TI= 662	2% (neonatal screening) [160, 161] 1.1% to 9.8% in various regions [162]	30500
Canada	0.5% +0.25% E [164]	1200 est	0.76% [163, 165]	5000 [8]
USA	0.4% -1.55% [167]	1379 (CAF est)	0.75%	100000 [166]
Trinidad &Tobago	3.5%-6.7% [168]	100	9.9% (9.32% by NBS)	No data
Colombia	No data	No data	7.9% [169] 5-12% in coastal areas [170]	No data
Cuba	0.45%	No data	3% [171]	4000 [172]
Suriname	1%	No data	7% (11.4% in Creoles [173]	No data
Country	**IMR/1000 livebirths**	**Under 5 mortality/1000**	**Life expectancy**	**Healthy life expectancy at birth HALE**
Argentina	6	6.9	77.98	75.39
Uruguay	5	5.8	78.16	75.44
Jamaica	10.9	12.4	72.37	70.5
Brazil	12.9	14.4	76.57	56.4
Canada	4	5	83.02	81.63
USA	5.1	6.2	79.74	76.33
Trinidad &Tobago	15	16.3	74.87	72.97
Colombia	11	12.8	77.51	72.83
Cuba	4.1	5	78.33	73.68
Suriname	15.4	17.2	72.79	62.4

Table 19. Health Expenditure and Performance in the Americas: HDI Rank, World Bank Data, and UHC Index

Country	HDI rank	WB rank	HE/cap WB data USD	HE/%GDP WB data	UHC index
Argentina	0.842	UMIC	863.71	10.56	79
Uruguay	0.809	High	1429.51	9.15	82
Jamaica	0.709	UMIC	325.72	6.61	74
Brazil	0.754	UMIC	700.71	10.31	80
Canada	0.922	High	6086.08	11.68	91
USA	0.921	High	11702.41	18.82	86
Trinidad & Tobago	0.810	High	1030.71	7.31	75
Colombia	0.752	UMIC	477.27	8.99	80
Cuba	0.767	UMIC	1186.16	12.49	83
Suriname	0.730	UMIC	459.56	6.77	63

Affected countries of the Americas are all either Upper Middle Income or high-income countries according to World Bank rankings. However, health expenditure varies considerably, and this is reflected in health performance; those with a low expenditure per capita (Jamaica, Brazil, Colombia and Suriname) having the highest IMR, under 5 mortality and the lowest life expectancy including Healthy life expectancy at birth HALE.

Beta thalassaemia is indeed a rare condition in the Americas but as a multi-organ disorder it requires daily treatment and constant multidisciplinary monitoring and care. Treatment is shared in the same clinical settings as SCD

- TIF data suggest that there are about 200- 300 affected births annually in the Americas. The patient population is unknown since there are no patient registries and national reports are rare. From TIF member associations reports, from some but not all counties of the region, we estimate 6500- 7000 patients with beta thalassaemia syndromes across the continent.
- Estimated costs along with other epidemiological information are scarce in the region. A recent, USA 2019, study indicated an average total healthcare costs per patient per year (PPPY) for regularly transfused patients at USD 128,062 [174]. These costs are much lower in other countries (for example in the UAE the mean annual direct cost was found to be USD 35,713 [175], which is likely to be nearer to the cost in counties like Brazil provided that optimum care is available.

The level of care and patient outcomes are known to be of a high level in reference centres, especially in north America. Little is known concerning patient care in the rest of the continent with the exception of **Brazil**, where an active patient driven organization (ABRASTA, a member of TIF) has promoted service development and guideline development [176]. In an evaluation of iron overload of 136 patients, 92% TDT, with a median age of 18 years, and median baseline ferritin 2.033ng/ml (range: 59-14,123) and LIC 8.4(1.0–51.0/9.4) mg/g dw. [177]. These results are indicative of a fair level of care in the major reference centres of Brazil.

This level of service development has not reached all patients across Brazil. In many Brazilian states access to health services is difficult because of the long distances but also because of the rarity of thalassaemia. In such a setting prevention programs such as screening are difficult to implement. Newborn screening is practiced and in one report β-thalassaemia was found in 1.96% of the samples tested [178]. In another report on 8,952 people, Sickle cell trait was detected in 2.49% (2.10 – 2.97%) and minor thalassemia 1.1% (0 0.84 – 1.43%).

Likewise in Argentina a 0.8% incidence of thalassaemic carriers among 4000 blood donors was diagnosed [179]. Optimal treatment for b-thalassaemia has been established in reference centres in Buenos Aires (Aurora Feliu Torres / Gabriela Sciuccati, communication to TIF) but not necessarily in all peripheral centres.

Trinidad &Tobago: these Caribbean islands have the highest prevalence of β- thalassaemia genes in the Americas. This is mainly among the 35.4% who are of Indian origin, brought form India in the 19th century as plantation workers; 3.5% carry β- thalassaemia. Only 63 patients are identified as being under treatment and the level of care has not reached optimal levels even though blood transfusion and chelation are provided free; multidisciplinary monitoring is still to be upgraded. In a recent poster describing the state of beta-thalassemia major patients, 90% had a pre-transfusion Hb of <8g/dl (ave 7.16g/dl) and significantly elevated serum ferritin levels [180].

USA: In this country a national surveillance registry exists for SCD and includes all thalassaemia syndromes but does not cover the whole country. Like the European countries, thalassaemia syndromes are increasing in the USA due to migrations, mainly from Asia and affecting more the west coast. The latest figures for β-thalassaemia and E/β-thalassaemia are of 1379 cases. SCD is much more common with around 70-100000 cases.

The US a Thalassaemia Clinical Research Network is a collaboration of the major reference centres in the country but does not cover all patients with thalassaemia since many live in areas where each medical unit serves a very small number of patients. In this respect also the USA resembles Northern Europe. The quality of care in refence centres and the Clinical Research Network is of a high level and innovative as well as conventional treatments are on trial.

In a study adult thalassaemia patients two groups were compared, those 18 to 39 years and those older than 40 years. The younger group were mostly Asian in origin and included thalassaemia syndromes such as haemoglobin E/b-thalassaemia, HbH Constant Spring and HbH disease; the older group were mostly of Greek or Italian ancestry and had predominantly β-thalassaemia (TDT & NTDT). The achievements in education and employment are similar to those of the European reference centres as is the control of iron overload (Serum ferritin in the last 12 months mean 2434ng/ml in the younger group and 1251ng/ml in the older group, LIC (by MRI) 10. 6mg/g dw SD10.5 in the younger group and 4.5mg/g dw in the older group). Complication rates are also similar to European reference centres. [181]. These outcomes reflect the achievements of current evidence-based protocols in large countries where the majority of patients benefit from experienced medical care, while some are treated in peripheral centres. Very few patients are not covered by health insurance.

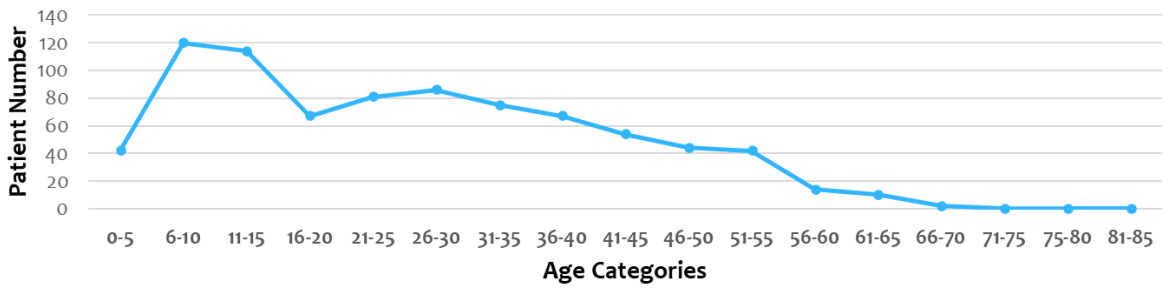

Figure 10. Age distribution of patients from the Cooley's Anemia Foundation Database 2021

This indicates a younger age group compared to refence countries in Europe, but the effect of recent migrations must be considered.

Carrier screening is limited and voluntary with no national policy. Newborn screening is, however, almost universal [182.]

Projected lifetime healthcare costs were estimated to be $7.1 million for patients with TDT at age 50 compared to $235,000 for matched controls. After age 36, each additional year of life added $152,482 to the total lifetime costs for patients with TDT and $7258 to those for matched controls. [183]. This study used administrative claims data to evaluate real-world clinical complications, treatments, HCRU, and healthcare costs in patients with TDT in the United States. However, indirect healthcare costs (e.g. absenteeism, presenteeism, etc.) were not included so total cost may be even higher.

In a recent study of thalassaemia related deaths in the USA, from 1999 to 2020, there were 2797 deaths, 74% had beta thalassemia and 18% had alpha thalassemia. Most deaths are still cardiovascular but 18% had malignancies. Infection which is so common in many thalassaemia populations was the cause of death in only 3% of cases. Overall, there is a decreasing trend in thalassemia-related mortality over the years. Weaknesses in this study include the lack of information on the comorbidity burden, or the prior interventions [184].

Canada: has almost as many thalassaemia patients as the USA – around 1200 with about 5000 SCD patients

WHO African Region (AFR)

Only 2 countries in this WHO region have a significant thalassaemia problem -these are Algeria, which is an Arab and Berber population similar its Maghreb neighbours, and Mauritius which has a large proportion of people of Asian origin.

Algeria: despite the absence of a national registry, a multicentre, retrospective, cross-sectional, descriptive study, conducted in 2017 indicated an increasing adult population.

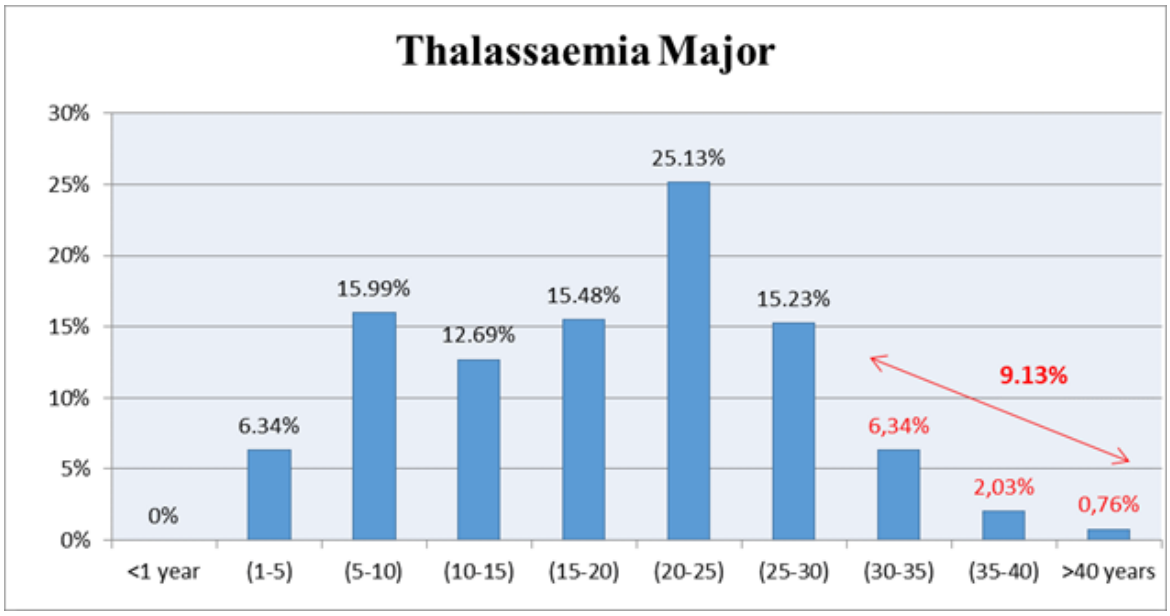

Figure 11. Figure 11. Age Distribution of Thalassaemia Major Patients in Algeria

Age distribution of Algerian thalassaemia patients [185]: Average age is 18,21 +/- 9 years. Average pre-transfusion Haemoglobin 8,05 g/dl (7-10,5 g/dl) and average serum ferritin is 3281ng/ml; Cardiac arrhythmias in 48.72%, Hepatic Fibrosis in 47.61%, Hypogonadism in 60.7%, Hypothyroidism in 21,67%, hypoparathyroidism in 14,31% and diabetes in 25,49%. In a newer report by Dr Djenouni (Conference Report 2024) she made the following comments on the current situation in 2024: the transfusion program for major thalassaemia is inadequate, due to insufficient blood donation. Only two chelators are available in Algeria: Deferoxamine and Deferasirox and there is a lack of infusion pumps for Deferoxamine use. Even so there is a reduction in the frequency of complications and an improvement in median survival.

β Thalassemia ranks second after sickle cell disorders in Algeria, with 0.1/1000 annual expected β-thalassaemia births compared to 0.17/1000 with SCD. The estimated number of thalassaemia patients is 1500-3000 compared to almost 5000 with SCD.

The average age of major thalassemia TDT is 17.90 years, [range 1-44 years], while that of intermediate form (NTDT) is 23 years old with extremes of [range1-61 years] [186]. Monitoring of iron overload is based mainly on serum ferritin while only 8.8% of patients received cardiac and hepatic MRI which is limited to the capital Algiers.

From information provided at a virtual meeting with TIF in September 2022, local experts informed TIF that two only iron chelation agents are available, but they are provided free of charge. The conclusion is that the burden of disease is high in Algeria with much effort to improve services outside the capital being required.

Mauritius: Mauritius is a small island in the Indian Ocean, with a population of approximately 1.25 million. 68% of the population are of Indian origin and thalassaemia is prevalent in this community. 3.85% carry β Thalassemia. In a TIF delegation visit in 2019, there were 110 known thalassaemia patients and around the same number of SCD patients. There was no clinical service specifically devoted to thalassemia and patients were transfused in various hospitals. However, a national Thalassaemia Society of Mauritius (TSM) was created in 2009 which has promoted service development and the training of both medical and nursing staff. The Ministry of Health has supported their effort, and free care is offered in public hospitals for all patients, with no out of pocket expenses. A "Standard protocols & guidelines for management of patients with thalassemia" was launched in 2022 with the collaboration of TIF and the Ministry. This development effort is ongoing and outcomes for patients are expected to improve in the coming years.

SURVIVAL DATA

In the European countries (WHO region), where around 1025 new annual affected births may be expected, there are 25200 recorded patients (in hospital/clinic/Regional/or national based registries). This is probably the most accurate record of patient numbers, compared to other regions of the world. In 20 years, there should be 45700 if there is no effective prevention program. This gives a ratio of births to patients of 0.04. In the Arab World 8240 new cases are expected with currently 91400 recorded patients and a ratio 0,09. In the WHO Southeast Asia region plus Pakistan, then estimate is of 257000 patients with 42000 expected annually. The ratio in this region is 0.163 indicating a much higher death rate in childhood. There is a gradation of survival across regions of the world reflecting a different burden of premature mortality.

Survival of patients in all countries depends on the birth cohort since older patients suffered from treatment which was suboptimal by today's standards during their early years. Iron toxicity damage was therefore inevitable even though chelation and monitoring improved over the years. An example is the Kaplan- Meyer chart from Cyprus.

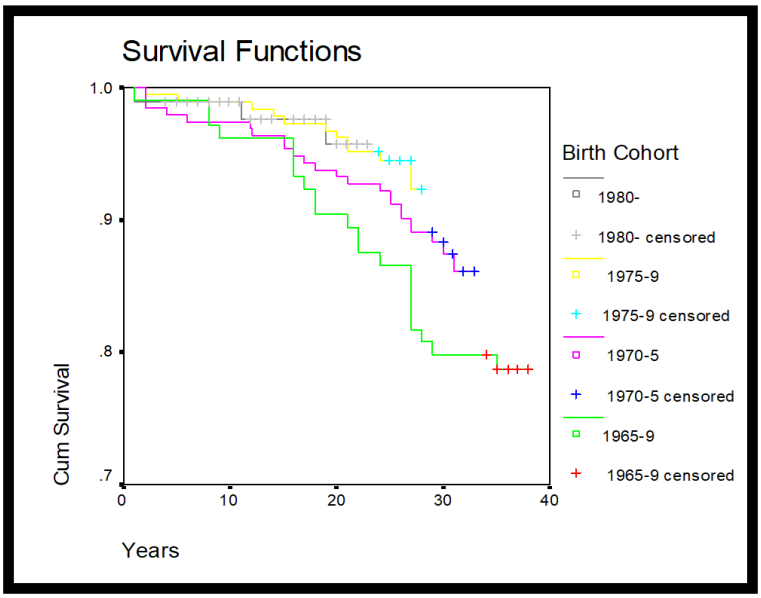

Figure 12. Survival Functions - Cyprus

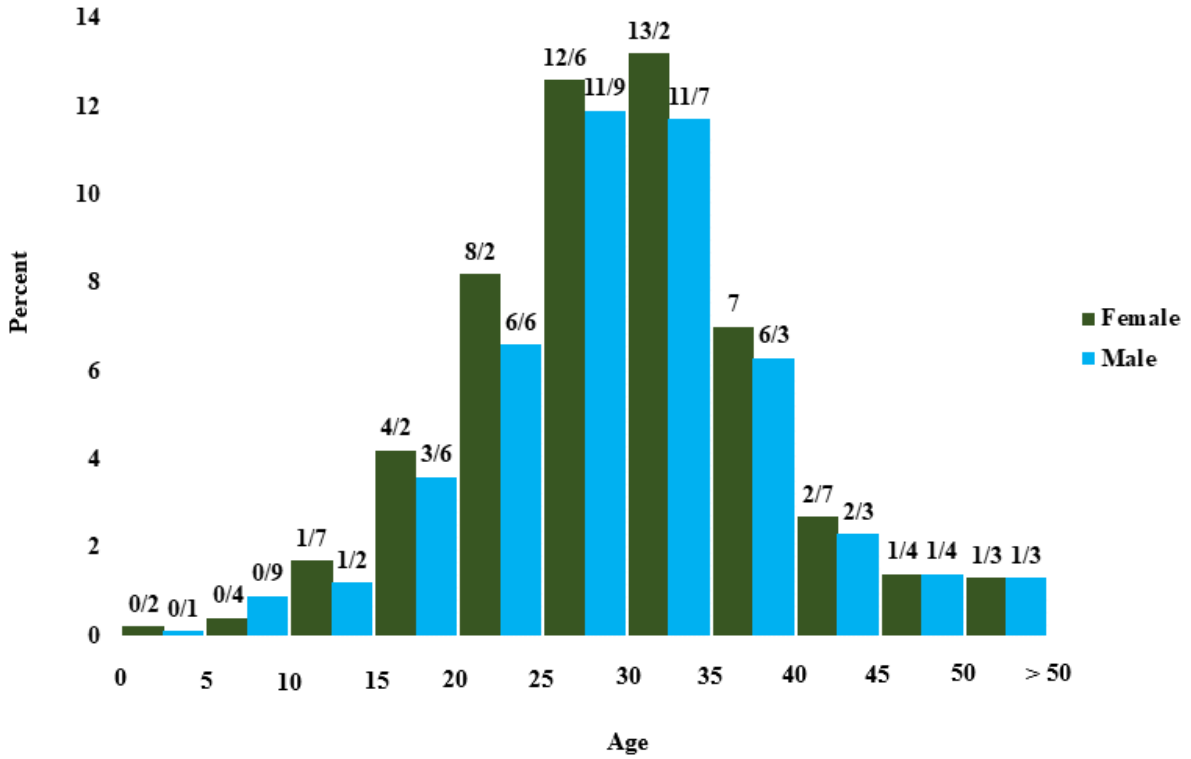

Figure 13. Distribution of 1385 transfusion-dependent patients by age and gender, Mazandaran Province, 2016

This current survival data bear witness to the successful provision of conventional treatment in Italy, Cyprus and Greece. This also holds true where the complication rates are concerned (see Table 1). It also demonstrates the limitations of conventional treatment in allowing for a 'normal' lifespan to all patients, even under the best conditions.

Another example is that of Taiwan (China): The analysis of patient survival data is based on a nationwide population-based cohort study [19] analysed between 2007–2011; the data was obtained from the Taiwanese National Health Insurance Research Database. After excluding those patients receiving hematopoietic stem cell transplantation, 454 patients were included. The median age was 17.2 years (range, 0.1–48.0 years), indicating a young population receiving less than optimum management, despite a good health infrastructure and universal coverage (99%); the NHI program in Taiwan has covered all treatment expenses since 1995. In addition, 58.1% patients being younger than 20 years, probably an indication of a poor prevention effort. However, survival probability was calculated to be satisfactory. This is a young population of patients with need to upgrade monitoring and treatment:

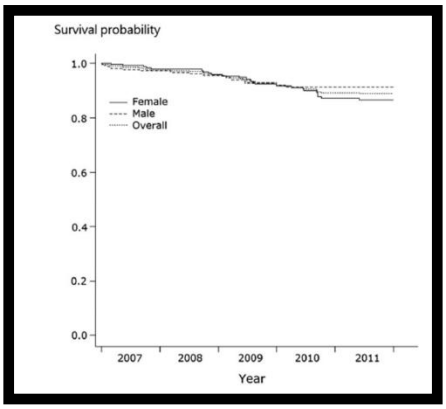

Figure 14. Survival probability of patients with thalassaemia major in Taiwan, 2007-2011. 44 (9.7%) of the 454 patients died. No significant difference in the survival probability between female and male patiens. (log-rank test, P = 0.57)

Table 20. Reference Countries

Country	Cyprus	Greece	Greece	Italy	Italy
Centre	2 centres (50%)	1 centre (Aghia Sophia)	National	MIOT centres	WEBTHAL 36 centres
Year	2020	2019	2015	2019	2020
Number of patients			2099		3149
Median age	44	33.3	36-45	31.17	37 (4-78)
Heart disease	8.8%	8.6%	28.14%	4.4%	30.2%
Hypogonadism	28.4%	21.6%			
Bone disease	33.7%				
Hypothyroidism	13%	20.7%			9.5%
Diabetes	14.7%	7.3%			8.3%
Malignancies		6.1%	6%		
HCV +					
Ferritin <1000	48.9%		56%		
Ferritin 1-2500	25.9%		30%		
Ferritin >2500	25.2%		14%		
Mean Ferritin					
Cardiac T2* >20	85.4%	86.5%	86.49%	88%	85%
Cardiac T2* 10-19	10.1%	7.4%	7.43%		12%
CardiacT2* <9	4.5%	6.1%	6.07%		3%
LIC <3	51%	52.1%	51.84%		45%
LIC 3-7	22.5%	18.5%	18.38%		29%
LIC 7-15	13%	14.6%	15.07%		16%
LIC >15	13.5%	13.5%	14.71%		10%

Table 21. Countries of Europe and Asia where programmes for TDT exist

Country	United Kingdom	Australia	Indonesia	Iran (Islamic Rep. of)	Iran (Islamic Rep. of)	France	Thailand	Malaysia	Sri Lanka	Egypt	Iraq	Maldives
Centre	National	National	Cipto centre	Shiraz	Mazandaran	National	Multicenter	National	National		Dohuk	National
Year	2019	2019	2018	2019	2019	2013	2017	2019	2019	2019	2019	2018
Number of patients	612		238	713		268	127	2676	1177		150	81
Median age	Adults	>18	>18	10-62	30± 9.7	21 (2-56)	27.8±11.4	10-14.9	13.2±7.6	13	13 (1-35)	
Heart disease	18%			72.6%		18.6%	4%HF				2.7%	
Hypogonadism				10.7%		47%	11%	22%			52.8%	
Bone disease	40%			15.9%								
Hypothyroidism						9.6%	7.1%				7.3%	
Diabetes	40%					7.8%	7.9%				3.3%	
Malignancies												
HCV +						20.6%					35.3%	
Ferritin <1000								18.18%		0%		11.8%
Ferritin 1-2500								35.17%		47.5%		34.2%
Ferritin >2500								46.65%		52.5%		53.9%
Ferritin mean					3300	1104 (120-8553)	2250±2313		2383			3339
Cardiac T2*>20		77.7%	82.7%		70.5%							
Cardiac T2*10-19		11.8%	11.4%		23.5%							
Cardiac T2* <9			5.9%		5%							
LIC <3			13.4%		32%							
LIC 3-7			20.6%		14.6%							
LIC 7-15		32.9%	29%		10.1%							
LIC >15			37%		2.9%							

Comments on the burden of disease

Even in high resource countries, traditionally offering optimal care, such as Italy, in a recent report 85% of patients suffer from one or more comorbidities; the most frequently reported comorbidities are osteoporosis (74.28%) and endocrine problems (54.28%), fertility issues in 40.95% and dental problems reported in 27.62%. Also, there are significantly reduced levels of HRQoL compared with the general population, influencing physical and social activities. Patients' perceived a high burden of disease, with fear of adverse events from treatment as well as the disease [187]. Very similar findings are reported from other clinical and social settings; one example being a study of patients from Malaysia [188].

Patients' quality of life can be severely affected by issues such as bone pain and leg ulcers which may not be life threatening. This particularly true of the 'milder' thalassaemia syndromes. In a report from Sri Lanka a new leg ulcer was recorded in 45 (22.2%) of 196 patients with HbE thalassemia, most irregularly transfused and with a steady state haemoglobin of 6.4 ± 0.2 g/dL. [189]. In Thailand from a total of 459 NTDT (87.6%) and 65 TDT (12.4%) adult patients, osteopenia/osteoporosis was detected in 69.8%, gallstones (67.6%), and abnormal vitamin D levels in 67.6%. These predispose to pain and an effect on the quality of life [190].

CONCLUSION

There is a considerable gap in published information on patient numbers, nationwide survival, morbidity and mortality rates that would support the better assessment of the level of contribution of thalassaemia to the national disease burden.

Such an assessment would help decisions to be made and appropriate budget allocations. It would support disease prioritization and development and/or strengthening of disease specific policies at the national level. Our findings, albeit incomplete and on occasions grossly estimated, suggest that these disorders contribute significantly to the country's disease burden and that many and multiple efforts are needed by competent authorities to alleviate the pain and suffering and the premature death of patients with these disorders.

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