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ORIGINAL ARTICLE

National registry of hemoglobinopathies in Greece: updated demographics, current trends in affected births, and causes of mortality

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Abstract

National registries constitute an invaluable source of information and contribute to the improvement of hemoglobinopathy management. Herein, we present the second updated report of the National Registry for Haemoglobinopathies in Greece (NRHG) and critically discuss the time trends in demographics, affected births, and causes of mortality. Thirty-eight Greek hemoglobinopathy units reported data from diagnosis to the last follow-up or death by retrospectively completing an electronic form. Four thousand thirty-two patients were eligible for inclusion; more than half of them had thalassaemia major. Compared to the previous report, a reduction in the total number of all hemoglobinopathies except for hemoglobinopathy "H" was evident. The total number of affected births was also reduced; most of them were attributable to diagnostic errors and lack of awareness. Importantly, data on iron overload are reported for the first time; although most patients had low or moderate liver iron concentration (LIC) values, a non-negligible proportion of patients had high LIC. The burden due to heart iron overload was less prominent. Cardiac- and liver-related complications are the major causes of morbidity and mortality. From 2000 to 2015, a decrease in heart-related deaths along with an increase in liver-associated fatalities was observed. The Hellenic Prevention Program along with advances in chelation regimens and iron status monitoring have resulted in improved patient outcomes. The NRHG gives insight into the effectiveness of prevention programs, the therapeutic management of hemoglobinopathies and associated outcomes. NRHG may contribute to the formulation of a roadmap for hemoglobinopathies in Europe and promote the implementation of effective public health policies.

Keywords Registry · Hemoglobinopathy · Thalassemia · Sickle cell disease · Greece

Introduction

Hemoglobinopathies constitute the most frequent inherited disorders worldwide. It has been estimated that up to 400,000 newborns are affected each year. Most cases occur in the Mediterranean countries, sub-Saharan Africa, the Middle East, the Indian subcontinent and the Southeast Asia; however, there are geographical variations even within the same region [1]. During the last decades, amelioration of transfusion regimens as well as monitoring and management of iron overload have led to improvement in survival and

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quality of life [2]. Despite the option of allogeneic transplantation in selected cases and the encouraging results of gene therapy [3], no definite cure is currently available in large scale.

Hemoglobinopathies have been identified as an emerging European public health issue in recent years, especially in view of the migration inflows stemming from countries with high disease prevalence [4]. Delineating the current status of hemoglobinopathies with registries can be valuable in terms of evaluating treatment protocols, preventive strategies and health system policies. Such registries may serve as a basis for addressing recommendations and formulating guidelines to enhance prevention, diagnosis, and patient care in a national, European, or even global setting [4]. In Europe, only few countries have provided data from national registries, whereas consecutive reports from the same registry are rather scarce. Furthermore, information on the impact of prevention programs, patient characteristics, long-term consequences of iron chelation treatment and deaths vary significantly among the reports [5–9].

The National Registry for Haemoglobinopathies in Greece (NRHG) was established in 2009 in order to identify and collect detailed epidemiological and clinical data of patients with hemoglobinopathies from all over the country and to demonstrate the value of a continuously updated national registry for the surveillance of health services. Following the first report including data from 2000 to 2010 [5], herein we present the data collected in the NRHG for patients with hemoglobinopathies from 2010 to 2015, unraveling the trends in demographics, affected births, and causes of mortality.

Patients and methods

The updated NRHG included all patients diagnosed with hemoglobinopathies including beta thalassaemia major (TM), beta thalassaemia intermedia (TI), hemoglobinopathy "H" (HH), sickle cell anemia (SCA), and double heterozygous HbS/β-thalassaemia (HbS/β-thal) from 2010 to 2015 in Greece. Information from the first NRHG report during 2000–2010 was also available for comparisons. Thirty-eight Greek hemoglobinopathy units reported data from diagnosis to last follow-up or death by retrospectively completing an electronic form that included the following: initials of the patients' name and their parents' names; the social insurance number; date of birth (dd-mm-yyyy); gender; genotype of the disease (if known); city/hospital; type of hemoglobinopathy, including TM, TI, HH, SCA, and HbS/β-thal. Furthermore, the number of new births and deaths of affected cases between 2010 and 2015 was registered. More specifically, the date and the reason of birth were recorded for each affected newborn, whereas the date, age, and cause of death were collected for the deceased patients. New data regarding liver and heart iron load in correlation with iron chelation status, such as (a) ferritin levels, (b) magnetic resonance imaging (MRI) T2* Liver, (c) MRI liver iron concentration (LIC), (d) MRI T2* Heart, (e) iron chelation treatment (as binary variable), and (f) splenectomy (as binary variable), were additionally included in this updated report. The data entry in the electronic database were thoroughly supervised using the unique social insurance number to prevent duplicate registrations in order to avoid overestimations, as a patient could be followed in more than one hemoglobinopathy units throughout his life, due to employment, business, or study reasons. Each patient was counted at the time of his first registration.

The study along with its ethical considerations was approved and supported by the Hellenic Society of Hematology. Oral informed consent was obtained from the patients or their parents or their next-of-kin for data inclusion.

Results

Thirty-eight hemoglobinopathy units throughout Greece provided data for the updated NRHG that had been collected from January 2010 to December 2015. The participation rate among Greek hemoglobinopathy units was 100%. The excluded patients due to lack of consent were estimated to be less than 1%. The total number of initially registered patients was 4295. However, 263 were duplicates since they had been registered by more than one different units. Therefore, the final number of recorded patients after the removal of duplicates at this second report of NRHG was 4032. Among them, 2099 (52.06%) patients were diagnosed with thalassemia major and received regular transfusions (TM), 873 (21.65%) patients were sporadically or non-transfused thalassaemic patients (TI or HH), and 1032 (25.6%) patients had sickle cell anemia (SCA) or S/β-thal, whereas 28 (0.69%) patients had no clear description of their disease.

The total number of hemoglobinopathy subtypes during 2010–2015 stratified by gender is depicted in Table 1. The corresponding data from the first NRHG report are also provided in order to make comparisons and present the relevant differences. The greatest reduction (− 16%) was shown among TM patients, while HbS/β-thal patients had the smaller reduction (− 2%). The number of TI and SCA patients also showed reduction. However, an increase of 20% was shown in patients with HH. The greatest reduction among males and females was shown in TM (− 18%) and SCA (− 17%) patients, respectively.

The total number of alive patients per age group during 2010–2015 is provided in Fig. 1 and Supplemental Table 1. 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)

Table 1 Number of hemoglobinopathy cases according to subtype and gender during 2000–2010 (January 1, 2000 to June 30, 2010) and 2010–2015 (July 1, 2010 to December 31, 2015) along with the corresponding percentage differences

	Male			Female			Total		
	2000–2010	2010–2015	%	2000–2010	2010–2015	%	2000–2010	2010–2015	%
TM	1179	967	− 18	1301	1132	− 13	2485	2099	− 16
TI	326	293	− 10	427	366	− 14	756	660	− 13
HH	87	109	25	91	104	14	178	213	20
SCA	76	67	− 12	129	107	− 17	205	177	− 14
S/β-thal	381	366	− 4	490	483	− 1	875	855	− 2

Patients with missing data on sex or disease subtype are not included

TM thalassemia major, *TI* thalassemia intermedia, *HH* hemoglobinopathy "H", *SCA* sickle cell anemia, *S/β-thal* double heterozygous HbS and β-thal

patients, including SCA and S/β-thal. HH patients were widely distributed among more than two age groups. Interestingly, there are also patients older than 61 years in all age groups. Among disease subgroups, TI and HH showed the highest percentage of patients older than 61 years (18.9% and 18.4%, respectively), whereas TM had the lowest (1.3%).

Data on splenectomy status were available for 69.9% of the included patients. The highest splenectomy percentage was shown among TI and TM patients ($n = 250$, 46.82% and $n = 659$, 46.08%, respectively), whereas the lowest among HH patients ($n = 16$, 10.26%).

Data on ferritin levels were available for more than one third of the patients included in the registry. Importantly, more than half of TM and TI patients had ferritin levels less than 1000 ng/dl, whereas less than 14% of the cases had very high ferritin values (above 3000 ng/dl) in all subgroups.

Among registered patients, 28.4% had available data on LIC (Table 2). Among TM patients, 51.8% had LIC less than 3 mg/g/dw and 14.7% had LIC higher than 15.1 mg/g/dw. The corresponding percentages for TI patients were 36.4 and 11.5%, respectively. Furthermore, LIC values according to age groups are depicted in Table 3. Most patients had LIC values less than 7 mg/g/dw in almost all age groups.

Information about iron chelation therapy was available for 2230 (55.3%) of the registered cases (Table 4). Overall, 1603 (71.9%) patients received treatment with chelation agents

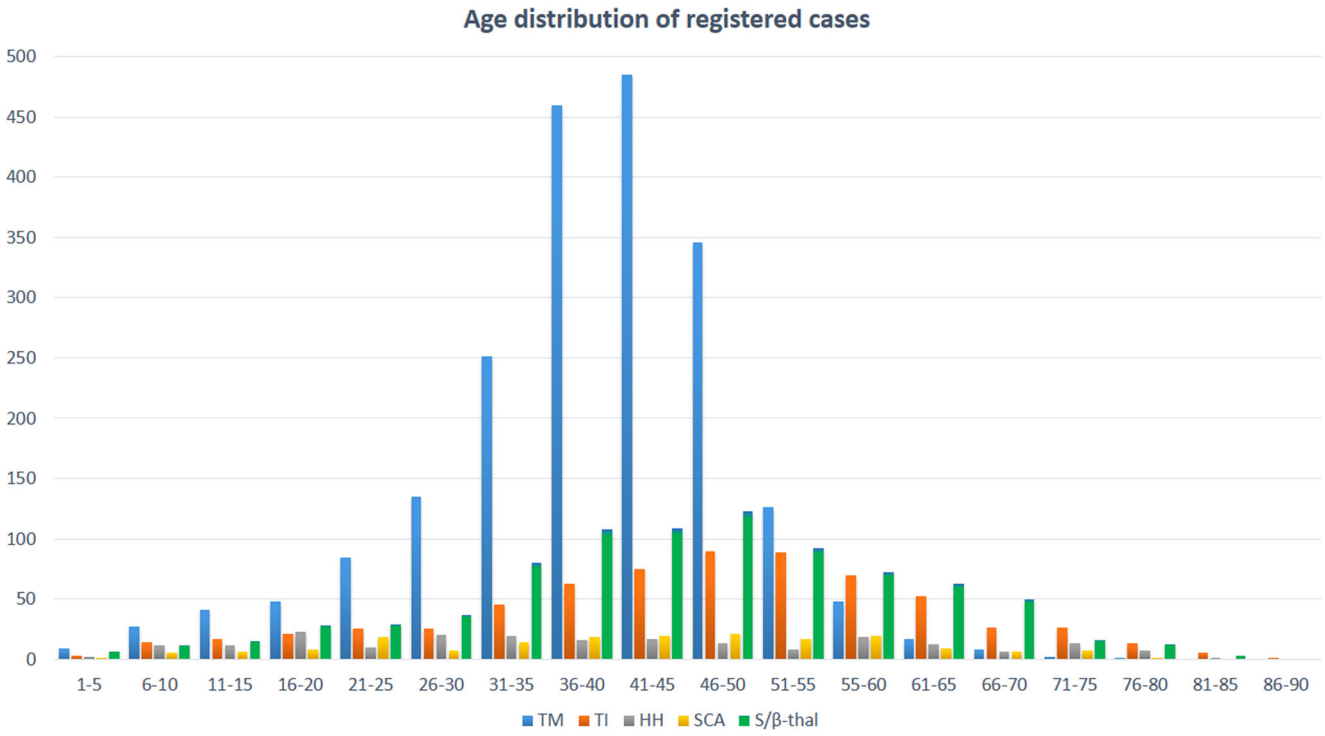

Fig. 1 Distribution of registered cases in the NRHG according to age groups. The peak of patient distribution corresponds to the age group of 36–45 years regarding TM, 46–55 years among TI, and 41–50 years among SCD patients. TM thalassemia major, TI thalassemia intermedia, HH hemoglobinopathy "H", SCA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

Table 2 Patient distribution according to liver iron concentration (LIC) values and disease subtype

	TM (*n*)	%	TI (*n*)	%	HH (*n*)	%	SCA (*n*)	%	S/β-thal (*n*)	%
LIC < 3 mg/g/dw (*n* = 543)	423	51.84	76	36.36	5	50.00	7	43.75	32	34.41
LIC 3.1–7 mg/g/dw (*n* = 239)	150	18.38	61	29.19	0	0.00	3	18.75	25	26.88
LIC 7.1–15 mg/g/dw (*n* = 207)	123	15.07	48	22.97	5	50.00	4	25.00	27	29.03
LIC > 15.1 mg/g/dw (*n* = 155)	120	14.71	24	11.48	0	0.00	2	12.50	9	9.68
Total (*n* = 1144)	816		209		10		16		93	

TM thalassemia major, *TI* thalassemia intermedia, *HH* hemoglobinopathy "H", *SCA* sickle cell anemia, *S/β-thal* double heterozygous HbS and β-thal

during 2010–2015. More specifically, among TM, TI, HH, SCA, and S/β-thal patients, 98.3%, 61%, 16.5%, 11.9%, and 17.1% were under chelation therapy, respectively.

The distribution of patients under chelation therapy according to their LIC values and disease subtype is shown in Table 5. Among TM and TI patients, 14.8% and 11.1% had LIC values above 15.1 mg/g/dw, respectively, whereas 14.6% and 25.2% between 7.1 and 15 mg/g/dw, respectively.

Details on heart iron overload (T2*) were available for 1078 (26.7%) patients (Table 6). Only 6.1% of TM and 6.9% of TI patients presented severe iron overload (MRI T2* Heart < 9 ms), whereas 7.4% of TM and 7.5% of TI cases showed moderate iron overload (MRI T2* Heart 10–19 ms). The vast majority of patients had normal MRI T2* Heart values > 20 ms in all disease subgroups.

The total number of affected births was 110, 74, and 114 during 2001–2005, 2006–2010, and 2011–2015, respectively (Table 7). There was a notable increase of affected births during 2011, in which 15 new TM, 13 new TI, and 17 new HH were registered. From 2012 to 2015, new hemoglobinopathy cases declined steadily. Table 8 shows the annual number of affected births according to the main causes during 2010–2015. The main causes of affected births during the period 2010–2015 were as follows: (1) laboratory, diagnostic, or obstetrician error (inadequate control, wrong or incomplete parent-mother control, non-control of alpha-globin genes, wrong evaluation of electrophoresis) (21.4%); (2) absence/unawareness of screening tests (due to obstetricians' malpractice or unknowledge about screening test, no father or mother tested, no prenatal diagnosis, or late arrival of the couple after the 23nd week of pregnancy) (18.6%); (3) social reasons (poor social environment, parental decision, refusing prenatal diagnosis, adoption, illegitimate child—out of marriage) (18.5%); (4) absence or misleading genetic counseling (10%); (5) religious reasons (2.9%); (6) lack of gametes donor's screening during in vitro fertilization (IVF) (2.1%); (7) not specified (26.4%).

The causes of deaths among thalassaemia, including TM and TI, and SCD, including SCA and S/b-thal, patients during 2010–2015 compared to 2000–2010 are depicted in Table 9. Regarding the total number of registered patients between 2000 and 2015, median (range) age at death was 44.1 (4–87). Among patients with thalassaemia, 28.1% and 51% of deaths were attributable to heart disease during 2010–2015 and 2000–2010, respectively, whereas liver disorders [hepatocellular carcinoma (HCC) and liver failure] led to 23.4% and 18.5% of the total number of deaths in the two time periods, respectively. In this second NRHG report, microbial infections were considered responsible for 6.6% of reported deaths, as compared to 7.2% in the first NRHG report. Supplemental Figure 1 and Supplemental Table 2 show the time trend of number of deaths of thalassemia patients due to heart and liver disease separately between 2000 and 2015. A reduction in the number of deaths attributable to heart disease and an increase in those attributed to liver disorders is evident. More specifically, heart-related deaths were significantly reduced during

Table 3 Patient distribution (*n*) according to liver iron concentration (LIC) and age groups (*n* = 1144)

	0–5	6–10	11–15	16–20	21–25	26–30	31–35	36–40	41–45	46–50	51–55	56–60	61–65	66–70	71–75	76–80	81–85
LIC < 3 mg/g/dw (*n* = 543)	0	3	4	8	11	8	37	105	151	110	57	29	8	5	3	4	0
LIC 3.1–7 mg/g/dw (*n* = 239)	1	2	5	5	6	10	21	44	55	40	23	13	6	3	4	1	0
LIC 7.1–15 mg/g/dw (*n* = 207)	0	0	5	6	5	1	32	46	34	27	20	10	11	4	3	2	1
LIC > 15.1 mg/g/dw (*n* = 155)	0	0	0	1	7	16	25	41	24	20	8	2	4	4	1	2	0

Table 4 Patient distribution according to the administration of chelation therapy and disease subtype

	TM	%	TI	%	HH	%	SCA	%	S/β-thal	%
Iron chelation yes	1288	98.32	225	60.98	15	16.48	8	11.94	67	17.05
Iron chelation no	22	1.68	144	39.02	76	83.52	59	88.06	326	82.95
Total ($n = 2230$)	1310		369		91		67		393	

TM thalassemia major, *TI* thalassemia intermedia, *HH* hemoglobinopathy "H", *SCA* sickle cell anemia, *S/β-thal* double heterozygous HbS and β-thal

2000–2006 and remained stable thereafter, whereas liver-related deaths rise steadily from 2000 to 2015. Among SCD patients, the main causes of death during 2010–2015 were heart disease (14.9%), liver disorders (14.9%), and stroke (13.4%). Compared to 2000–2010, an increased trend in renal failure and heart disease was noted, whereas decreased percentages were shown in pulmonary disease (emboli/hypertension), stroke, and malignancy. Importantly, it should be noted that hepatocellular carcinoma is among the major causes of death in all hemoglobinopathy subgroups. As depicted in Supplemental Figure 2, the majority of deaths were observed among patients with TM between 46 and 50 years of age followed by the 41–45 age group, while for TI patients, the majority of deaths were observed between 61 and 65 years of age.

Discussion

This second NRHG report presents the updated data (2010–2015) of the collaborative effort of Greek clinicians to provide an overview of hemoglobinopathies status in Greece. Importantly, previously unpublished data regarding heart and liver iron load in correlation with iron chelation status are being also reported. Furthermore, it describes the time trends in births and deaths and depicts their dynamic change.

Among the 4032 patients included in this report, more than half suffered from TM, a quarter of them had SCD and one fifth of them were diagnosed with TI or HH. Compared with the first NRHG report (2000–2010) [5], a decrease by 16%, 13%, 14%, and 2% was clearly shown regarding TM, TI, SCA, and S/β-thal cases, respectively. This may be attributed to the effectiveness of the continuously improving prevention program that is being implemented in Greece during the last four decades, along with the deaths of existing patients. Indeed, the number of affected births had a decreasing trend during 2010–2015 and it was lower than the previous decade. However, the number of HH patients was increased by 20%. HH has a relatively benign disease course and, therefore, parents may opt for the continuation of pregnancy during prenatal counseling. Another reason may lie in the underreporting of HH in the first NRHG report in combination with a more complete report rate in the current report.

The reported causes of affected births have been substantially differentiated compared to the previous report [5]. Laboratory, diagnostic, or obstetrician errors are jointly present at the top of the list, followed by absence and/or unawareness of screening tests. In contrast, lack of medical care due to financial reasons or low educational level was considered as the primary cause for more than one third of the affected births during 2000–2010 [5].

Prevention of affected births constitutes the mainstay of the armamentarium against hemoglobinopathies, taking into consideration that no radical cure is currently available for the vast majority of patients. Disease awareness among the general population and health professionals along with timely recognition of carriers, genetic counseling, and the possibility of prenatal testing or pre-implantation diagnosis are key elements in disease prevention. Their importance is highlighted in countries with relatively high prevalence of hemoglobinopathies. In Greece, a well-organized prevention program has been established since 1974 and is universally effective during all these decades. In the absence of any prevention measures, 150 to 200 births would have been expected each year; however, only 319 affected births were reported during 2000–2015 instead of 2250–3000.

Population prenatal screening in Greece is implemented by the National Thalassaemia Center and its collaborating network. Screening is addressed to all couples at reproductive age. The principal aim is to identify carriers and couples at risk of giving birth to an affected child. Screening methods include full blood count and biochemical analysis including

Table 5 Distribution of patients (n) undergoing iron chelation treatment according to their liver iron concentration (LIC) values and disease subtype

	TM	TI	HH	SCA	S/β-thal	Total
LIC < 3 mg/g/dw	415	50	3	2	8	478
LIC 3.1–7 mg/g/dw	147	36	0	1	11	195
LIC 7.1–15 mg/g/dw	116	34	2	1	12	165
LIC > 15.1 mg/g/dw	118	15	0	0	4	137
Total	796	135	5	4	35	975

TM thalassemia major, *TI* thalassemia intermedia, *HH* hemoglobinopathy "H", *SCA* sickle cell anemia, *S/β-thal* double heterozygous HbS and β-thal

Table 6 Distribution of patients with available data according to T2* Heart (T2*H) values stratified by disease. T2*H > 20 ms is considered normal

	TM	%	TI	%	HH	%	SCA	%	S/β-thal	%
T2*H > 20 ms $n = 938$	698	86.49	125	85.62	11	84.62	10	100.00	94	92.16
T2*H 10–19 ms $n = 81$	60	7.43	11	7.53	2	15.38	0	0.00	8	7.84
T2*H < 9 ms $n = 59$	49	6.07	10	6.85	0	0.00	0	0.00	0	0.00
Total: $n = 1078$	807		146		13		10		102	

TM beta thalassemia major, *TI* beta thalassemia intermedia, *HH* hemoglobinopathy "H", *SCA* sickle cell anemia, *S/β-thal* double heterozygous HbS/β-thalassaemia

quantitative analysis of hemoglobin by HPLC or capillary electrophoresis. Genetic counseling is provided at couples at risk which are advised toward identification of the underlying globin gene mutations through molecular testing. All these tests are offered free of charge according to the current national legislation. In cases of ongoing pregnancy, couples at risk are offered prenatal testing usually around the 12th week of gestation, followed by genetic counseling. The reported epidemiological trends may be partially attributed to the gradual but universal implementation of screening guidelines in Greece. As experience accumulates, greater compliance among both care providers and patients is feasible. Therefore, the Hellenic Prevention Program (HPP) may serve as a model for other European countries with historically low disease prevalence that face the problem of increasing affected births mainly due to migratory flows in the recent years. Compared with other European countries that usually offer neonatal screening aiming to the early treatment initiation, the HPP is focused on carrier detection in order to ultimately decrease the number of affected births.

As aforementioned, NRHG also unravels the causes of affected births and provides the basis for suggesting further improvements. Awareness programs all over the country are considered indispensable in order to educate both the public and health carriers and formulate informed attitudes and perceptions toward hemoglobinopathies. Furthermore, a national quality control system, assuring both the qualification of specialized laboratory geneticists along with the implementation of national guidelines by certified laboratories, would eliminate laboratory-associated diagnostic mistakes. In this context, an increasing number of private laboratories that offer both population screening test and prenatal molecular analysis has to be noted during the last years. Unfortunately, a rigorous quality control system in the private sector has not been universally implemented yet. Thus, the reported increase of affected births in 2011 might be partially attributed to prenatal misdiagnosis by such laboratories, which temporally coincides to the increase in the number of private centers.

Therapeutic advances including better monitoring and management of the complications have increased the life expectancy of individuals with hemoglobinopathies. The improved survival of patients is also attributable to the oral iron chelation treatment improvements, including the combined chelation regimens, along with the early detection of iron overload with serial biochemical assessments and the introduction of heart and liver MRI [6, 10]. One quarter of all patients survive up to 55 years, whereas several registered patients are older than 61 years in all hemoglobinopathy groups, which is also observed in other European registries. According to an Italian study lasting 25 years that included data from 977 patients with TM, 68% of the affected individuals were alive at the age of 35 [11]. Patients born in the more

Table 7 Total number of affected births according to disease subtype during 2001–2005, 2006–2010, and 2011–2015. Detailed data are provided for the years 2010–2015

	2001–2005	2006–2010	2011–2015	2010	2011	2012	2013	2014	2015
Total cases	110	74	114	26	54	19	16	16	9
TM	59	25	45	6	15	11	6	9	4
TI	14	15	21	8	13	3	0	1	4
HH	12	13	24	8	17	3	3	1	0
SCA	9	7	8	4	2	0	4	2	0
S/β-thal	16	9	9	0	5	2	2	0	0
N/S	0	5	6	0	2	0	1	3	1

TM thalassemia major, *TI* thalassemia intermedia, *HH* hemoglobinopathy "H", *SCA* sickle cell anemia, *S/β-thal* double heterozygous HbS and β-thal, *NS* not specified

Table 8 Annual number of affected births according to the main causes during 2010–2015

	2010	2011	2012	2013	2014	2015	Total
Not specified	4	8	4	8	9	4	37
Absence or misleading genetic counseling	0	8	4	0	2	0	14
Absence/unawareness of screening tests	4	9	5	4	3	1	26
Laboratory, diagnostic, or obstetrician error	10	14	3	2	0	1	30
Religious reasons	3	1	0	0	0	0	4
Social reasons	4	13	3	1	2	3	26
Lack of gametes donor's screening in IVF	1	1	0	1	0	0	3
Total	26	54	19	16	16	9	140

IVF in vitro fertilization

recent years had improved both overall and complication-free survival [11, 12]. Another Greek study has supported that the expected survival of a TM patient born after 1975 who is treated with regular transfusions and appropriate chelation may exceed the 50 years [13]. However, the need for lifelong medical care significantly adds to the economical burden of the disease [5]. Thus, restricting affected births to the minimum may allow the health authorities to provide the best supportive care to patients.

Regarding patients with SCD, our data show that most registered patients belong to the 35–55 age group, whereas there is a significant number of alive patients older than 61 years. These results confirm older reports stemming from the USA and UK supporting an improvement in the survival of SCD individuals [14, 15]. In a recent study conducted in the USA approximately 95% of neonates with SCD reach age 18 years; nevertheless, adults suffering from severe forms of SCD have a life span that is 20–30 years shorter than the general population [16, 17].

One of the most important causes of morbidity and mortality is iron overload. Regular transfusions and increased intestinal iron absorption are the main reasons of excessive iron levels among patients with TM and TI, respectively. Iron overload constitutes a cumulative process with advancing age, has an additive impact on the function of vital organs, such as heart and liver, and ultimately leads to life-threatening complications or even death. In the current study, data regarding iron overload indices among Greek patients with hemoglobinopathies are reported for the first time.

Serum ferritin levels have been traditionally used for monitoring iron overload since they reflect total iron storage in the body. In this NRHG report, less than 14% of the registered

Table 9 The causes of deaths among thalassaemia (TM and TI) and sickle cell disease (SCA and S/b-thal) patients during 2000–2010 (January 1, 2000 to June 30, 2010) and 2010–2015 (July 1, 2010 to December 31, 2015), expressed as absolute numbers (percentage)

	THAL 2000–2010		SCD 2000–2010		THAL 2010–2015		SCD 2010–2015	
	n	%	*n*	%	*n*	%	*n*	%
Pulmonary embolism	5	3.31	10	11.1	8	4.79	5	7.46
Acute chest syndrome	1	0.66	0	0	0	0	4	5.97
Heart disease	77	50.99	8	8.89	47	28.14	10	14.93
HCC	19	12.58	9	10	28	16.77	2	2.99
Liver failure	9	5.96	13	14.44	11	6.59	8	11.94
Stroke	7	4.64	14	15.56	5	2.99	9	13.43
Renal failure	1	0.66	4	4.44	8	4.79	6	8.96
Sickle cell crisis	0	0	3	3.33	0	0	0	0
Multiorgan failure	1	0.66	2	2.22	2	1.20	1	1.49
Microbial infections	10	6.62	7	7.78	12	7.19	5	7.46
Malignancy other than HCC	8	5.30	7	7.78	10	6.00	4	5.97
Other causes (HIV, car accident)	9	5.96	7	7.78	14	8.38	5	7.46
Unknown causes: cardiac arrest	0	0	0	0	17	10.18	6	8.96
Unknown causes	4	2.66	6	6.68	5	2.98	2	2.98
Total	151	100	90	100	167	100	67	100

NA not available, *THAL* thalassaemia, *SCD* sickle cell disease, *HCC* hepatocellular carcinoma

patients had very high ferritin values across all disease subgroups. In the recent years, MRI using T2* sequence has become the most common modality to diagnose and evaluate myocardial and liver iron concentration specifically. Herein, the majority of patients had normal MRI T2* Heart values > 20 ms in all disease subgroups. The value of cardiac MRI is highlighted by the reduction in the risk of heart-related death that is shown following the first MRI examination [18]. Apart from the efficacy of iron chelation and the risk of cardiac mortality, heart MRI can provide useful information regarding patient compliance and, therefore, help clinicians to adapt treatment strategies and educate patients [19].

In our report, more than 50 and 30% of TM and TI patients, respectively, had an LIC value less than 3 mg/g/dw. In both patient groups, less than 15% had LIC values higher than 15.1 mg/g/dw. Interestingly, a non-negligible number of thalassaemia patients presented with moderate to severe LIC. According to most current guidelines the target LIC should be between 3 and 7 mg/g/dw [20]; however, the Greek guidelines encourage the further decrease of LIC values to less than 3 mg/g/dw. Furthermore, high level of treatment compliance among the Greek patients also contributes to the reported low LIC values. However, it has to be noted that a small proportion of patients had data available on LIC values and were included in the corresponding analyses. Thus, the interpretation and generalization of the results should be cautious, since the possibility of referral bias cannot be entirely ruled out. Accumulating evidence points to the fact that there is an increased incidence of morbidities at LIC values above 6 mg/g/dw even among patients with TI [21, 22]. Taking into consideration all the above, a monitoring and treatment algorithm has been proposed. Chelation treatment should start in all patients with serum ferritin levels above 800 ng/mL and those between 300 and 800 ng/mL and LIC above 5 mg/g/dw. All patients with serum ferritin levels 300–800 ng/mL should be yearly monitored with MRI T2* Liver [22]. Serum ferritin levels along with liver and heart MRI T2* evaluation have a strong prognostic and predictive value for development of complications [23].

Close monitoring and early initiation of chelation therapy are considered as the backbone of preventing and even reversing the complications due to iron overload. In our report, 98% of TM and 61% of TI patients were under iron chelation therapy. Most of these patients had LIC values below 7 mg/g/dw. However, more than 10% had severe LIC, which underlines the need for optimization of chelation strategies throughout the country based on consensus national guidelines. Oral iron chelation regimens contribute to the elimination of noncompliance that is seen due to the chronic patient discomfort. There is high-quality evidence supporting the effectiveness of different regimens against iron overload and its complications, as well as the survival benefit especially for TM patients [24].

Heart- and liver-related deaths are the major causes of mortality among thalassaemia and SCD patients. Cardiac disease was considered responsible for the majority of the deaths among thalassaemia patients during 2000–2010 and remained at the top of the list during 2010–2015. This finding is in accordance with the data reported by other registries [9, 11, 25]. However, there is a clear decrease in the number of deaths attributable to heart disease in the second NRHG report compared to the first one [5], which confirms similar trends reported in Italian and UK registries [11, 25]. Clinician sensibilization on management of myocardial overload along with the active surveillance of MRI findings and the improvement of chelation regimens have contributed to the decline in heart-related death rates [26]. Iron overload, hepatitis infection, and liver neoplasms are associated with liver cirrhosis and subsequent liver failure that may lead to death [26]. In NRHG, liver disorders constitute the second leading cause of death among thalassemia patients with an increasing trend from 2004 onwards. Furthermore, it should be noted that the dynamics of iron deposition and clearance differ significantly between liver and heart. Changes in cardiac iron status present a longer time lag than those in liver iron status; thus, cardiac and liver iron burden may vary [27, 28]. Thus, at the time of initiation of chelation therapy, iron overload may have already induced liver damage, whereas the heart is spared. Regarding SCD, the observed increase in heart-related deaths in the second NRHG report may be a consequence of both underlying coronary artery disease and iron overload due to transfusions. Although it has been shown that SCD patients undergoing chronic transfusions may not present significant heart iron loading, suboptimal management of iron overload can be potentially fatal [29, 30]. However, our data on cardiac MRI did not reveal any significant burden that could justify the increased heart-related deaths, despite the limited number of patients with available information. Furthermore, it should be noted that the increased life expectancy of SCD patients results in the development of cardiovascular complications, such as pulmonary hypertension, vasculopathy, and heart dysfunction, that are significant risk factors for cardiac-related mortality [31]. A large proportion of the observed deaths may be attributed to coronary artery disease leading to fatal outcomes. Thus, the need for robust surveillance programs and regular monitoring of cardiovascular indices among hemoglobinopathy patients should be repeatedly highlighted.

Microbial infections are the third leading cause of death among patients with thalassaemia and SCD, which is in accordance with other reports, as well [32–34]. Early identification and prompt management of infections can reduce the associated morbidities and mortality [35]. Recognized predisposing factors for microbial infections include splenectomy, iron overload, severe anemia, facial deformities, gallstones, and advanced age [35–37]. Splenectomy is a major risk factor and mainly predisposes to infections due to Gram-negative

microorganisms [38, 39]. In this NRHG report, almost half of thalassaemia patients had undergone splenectomy. From a pathophysiological aspect, complex alterations in cell-mediated immunity due to chronic blood transfusions and immune activation along with iron overload ultimately result in functional deregulation of immune system and susceptibility to infections [40]. Antibiotic prophylaxis along with adherence to vaccination program should be strongly considered to prevent infections, especially among patients with SCD [41].

Furthermore, the NRHG revealed the emerging problem of HCC-related deaths among patients with hemoglobinopathies. Although most events were observed among TM patients belonging to the 41–50 age groups, cases younger than 40 years old were also registered, while for TI patients, the majority of deaths were observed between 61 and 65 years of age. HCC represents the third most frequent cause of cancer-related death globally and its management is rather challenging [42]. HCC development is multifactorial including exposure to hepatitis viruses, whereas the time length of exposure is proportionate to HCC risk [43]. Thus, exposure of hemoglobinopathy patients due to transfusions early in life may lead to HCC presentation at a young age. In this context, surveillance and high clinical suspicion is of outmost importance, since they can significantly improve patient prognosis [44].

A possible limitation of the second NRHG report may pertain to the missing data in several variables in relation to the total number of registered patients. Although important and original results have been derived from the available information, their robustness could be improved. Furthermore, there was no other independent data source available in order to externally evaluate patient inclusion rate. In this context, national health authorities should closely monitor and necessitate the complete report of all patient data in favor of public health. Moreover, the necessary equipment and high-quality services should become universally available.

In conclusion, the continuously updated registry of hemoglobinopathies in Greece may contribute to reveal the current number, status, and quality of life indices of patients; help the national health authorities in formulating more effective policies; and have a close overview of the registry in order to assure more complete reporting of data, improve health care providers and public awareness regarding prevention and prenatal testing, and establish national guidelines and quality standards for genetic counseling and prenatal testing. Furthermore, NRHG could provide a conceptual framework for other European and Mediterranean countries to determine strategies to effectively manage the increasing incidence of hemoglobinopathies.

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Authors' contributions E. Voskaridou was the principal investigator and designed the study. E. Voskaridou and I. Papassotiriou took primary responsibility for the paper and wrote it. All authors collected and analyzed the data. E. Voskaridou and I. Papassotiriou performed the statistical analyses. All authors contributed to the critical revision and approved the version to be published.

Compliance with ethical standards

The study along with its ethical considerations was approved and supported by the Hellenic Society of Hematology.

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Human participants and/or animals For this type of study, formal consent is not required.

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