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REVIEW ARTICLE

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Changing patterns in the epidemiology of β-thalassemia

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Abstract

β-thalassemia major is an inherited hemoglobinopathy that requires lifelong red blood cell transfusions and iron chelation therapy to prevent complications due to iron overload. Traditionally, β-thalassemia has been more common in certain regions of the world such as the Mediterranean, Middle East, and Southeast Asia. However, the prevalence of β-thalassemia is increasing in other regions, including Northern Europe and North America, primarily due to migration. This review summarizes the available data on the changing incidence and prevalence of β-thalassemia as well as factors influencing disease frequency. The data suggest that the epidemiology of β-thalassemia is changing: Migration has increased the prevalence of the disease in regions traditionally believed to have a low prevalence, while, at the same time, prevention and screening programs in endemic regions have reduced the number of affected individuals. Various approaches to prevention and screening have been used. Region-specific prevention and treatment programs, customized to align with local healthcare resources and cultural values, have been effective in identifying patients and carriers and providing information and care. Significant challenges remain in universally implementing these programs.

KEYWORDS

beta-thalassemia major, incidence, epidemiology

1 | INTRODUCTION

β-thalassemias are a heterogeneous group of hereditary hemoglobinopathies characterized by defects in the β-globin chain of hemoglobin and autosomal recessive inheritance. Homozygous or compound heterozygous forms have an imbalance in the production of α- and non–α-globin chains, resulting in ineffective erythropoiesis and decreased production of normal hemoglobin A.[1]

Patients with β-thalassemia major have severe chronic hemolytic anemia and require regular blood transfusions from early childhood.[1-3] Chronic blood transfusion therapy is typically combined with iron chelation therapy (ICT) to prevent complications due to iron overload, such as cardiac morbidity, liver disease, and endocrine dysfunction.[1-3]

Patients with β-thalassemia intermedia have symptoms in between carriers and those with β-thalassemia major: Anemia is often moderate, but patients may still have morbidity due to ineffective erythropoiesis and hemolysis, including ulcers, pulmonary hypertension, and pain. Some patients require occasional blood transfusions, although less frequently than patients with β-thalassemia major.[1,2]

Historically, the prevalence of β-thalassemia has been highest in the Mediterranean region, the Middle East, and Southeast Asia and lowest in Northern Europe and North America.[4] Due to migration patterns, β-thalassemia is increasingly more common in non-endemic regions,

including Western Europe and North America.[4] In this review, we discuss changing patterns in the incidence and prevalence of β-thalassemia in Europe, North America, the Middle East, and Southeast Asia, providing evidence for the regional burden that this disease poses.

2 | INCIDENCE OF β-THALASSEMIA

According to a 2008 report from the World Health Organization, more than 40 000 infants are born with β-thalassemia each year, of whom about 25 500 have transfusion-dependent β-thalassemia.[5] The annual numbers of expected newborns with β-thalassemia are 20 420 in Southeast Asia, 9914 in the Eastern Mediterranean region, 1019 in Europe, and 341 in North, Central, and South Americas.[5] In Thailand alone, at least 625 new β-thalassemia major and 3250 new cases of β-thalassemia/hemoglobin E (Hb E) are expected each year (1 in 180 births), and more than 55 000 surviving patients have transfusion-dependent thalassemia.[6]

Few European countries have reported incidences of β-thalassemia major. In Belgium, the incidence is 1 in 25 000 neonates.[2] A French registry study reported an incidence of 1 in 112 881 births between the years 2005 and 2008.[7] The Greek National Registry for Hemoglobinopathies reported a significantly lower incidence of β-thalassemia than expected based on the prevalence of carriers, thereby demonstrating the efficacy of thalassemia prevention programs.[8]

TABLE 1 Frequency of β-thalassemia in Southeast Asia

Country	Prevalence of β-thalassemia per 100 000 persons[a] (year)	β-thalassemia carrier rate, % (year)	Availability of screening program[b] (year of initiation)			References
			Premarital/ carrier	Prenatal	Newborn	
China	—	3.0-6.0 (2007)	NR	NR	NR	16
	—	1.1-2.3 (2011)	No	No	No	17
	—	2.72 (2013)	NR	NR	Local (2013)	18
	526 (1981) 4526 (2012)	—	NR	NR	NR	19
Cambodia	—	3.0 (2005)	NR	NR	NR	20
Hong Kong	—	3.5 (2007)	NR	NR	NR	16
India	—	3.0-4.0 (2007)	Regional (NR)	Regional (NR)	NR	16
	1660 (2005-2015)	4.6 (2005-2015)	Voluntary (NR)	NR	NR	21
	1250 (2014-2015)	8.64 (2014-2015)	No	No	No	22
Indonesia	—	3.0-10.0 (2005-2007)	NR	NR	NR	16,20
Laos	—	3.6 (NR)	NR	Yes (NR)	NR	23
		9.0 (2005)	NR	NR	NR	20
Malaysia	—	4.5 (2007)	NR	NR	NR	16
		3.0-5.0 (2005)	NR	NR	NR	20
	—	12.8 (2008)	No	No	No	24
Myanmar	—	0.5-3.4 (2007)	NR	NR	NR	16
		4.0 (2005)	NR	NR	NR	20
Pakistan	—	5.5 (2010)	No	No	No	25
Philippines	—	1.2 (2005)	NR	NR	NR	20
Singapore	—	0.93 (2007)	NR	NR	NR	16
Sri Lanka	—	2.2 (2007)	No	No	No	16
Taiwan	—	1.0-3.0 (2007)	NR	NR	NR	16
Thailand	—	1.1 (2005)	NR	NR	NR	26
	—	3.0-9.0 (2007)	NR	NR	NR	16
	—	1.0-9.0 (2005)	NR	NR	NR	20
Vietnam	—	1.5 (2007)	NR	NR	NR	16
		1.6-25.0 (2005)	NR	NR	NR	20

Abbreviation: NR, not reported.

[a]Prevalence values were converted into number of patients per 100 000 for consistent reporting; therefore, they are estimates.

[b]As published in the reference.

Similarly, an Iranian study showed a decline in affected birth rate from 2.53 per 1000 births in 1995 to 0.82 per 1000 births in 2004.[9] In Oman, between the years 2005 and 2007, the incidence of β-thalassemia major was 0.08%, with a carrier rate of 2.6%.[10] Approximately 10 years earlier in 1995, the incidence was reported to be 0.4 per 1000 births.[11] In Iraq, the incidence of β-thalassemia decreased from 72.4 per 100 000 live births in 2010 to 34.6 per 100 000 live births in 2015.[12] A comprehensive National Hemoglobinopathy Control Program was implemented by law and came into force on October 24, 2002, in 33 provinces of Turkey and, by 2008, a 90% reduction in affected newborns in Turkey was achieved.[13]

In the United States, β-thalassemia remains a rare disease; in the state of California, the reported incidence is 1 in 55 000 newborns.[14]

3 | PREVALENCE OF β-THALASSEMIA

Worldwide, approximately 1.5% of people are β-thalassemia carriers.[4] Although the overall combined number of patients with the disease and those who are carriers is known in most countries, significant variations occur even within small geographic regions.[4,15]

The prevalence and carrier rates of β-thalassemia are relatively high in Southeast Asia (Table 1).[16-26] For example, the reported prevalence ranges from 1.25% to 1.66% in India [21,22] but is approximately 2.21% in China.[18,19] Carrier rates range from 0.5% in Myanmar [16] to 12.8% in Malaysia.[24] The most recent data on β-thalassemia carrier rates in Southeast Asia are summarized in a review.[20]

In the Middle East, the prevalence of β-thalassemia is traditionally high due in part to a high carrier rate and a cultural preference for consanguineous marriages (Table 2).[11,12,15,16,27-31] However, the introduction of prevention programs in many countries in this region has led to a decrease in prevalence over the last decades.[15]

In some European countries, the prevalence of β-thalassemia and other major hemoglobinopathies is increasing due to migration, and major hemoglobinopathies are now the most common genetic rare disease in Europe (Table 3).[7,13,15,16,32-42] As of 2007, new cases of hemoglobinopathies occurred at a comparable frequency throughout Northern, Western, and Southern Europe.[33] Although birth rates are decreasing in the general population, affected birth rates remain relatively high among some at-risk migrant groups.[33] The effect of migration is illustrated by the increased prevalence of β-thalassemia observed in the United Kingdom. In the 1960s,

TABLE 2 Frequency of β-thalassemia in the Middle East

Country	Prevalence of β-thalassemia per 100 000 persons[a]	β-thalassemia carrier rate (year)	Screening program available[b] (year of initiation)			References
			Premarital/carrier	Prenatal	Newborn	
Bahrain	9 (2007)	2.0% (2007)	Voluntary (1991); mandatory (2004)	Yes (1994)	Yes (2007)	16
	—	2.9% (2013)	NR	NR	NR	27
Egypt	—	9.0%-10.0% (NR)	NR	No	NR	28
	—	5.3%-9.0% (2007)	No	No	No	16
	—	4.5% (2013)	NR	NR	NR	27
Iran	—	5.7/1000 (1997-2011)	Yes (1995)	Yes (1995)	NR	29
	—	4.0%-8.0% (NR)	NR	NR	NR	15
Iraq	—	3.7% (2006)	Pilot (2006)	Pilot (2006)	NR	30
	—	33.5/100 000 (2010) 37.1/100 000 (2015)	Yes (NR)	NR	NR	12
Jordan	—	3.0%-5.9% (2013)	NR	NR	NR	27
Lebanon	-	2.0%-3.0% (2007)	Mandatory (1994)	Yes (1994)	NR	16
Oman	40[c]	4.0% (1995)	No	No	NR	11
Palestine	—	3.0%-4.0% (1996-2015)	Yes (2001)	NR	NR	31
Qatar	—	2.0%-3.0% (NR)	NR	NR	NR	15
Saudi Arabia	—	1.0%-15.0% (2013)	NR	NR	NR	27
United Arab Emirates	—	8.5% (2013)	Mandatory (2012)	Yes (NR)	Yes (NR)	27

Abbreviation: NR, not reported.

[a]Prevalence values were converted into number of patients per 100 000 for consistent reporting; therefore, they are estimates.

[b]As published in the reference.

[c]Specified as β-thalassemia major.

TABLE 3 Frequency of β-thalassemia in Europe

Country	Prevalence of β-thalassemia per 100 000 persons[a]	β-thalassemia carrier rate, % (year)	Availability of screening program[b] (year of initiation)			References
			Premarital/ carrier	Prenatal	Newborn	
Albania	65 (NR)	–	NR	NR	NR	33
Austria	1 (NR)	–	NR	NR	NR	33
Belgium	2 (NR)	–	NR	NR	Regional (1994)	33
	0.69 (2007)	–	NR	NR	Regional (NR)	16
	3.65[c] (2007	–	NR	No	Regional (1994)	34
	0.5 (2008)	–	NR	NR	Regional	35
Bulgaria	25 (NR)	–	NR	NR	NR	33
	3.66 (2012)	–	NR	NR	NR	36
Cyprus	563 (NR)	–	Yes (NR)	NR	NR	33
	–	15.0 (2007)	NR	Yes (1978)	NR	16
	90 (1995-2015)	–	Yes (1978)	NR	NR	37
Denmark	4 (NR)	–	Yes (NR)	Yes (NR)	NR	33
Finland	1 (NR)	–	NR	NR	NR	33
France	4 (NR)	–	Local (NR)	NR	Yes (2000)	33
Corsica	0.58 (2007)	0.7-3.1 (2007)	NR	NR	Targeted (1994)	16
	–	3.0 (2009)	NR	NR	NR	7
Germany	3 (NR)	–	NR	NR	NR	33
	0.55 (2007)	–	NR	NR	NR	16
Greece	25 (2000-2015)	–	Yes (1973)	Yes (1973)	NR	38
	–	8.0 (2007)	NR	Yes (1973)	NR	16
Italy	36 (NR)	–	Yes (NR)	NR	NR	33
	–	1.0-12.0 (2007)	Regional (NR)	Regional (1970s)	NR	16
	–	10.0-16.0 (NR)	NR	NR	NR	15
Ireland	1 (NR)	–	NR	NR	NR	33
Luxembourg	2 (NR)	–	NR	NR	NR	33
Malta	24 (NR)	–	NR	NR	NR	33
The Netherlands	5 (NR)	–	Yes (NR)	NR	Yes (2007)	33
Norway	4 (NR)	–	NR	NR	NR	33
Portugal	1 (NR)	–	Yes (NR)	NR	NR	33
	0.38 (2007)	–	NR	NR	NR	16
Romania	3 (NR)	–	NR	NR	NR	33
Spain	1 (NR)	–	NR	NR	NR	33
Menorca	– –	0-5.0 (2007) 2.7 (2007)	NR	NR	Regional (NR)	16
Sweden	6 (NR)	–	NR	NR	NR	33
Switzerland	5 (NR)	–	NR	NR	NR	33
Turkey	–	1.66 (NR)	NR	NR	NR	39
	5.7 (1995-2000)	4.3 (1995-2000)	Regional, voluntary (2003)	Regional (2003)	NR	13
	–	3.0 (1997-1998) 3.1 (2012-2013)	Regional (1997)	NR	NR	40
	–	1.06-6.80 (2003-2013)	Regional, mandatory (2003)	NR	NR	41
	–	2.67 (NR)	NR	NR	NR	42

(Continues)

TABLE 3 (Continued)

Country	Prevalence of β-thalassemia per 100 000 persons[a]	β-thalassemia carrier rate, % (year)	Availability of screening program[b] (year of initiation)			References
			Premarital/ carrier	Prenatal	Newborn	
United Kingdom						
Scotland	3 (NR)	—	NR	Yes (2000)	Yes (2000)	33
England & Wales	10 (NR)					
Former Yugoslavia	3 (NR)	—	NR	NR	NR	33

Abbreviation: NR, not reported.

[a]Prevalence values were converted into number of patients per 100 000 for consistent reporting; therefore, they are estimates

[b] As published in the reference.

[c]Specified as β-thalassemia major.

10% of the population of Cyprus migrated to London as a result of civil war.[43,44] Of approximately 57 000 migrants, 17% were carriers of β-thalassemia, resulting in a prevalence of 7 per 1000 neonates.[45] Around the year 1999, the prevalence in the United Kingdom had increased by approximately 14 persons per year, because the number of births exceeded the annual number of deaths, and approximately 2 or 3 children migrated to the United Kingdom each year.[44] In the first years of the 21st century, the prevalence of β-thalassemia major decreased to 0.3 to 10 per 1000 in different parts of the United Kingdom.[33] Currently, most patients with β-thalassemia in the United Kingdom have a Pakistani or Indian background.[46]

In the United States, the prevalence of β-thalassemia has increased approximately 7.5% over the last 50 years.[47] The Cooley's Anemia Foundation maintains a voluntary patient registry and has identified 1270 patients with β-thalassemia (as of September 19, 2019), mostly on the East and West Coasts (Janet Kwiatkowski, MD, MSCE, personal communication).

4 | FACTORS AFFECTING INCIDENCE AND PREVALENCE IN DIFFERENT COUNTRIES/ REGIONS

Multiple factors contribute to the changing epidemiology of β-thalassemia. These factors include migration, implementation of β-thalassemia prevention programs, and improved survival rates.[15,33]

4.1 | Migration

In 2017, the global number of refugees reached an all-time high of 25.4 million,[48] including many people from regions where β-thalassemia is endemic, such as Syria, Afghanistan, and Myanmar. Several countries have experienced significant increases in the number of refugees that they host such as Germany, Greece, Italy, Turkey, Lebanon, Iran, and Pakistan.[48]

Recently, Italy has accepted many refugees who crossed the Mediterranean Sea, demonstrated by the more than 126 000 applications for asylum submitted in 2017.[48] In one study of patients with β-thalassemia in the Italian region of Umbria, 60% of the study population was diagnosed between 2012 and 2015 and the remaining 40% between 1988 and 2011.[49] These data were in line with an increase in immigrants in the region: Immigrants accounted for 5% of the Umbrian population in 2004, rising to 11% in 2014.

In Turkey, an estimated 3.4 million Syrian refugees have entered the country since 2011, with 276 158 babies being born to Syrian couples living in Turkey between 2011 and 2017.[50] These couples were not covered by the premarital screening program that was widely implemented in Turkey in 2002. In 18 pediatric hematology/ oncology centers throughout Turkey, 318 children from 235 refugee families had β-thalassemia (mean age 8.1 years); most of these patients presented with an inadequate transfusion and chelation history. A total of 72 of 318 affected children from refugee families were born in Turkey, indicating an urgent plan to screen refugee couples at risk for hemoglobinopathies.[51]

In the United States, the incidence and prevalence of β-thalassemia has increased significantly because of an increase in immigration from Asian countries in the past decades,[52,53] as well as an increased adoption rate of children with β-thalassemia from China and other countries. According to the Cooley's Anemia Foundation, 12% of patients with β-thalassemia in their US patient database were adopted from other countries.[54]

In Asia, economic growth in several emerging countries, such as Thailand and Malaysia, has drawn millions of immigrant workers from neighboring countries who lack standardized care for thalassemia—a result likely to lead to an increased thalassemia burden in the near future.[55]

4.2 | Prevention programs

Comprehensive prevention programs include public education, genetic counseling, and population screening, accompanied by prenatal diagnostics. Effective public education is the initial step for all prevention programs. An Iranian study showed that 69% of people who are β-thalassemia carriers were insufficiently knowledgeable regarding the prevention of β-thalassemia in their potential offspring,

and only 13% participated in screening.[56] In many European countries, including France, The Netherlands, Italy, Spain, and the United Kingdom, local and national campaigns are often driven by patient organizations and aim to improve education and awareness for hemoglobinopathies.[32] Such campaigns are most successful if they include the broader community, including educational and religious organizations.[32,57]

Screening programs are being developed in multiple countries and are tailored to local needs and customs.[4] Currently, many screening programs are often unstructured and highly dependent on the knowledge of healthcare professionals and patients.[32] Screening programs generally target possible carriers or at-risk patient populations.[32] Population screening, premarital screening, preimplantation genetic diagnosis, and prenatal diagnosis offer information and choices to at-risk individuals and couples.[44] Factors for efficacy include cultural aspects such as awareness, stigmatization, religious considerations, and whether pregnancy discontinuation (in the event of an affected fetus) is legal and morally accepted in the respective country.[58]

While participation in screening programs takes place on a voluntary basis in most countries, some countries have chosen to implement mandatory premarital screening for β-thalassemia (Tables 2 and 3). Following a participation rate of only 20% in voluntary premarital counseling, the government of Bahrain decided to make the screening program mandatory in 2004, although the autonomy of the couple regarding testing is fully respected.[16] Other countries with mandatory screening programs include Lebanon,[16] Turkey,[41] and the United Arab Emirates.[27]

These programs are well established in many European countries where β-thalassemia has been historically endemic, such as Greece, Italy, and Cyprus, and in countries that receive a high number of immigrants from endemic countries, such as the United Kingdom and France.[32] In Italy, policies for the prevention of hemoglobinopathies have been in place since the 1970s.[59,60] Free voluntary carrier screening as well as prenatal and preimplantation genetic diagnostics are available nationwide.[57,60] Increasing awareness among the general population, leading to acceptance of screening, has been a major success factor of the Italian prevention program.[32,60] In a report covering 40 years of experience with a screening program in Sardinia, the main causes of affected births (3-5 annually in recent years) were false paternity and decline of prenatal screening and pregnancy termination.[59,60] In Sicily, an 85% decrease in the incidence of β-thalassemia major and sickle cell anemia (from 1 in 245 live births to 1 in 2000) has been documented following 30 years of preventative measures, which included legislative action, a public awareness campaign, screening and carrier diagnostics, genetic counseling, and prenatal diagnosis.[61] In addition, a universal screening program for hemoglobinopathies is active for couples before and/or after conception, according to Italian law, given that Italy is considered an area endemic for hemoglobinopathies.[61]

In Cyprus, a prevention program was introduced in 1973 and has led to a significant decrease in the number of affected babies born.[45] Similarly, the Greek National Prevention Program for thalassemia and other hemoglobinopathies was initiated in 1974 and includes education and prenatal diagnosis. The program led to a significant decrease in the number of affected newborns, from 150 to 200 new cases per year before the screening program, to fewer than 5 cases per year by 2010.[8,62] Except for an unexplained increase in 2011, the number of affected births has been declining for β-thalassemia major and has remained low for β-thalassemia intermedia.[38] The main causes of affected births were lack of medical care due to financial reasons or low educational level (34%), unawareness of screening tests (23%), religious reasons (13%), social or bioethical reasons (13%), and misinterpretation of test results or laboratory errors (13%) [8]; another study pinpointed carrier misidentification as the main reason for affected births.[62]

In Turkey, a comprehensive national hemoglobinopathy control program focused on premarital screening was implemented in 2002. Although official reports from Turkey indicated a significant reduction in the number of affected births in 2008,[13] follow-up registry data suggested a consistent decrease only after 2009.[63] This reduction was also observed in other Turkish studies.[40,41] The prevalence of β-thalassemia carriers remained stable (range 2.0%-3.8%) in the Muğla province of Turkey during roughly the same time period (1997-2012); however, the authors acknowledged that prevalence varies significantly between regions.[40]

Other successful screening programs in Asia have been aimed at the general population or at specific target groups. In Thailand, the national program for prevention and control for severe thalassemia syndromes, including β-thalassemia major and β-thalassemia/Hb E, was established in 1994. This program offers full reimbursement for carrier screening in pregnant women and their partners.[64] In more recent years, this has resulted in a remarkable decrease of new patients, largely because the Thai government legally allows termination of pregnancy before 24 weeks of gestation for women with a molecularly confirmed affected fetus with severe thalassemia syndromes, including β-thalassemia major and β-thalassemia/Hb E.[65,66]

Similar screening strategies have been applied successfully in Albania, Canada, Myanmar, and Malaysia.[67-70] The National Thalassemia Major Prevention Program was introduced in Taiwan in 1993 and led to a 91% reduction in the incidence of β-thalassemia major between 1986 and 1995.[71]

Since the introduction of mandatory premarital screening in Saudi Arabia in 2004, the prevalence of β-thalassemia decreased from 32.9 to 9.0 per 1000 persons screened in 2004 and 2009, respectively ($P < .001$).[72] In Iran, the β-thalassemia prevention program was introduced in 1991, and, by 2001, more than 2.7 million couples had been screened.[73]

Utilization of prenatal testing can vary by ethnic group. In the United Kingdom, the utilization rate was more than 90% in couples of Mediterranean origin but only 20% in couples of Asian (mainly Pakistani) origin.[44] In Southeast Asia, Thailand has paved the way for prenatal screening and prenatal diagnosis of thalassemia, as mentioned above; illustrating this, a pilot study of international collaboration between Thailand and Laos primarily focusing on prenatal diagnosis proved to be an effective way to

identify thalassemia carriers.[74,75] Screening of pregnant women and their partners took place in Laos, and laboratory samples were analyzed in the neighboring country of Thailand.[75] However, a recent survey of migrant workers in Thailand, especially those from Myanmar and Cambodia, showed that there is insufficient knowledge about all aspects of thalassemia, including prevention and control, because no national program exists for thalassemia and infrastructure to support screening is lacking.[55]

Traditionally, obstacles to the efficacy of prevention programs have been consanguineous marriages, religious beliefs, and low socioeconomic status. Consanguineous marriages are a particularly common tradition in many regions where β-thalassemia is endemic, such as North Africa and the Middle East, thereby increasing the risk of autosomal recessive diseases.[15] In a Turkish observational prospective study of 1988 patients, of whom 94% were diagnosed with β-thalassemia major or intermedia, almost one-half (48%) were born to consanguineous parents.[63] Similarly, an Egyptian study of 44 patients with β-thalassemia reported that 60.6% had consanguineous parents.[28]

Another possible limitation of screening programs is the unwillingness of healthcare professionals to offer prenatal diagnostic screenings and pregnancy terminations to their patients. In a Malaysian questionnaire study, 98% of healthcare professionals agreed that they would discuss prenatal diagnostics with their patients, whereas only one-half of them were prepared to discuss termination of pregnancy.[76] The most frequently cited reasons not to discuss termination of pregnancy were the disease not being considered serious enough (54.9%) and abortion not being allowed by their religion (17.6%) or by law (13.7%).[76]

Defining the prevalence of the disease in each country is important to properly organize health system resources. Hemoglobinopathies have an important impact on healthcare.[32] Between the years 1997 and 2010, a total of 4506 patients with hemoglobinopathies in a Greek registry were found to require 18% of the country's total red blood cell supply.[77] β-thalassemia also poses a significant economic burden on healthcare systems. In the United Kingdom, total healthcare expenditure attributable to managing β-thalassemia major over 50 years was estimated to be USD 720 201 at 2013-2014 prices.[78] A study of 331 patients with β-thalassemia in Greece found that the mean annual cost per patient, including all treatment strategies, was EUR 32 064 for the period 2009 to 2011, a value that increased from EUR 30 997 in 2009 to EUR 32 564 in 2011.[79] In Iran, a study of the economic burden of β-thalassemia major found that the average annual cost per patient was USD 8321.80, regardless of the cost of lost welfare.[80] A study from Thailand showed that at least one-third of the cost per patient was associated with the cost of ICT. With the current pricing of ICT, the estimated lifetime need for ICT for the entire patient population could cost up to many billions of dollars.[6]

A 2014 cost-benefit analysis of β-thalassemia prevention in northern Israel found that the cost of preventing one affected newborn was USD 63 330; in comparison, the cost of treatment for one patient over a 50-year period was USD 1 971 380.[81] Therefore, prevention of 45 affected newborns over 10 years represents a net saving of USD 88.5 million (or USD 76 million once costs of the prevention program have been deducted).[81]

4.3 | Survival

Survival rates have significantly improved in countries with adequate health resources where clinicians and patients adhere to guidelines.[32] Indeed, current therapeutic approaches with adequate blood transfusions and timely and appropriate control of iron overload have transformed a pediatric disease with short life expectancy into a chronic disease with prolonged survival.[3]

The two main factors affecting survival rates in patients with transfusion-dependent thalassemia (TDT) are lack of adequate blood transfusions, particularly in developing regions of the world, and complications due to iron overload. Worldwide, an estimated 25 500 infants with TDT are born every year; overall, only about 12% of these patients receive blood transfusions, with 2.7% of patients with TDT transfused in Africa and Western Pacific regions and 52.4% of patients with TDT transfused in the Americas.[5]

For patients who receive regular blood transfusions, iron overload can lead to significant morbidity of the heart, liver, and endocrine glands.[3] Among the nearly 100 000 patients worldwide living with TDT, only 39% receive adequate ICT, and approximately 3000 of these patients die annually because of complications related to iron overload.[5]

The risk of death due to iron overload has decreased since the introduction of ICT in 1967, when deferoxamine was first introduced, followed by the oral ICTs deferiprone and deferasirox, which were introduced in 1999 and 2006, respectively.[44,82,83] In an observational study of 539 patients with β-thalassemia in Cyprus, overall survival improved after the year 2000 [84]; updated analyses from this study demonstrate that survival to age 30 between 2000 and 2018 increased by 8 percentage points compared with the period of 1980 to 1999, and ICT with either deferiprone or deferasirox was an independent predictor of survival.[85] Increased use of hematopoietic stem cell transplantation [86] and cardiac iron monitoring with magnetic resonance imaging have also helped improve survival rates and reduce complications related to iron overload.[87]

Although rates of survival and complication-free survival continue to improve as a result of better treatment options, new complications are also emerging in long-term survivors.[83,88] In a study of 4506 patients with hemoglobinopathies registered at 43 treatment centers in Greece, the number of deaths due to β-thalassemia steadily decreased from 2000 to 2010, with heart disease (52.3%) and liver carcinoma (13.8%) being the most common causes of death.[8] An update of this registry showed that the total number of patients with thalassemia major decreased as age increased, with the majority of patients being middle-aged.[38] In a retrospective cohort study that included 911 patients with β-thalassemia in Iran, the 20-, 40-, and 60-year survival rates were 85%, 63%, and 54%, respectively.[89] Education, marital status, ferritin level, and presence of comorbidities significantly influenced survival rates.

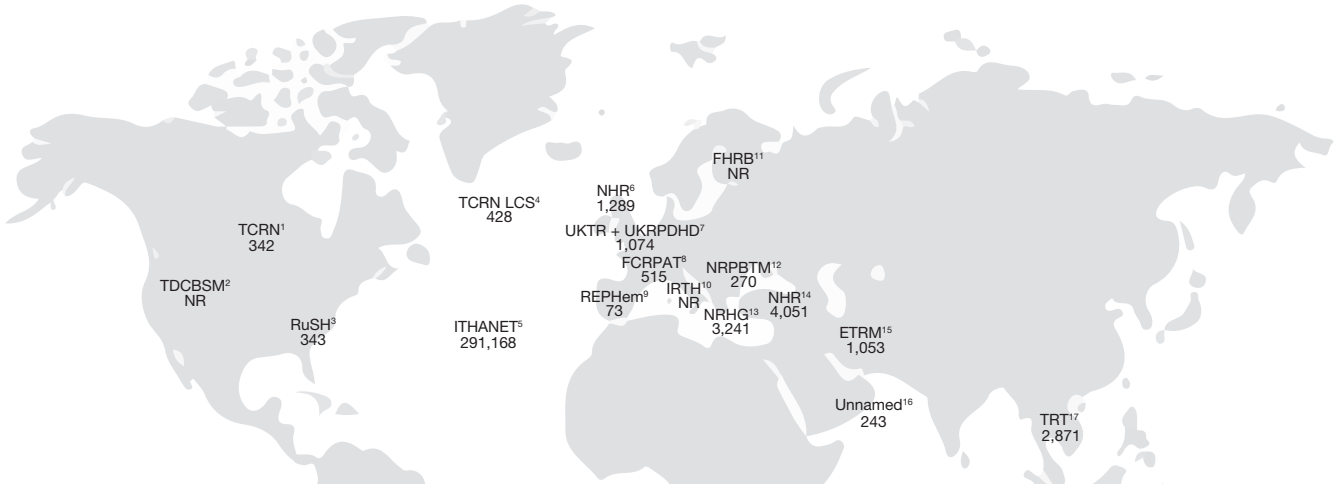

FIGURE 1 β-thalassemia registries†. 1. Thalassemia Clinical Research Network[94,95]—Canada, USA. 2. Thalassemia Data Collection and Blood Safety Monitoring—USA. 3. Registry and Surveillance System for Hemoglobinopathies[93]—USA. 4. Thalassemia Clinical Research Network Longitudinal Cohort Study[95]—Canada, UK, USA. 5. ITHANET[92]—59 countries. 6. National Haemoglobinopathy Registry[46]—UK. 7. United Kingdom Thalassaemia Register[5,44] and United Kingdom Register for Prenatal Diagnosis for Haemoglobin Disorders[44,97]—UK. 8. French Certified Registry of Patients Affected by Thalassemia[7,98]—France. 9. National Registry of Hemoglobinopathies[99]—Spain. 10. The Italian Registry for Thalassemia and Hemoglobinopathies—National Institute of Health–Italy. 11. Finnish Hematology Registry and Clinical Biobank–Finland. 12. National Registry of Patients with Beta-Thalassemia Major[36]–Bulgaria. 13. National Registry for Hemoglobinopathies in Greece[8,38]–Greece. 14. National Haemoglobinopathy Registry[100]—Turkey. 15. Electronic Thalassemia Registry Mazandaran[101]—Iran. 16. Unnamed[11]—Oman. 17. ThalRThai (V. Viprakasit, personal communication)—Thailand. † Only includes registries that offer at least partial information and/or publications in English; known numbers of patients with beta-thalassemia are shown as per publication date or August 2020, whichever came first

Comparable results were reported by Zamani and colleagues, who reported 10-, 20- and 30-year survival rates of 98.3%, 88.4%, and 80.5%, respectively.[90] In contrast, in Thailand, only 20% of patients with β-thalassemia major reached their fourth decade of life, mainly because they received inadequate blood transfusions and ICT in the past.[91] Therefore, it is unsurprising that the number of surviving patients with β-thalassemia major in the current registry was lower than one would expect based on genetic epidemiology alone (Figure 1).[5,7,8,11,38,44,63,91,92]

5 | DISCUSSION

Most of the data included in this review derives from published registries for hemoglobinopathies in general and β-thalassemia specifically (Figure 1). Registry data provide epidemiological data as well as information on the effectiveness of treatment, screening programs, and public health and education programs using one or more data sources.[11,32] As of July 2018, a total of 149 organizations from 45 countries were participating in an electronic network called ITHANET, which aims to collect data, disseminate knowledge, harmonize treatment, and coordinate research and prevention programs for hemoglobinopathies.[92]

The changing patterns of thalassemia prevalence in different parts of the world are mainly affected by changes in the number of births of new patients and are largely influenced by prevention programs, population migration, and improved survival of patients with β-thalassemia. Historically, β-thalassemia is highly prevalent in the Mediterranean, Middle East, and Southeast Asia, and migration patterns have increased the prevalence of this hemoglobinopathy in North America and Northern European countries. Importantly, the increasing prevalence in these countries has increased the burden on healthcare systems. As long as migration to these regions continues, for example, due to economic, social, or environmental reasons, the prevalence of β-thalassemia will continue to increase until the point is reached where large-scale preventive measures are implemented. The COVID-19 pandemic has significantly diminished migration, but its long-term consequences remain to be seen.

Overall, thalassemia screening programs have reduced the number of affected births, particularly in countries where β-thalassemia is prevalent. Voluntary prenatal screening is preferred in Southeast Asia and Europe, whereas in other areas, like in some Middle East countries, mandatory premarital screening exists. It is unlikely that many European countries will follow their example, as healthcare decisions are generally considered to be personal decisions in this region. An increasing number of informed couples, however, complete at-risk pregnancies due to the growing availability of supportive treatments (eg, red blood cell transfusions, oral ICT), approved therapies (eg, luspatercept), and curative options (eg, bone marrow transplantation). Although many countries have effective screening and prevention programs in place, increased focus on education and awareness is needed to identify patients and carriers and provide all patients with the care they need, in addition to offering at-risk

couples options to prevent future affected offspring. Changing national legislation to allow termination of pregnancy in case of a fetus with β-thalassemia could also play a role in reducing the occurrence of this disease. Political and religious aspects, however, may be difficult to influence, often change over time, and can result in local differences in legislation. For example, pregnancy termination was deemed legal by the US Supreme Court in 1973, but many states have since restricted its use by making it illegal for doctors to terminate the pregnancy unless the mother's life is threatened or by not allowing insurance coverage for the procedure. Furthermore, while most European countries allow termination in late stages of the pregnancy in case of an affected fetus, few countries in the Middle East and North Africa allow an abortion in case of fetal impairment.[96]

Further research is needed to determine how to best implement screening and prevention programs in each region. The most important factors, such as prevalence, access to healthcare, cultural habits, and political and religious beliefs, vary locally and require different solutions for barriers to be overcome. Analyzing determinants of effective projects that prevent hemoglobinopathies and other diseases and sharing best practices internationally can help the further development of current as well as new prevention programs.

It can be difficult to measure the specific incidence and prevalence of β-thalassemia in countries where β-thalassemia is relatively rare and no screening programs are available. Differences in methodology in data collection and reporting further limit the availability of epidemiologic data. Most studies do not differentiate between the frequency of β-thalassemia major and intermedia, while others include other hemoglobinopathies, such as sickle cell disease or α-thalassemia. Collecting and publishing data for β-thalassemia overall and for its subtypes separately will help provide more insight into the epidemiology of this disease, especially if these data were to be reported by regions within a country where relevant differences between regions exist.

For observational studies, including registries, insufficient reporting of patients as well as missing data in registries may limit the robustness of the study results. Thus far, few registries have published longitudinal data, making it difficult to draw conclusions about trends in epidemiology over time. Micromapping and longitudinal follow-up are needed to improve the knowledge and understanding of the epidemiology of β-thalassemia in traditionally non-endemic countries.

In conclusion, the patterns of β-thalassemia have changed considerably over the past decades. The implementation of prevention and screening programs has lowered the prevalence and incidence of β-thalassemia in regions with a historically high number of carriers and patients. Many cultural, political, and financial barriers to these programs still exist which often require a long time to change. In contrast, migration has resulted in an increased number of patients in regions where the disease was traditionally rare, such as North America and Northern European countries. Healthcare systems worldwide will need to continuously adjust to reduce the burden of this disease and improve the health, life expectancy, and quality of life of patients and carriers of β-thalassemia.

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CONFLICT OF INTEREST

AK received honoraria from Apo Pharma, Bristol Myers Squibb, and Novartis, and has served as a consultant for Agios, Bristol Myers Squibb, CRISPR Therapeutics, Novartis, and Vifor Pharma. GLF received research funding from Bristol Myers Squibb, Novartis, and Roche, and has served as a consultant for bluebird bio, Bristol Myers Squibb, F. Hoffman-La Roche Ltd, and Novartis. YA received research funding from Bristol Myers Squibb, Cerus, La Jolla Pharmaceutical, Novartis, and Terumo, has served on the speakers bureau on behalf of Novartis, has received honoraria from Cerus, and has participated in a data monitoring committee at CRISPR Therapeutics and scientific steering committees at Protagonist Therapeutics. VV received research funding from Agios, Bristol Myers Squibb, F. Hoffman-La Roche Ltd, Novartis, and Protagonist Therapeutics, and has served as a consultant for Agios, Bristol Myers Squibb, F. Hoffman-La Roche Ltd., Novartis, and Protagonist Therapeutics.

AUTHOR CONTRIBUTIONS

All authors have reviewed the manuscript, believe it represents valid work, and approve it for publication. All authors participated in research design, performance of the research, data analysis, and writing of the manuscript.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated during the current study.

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