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LETTER TO THE EDITOR

Prevalence and mortality trends of hemoglobinopathies in Italy: a nationwide study

Short title: Hemoglobinopathies in Italy

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DATA SHARING AND DATA AVAILABILITY

Data can be made available upon reasonable request to the corresponding author.

AUTHORS CONTRIBUTIONS

Study conception and design: BG, AG, GLF. Data collection: BG, SB, MC, EC, RDM, AG, MRG, GG, RL, FL, AM, RO, AP, SP, AGP, VMP, RR, GRo, GRu, MZ. Statistical analysis: BG, FBP. Review and interpretation of results: FBP, KMM, LDF, GLF. Manuscript drafting: BG, FBP, LDF, KMM. Manuscript review for important

intellectual content: all authors. All authors approved the manuscript before submission.

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CONFLICTS OF INTEREST

All authors declare that they have no conflicts of interest.

Data on the global burden of hemoglobinopathies, including the thalassemias and sickle cell disease (SCD), are mostly derived from modelling estimates of carrier frequencies and may not necessarily reflect the actual prevalence of clinically significant forms.[1-4] Survival data are also limited to select cohorts, which may not represent the entirety of the patient population in the country.[5-7] The life expectancy and geographical distribution of the thalassemias and SCD in Italy has considerably changed due to advances in management, patients' mobility, and migration fluxes.[6, 8, 9] We herein present the first nationwide cross-sectional survey to assess the prevalence of hemoglobinopathies in Italy. Survival trends were also compared to the general population using a cohort of patients followed over 50 years at reference centers.

Following the constitution of the "National Network of Thalassemia and Hemoglobinopathies" (Legge 205/17, art1, comma 437), we conducted a cross-sectional national survey in December 2019 through the "Società Italiana Talassemie ed Emoglobinopatie" (SITE) aided by the ForAnemia Foundation and the "Associazione Italiana di Emato-Oncologia Pediatrica" (AIEOP). The survey was conducted in adherence with national regulations and data protection policies. Following identification of healthcare facilities that cared for hemoglobinopathies, data were collected on the current number of alive patients, their age (grouped as 0-5, 6-18,19-35,36-50,51-65, ≥66 years), sex (male *vs* female), and hemoglobinopathy type. We categorized patients as having transfusion-dependent thalassemia (TDT), non-transfusion-dependent thalassemia (NTDT), and SCD using standard international criteria. Patients identified in this survey are hereafter referred to as the 'survey population'.

To estimate survival and cause-specific mortality trends, we also conducted a retrospective cohort analysis of all patients attending eight of the regional reference centres from 1970 onwards who were followed until death, loss to follow up, or December 2019; the eight centers were distributed across the entire Italian territory (hereafter referred to as the 'survival cohort'). The survival cohort analysis was based on databases approved by the Ethical Committees of the participating centers. Kaplan-Meier survival curves were constructed to estimate median survival, and the long-rank test was used for comparisons. Demographics and mortality of the general Italian population from the year 2019 were used for comparisons and obtained from the official ISTAT database (http://dati.istat.it/). Causes of death were classified according to the primary cause based on the ICD-10 code recorded on death certificates, to allow comparisons with the general population. For each cause of death, we calculated the proportionate mortality ratio (PMR) between hemoglobinopathies and the general population considering four different age groups (0-19, 20-39, 40-59, ≥60 years), adapted to previous data on life expectancy of hemoglobinopathy patients.[10] The overall risk of death in hemoglobinopathies was also compared to the general population using the age-standardized mortality ratio (SMR), based on the number of deaths reported for each hemoglobinopathy compared to counts which would be expected if survival was similar to the general population and considering 15 age groups (0-4, 5-9, …, 65-69, ≥70 years) for indirect standardization. The level of significance was set at 0.05.

The national survey was voluntary and a total of 131 facilities responded, involving all Italian regions. Twenty-three (17.6%) were recognized regional reference centers.

Patients with hemoglobinopathies were identified from blood banks (35.9% of facilities), hematology-oncology units (25.2%), pediatric units (20.6%), internal medicine units (10.7%), and other units (7.6%) (**Figure 1A**). A total of 9,517 patients with hemoglobinopathies were identified, including 5,205 TDT (54.7%), 1,964 NTDT (20.6%), and 2,348 SCD (24.7%).

The national density of patients with hemoglobinopathies in Italy was 16.0 patients/100,000 inhabitants: 8.7 patients/100,000 inhabitants for TDT, 3.3 patients/100,000 inhabitants for NTDT, and 3.9 patients/100,000 inhabitants for SCD. There was a heterogeneous distribution across the country with the highest prevalence of TDT in Sardinia, Sicily, and Calabria (South) (55.5, 27.5, and 16.6 patients/100,000 inhabitants, respectively), of NTDT in Sardinia, Liguria (Northwest), and Sicily (23.3, 8.5, and 7.8 patients/100,000 inhabitants, respectively), and of SCD in Sicily (8.8 patients/100,000 inhabitants) and the Northern regions of Italy (Liguria: 6.9, Veneto: 6.5, Piedmont: 6.3 patients/100,000 inhabitants) (**Figure 1B**, **Table 1**). The thalassemia allele is very frequent in the Southern (mediterranean) regions of Italy and on the Islands (Sardinia and Sicily) due to historic association with endemic malaria and population migrations, while SCD is endemic only in limited areas of the South and in the North in view of more recent immigration.

The highest proportion of patients was in the age group 36-50 years for both TDT and NTDT and in the age group 6-18 years for SCD. Males were significantly fewer than females both in TDT (males: 47.2%, 95% confidence interval [CI]: 45.8-48.6%; females: 52.8%, 95%CI: 51.4-54.2%) and NTDT (males: 45.6%, 95%CI: 43.4-47.9%; females: 54.4%, 95%CI: 52.1-56.6) (Chi-squared p <0.001); while no difference in

sex distribution was observed for SCD (males: 48.5%, 95%CI: 46.4-50.5%; females: 51.5%, 95%CI: 49.5-53.6) (Chi-squared p = 0.14) (**Figure 1C**). There was higher patient clustering under 50 years for both males and females compared to the general population (**Figure 1C**). We observed ageing of thalassemia due to a decrease of new births in the last 20 years, driven by the prevention program which started in the 1980s.[11, 12] A similar effect of the prevention program has been achieved in SCD for patients of local origin[13], although not reflected by the age distribution due to recent migration fluxes. Approximately, 80% of the SCD population under 30 years is of non-Caucasian origin.[13]

The survival cohort consisted of 4,207 patients (2,574 TDT, 818 NTDT, 815 SCD). Kaplan-Meier survival curves for the entire survival cohort and by hemoglobinopathy type and sex are illustrated in **Figure 2**. TDT patients showed shorter survival compared to both NTDT (p <0.0001) and SCD (p <0.0001) while survival was comparable between NTDT and SCD (p = 0.064). Females had better survival than males in TDT (overall median survival: 71.2 years, females: 71.8, males: 68.8), which has been previously attributed to better tolerance to iron toxicity.[6] No differences in survival were found between sexes for NTDT (overall median survival 95%CI low limit: 79.5 years, females: 79.5, males: 74.8) and SCD (overall median survival 95%CI low limit: 73.4 years, females: 72.4, males: 73.4). Our data are commensurate with survival reports from other Western countries.[6]

A total of 555 deaths (472 TDT, 51 NTDT, 32 SCD) were recorded in the survival cohort over the entire period of observation. Comparison of observed and expected deaths estimated a substantially increased risk of death for TDT (SMR = 9.0, 95%CI:

8.2-9.8) and SCD (SMR = 1.6, 95%CI: 1.1-2.2) compared to the general population. The SMR for NTDT was 0.9 (95%CI: 0.7-1.2) (**Supplementary Table S2**). Using 2019 data from the general population to inform expected deaths over the entire period of observation of the study cohort may be a limitation. However, even when mortality data for hemoglobinopathies were restricted to the last five years of observation (2015-2019), the same trends were observed with an SMR of 3.61 (95%CI: 2.71-4.51) for TDT, 2.26 (95%CI: 1.03-3.49) for SCD, and 0.80 (95%CI: 0.38-1.22) for NTDT. **Supplementary Figure S1** illustrates heatmaps for analysis of PMR calculated using the general population as reference.

The Italian public healthcare system is accessible to most patients in the country, making it feasible to identify patients through nationwide surveys of healthcare facilities. We relied on a catchment area that covered all provinces in Italy, allowing generalizability of retrieved prevalence data to reflect the true epidemiology of hemoglobinopathies across Italy. One limitation of our study was that participation in the survey was voluntary, so the possibility that some facilities did not take part cannot be excluded. This limitation is less relevant for TDT patients because they are regularly followed at facilities included in the SITE network. The situation is different for NTDT and SCD, especially with mild phenotypes, who are not continuously followed at specialized centres with sporadic access to emergency departments for acute events. This is also supported by a real-world study from Italy which reported that patients with SCD are unrecognized and undertreated.[9] Our data are aligned with previous estimations.[14] The Global Burden of Disease study estimates that for the year 2019, counts for Italy were 6497 (95%CI: 5432-7602) for thalassemia (compared with 7169 TDT/NTDT patients in this survey) and 2675

(95%CI: 2354-3015) for SCD (compared with 2348 SCD patients in this survey).[3, 15] Our data reflected a pre-Covid period, so changes in patient distribution and mortality trends may be observed in more recent years and will be identified in future surveys.

The age distribution of patients is approaching that of the general population in the first five decades of life, reflecting advances in care and prolongation of survival. Still, a diagnosis of TDT (especially in males) and to a lesser extent, SCD, leads to reduced life expectancy. The increased mortality of hemoglobinopathies compared to the general population should be a target for treatment optimization through conventional and novel therapies, although individualized approaches may be needed for patients with TDT, NTDT, and SCD based on current patient profiles and history of treatment and disease manifestations.

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Table 1. Distribution of patients across Italy.

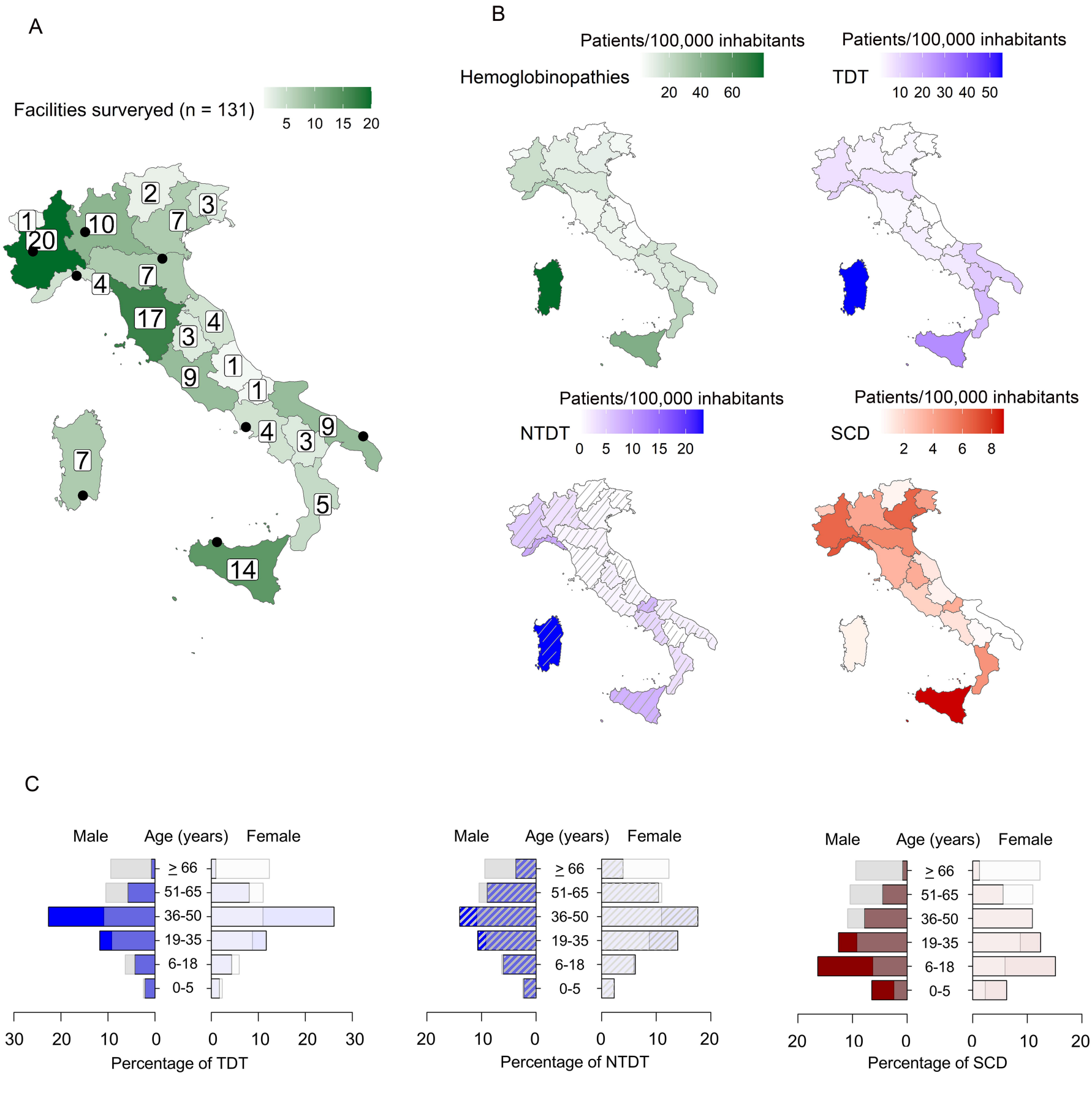
Region		Density (patients/100,000 inhabitants)			
		Hemoglobinopathies	**TDT**	**NTDT**	**SCD**
Piedmont	northwest	19.1	7.8	5.0	6.3
Aosta Valley	northwest	4.8	2.4	0.0	2.4
Liguria	northwest	26.2	10.8	8.5	6.9
Lombardy	northwest	10.7	3.8	2.9	3.9
Trentino-Alto Adige	northeast	1.3	0.4	0.1	0.8
Veneto	northeast	10.0	2.8	0.7	6.5
Friuli Venezia Giulia	northeast	5.1	0.7	0.2	4.1
Emilia-Romagna	northeast	13.6	7.4	1.1	5.2
Tuscany	center	6.4	2.5	0.5	3.4
Umbria	center	7.7	2.4	1.6	3.7
Marche	center	2.2	0.8	0.1	1.4
Lazio	center	8.1	4.7	1.2	2.2
Abruzzo	south	2.5	0.6	0.9	0.9
Molise	south	16.3	5.7	7.0	3.7
Campania	south	11.0	5.4	4.0	1.6
Apulia	south	14.3	12.3	1.6	0.4
Basilicata	south	13.6	13.0	0.0	0.5
Calabria	south	24.3	16.6	3.1	4.6
Sicily	islands	44.1	27.5	7.8	8.8
Sardinia	islands	79.7	55.5	23.3	0.9
Median of regional densities (IQR)		10.8 (6.1-17)	5.1 (2.4-11.2)	1.4 (0.4-4.2)	3.6 (1.5-4.8)
National density (Italy)		**16.0**	**8.7**	**3.3**	**3.9**

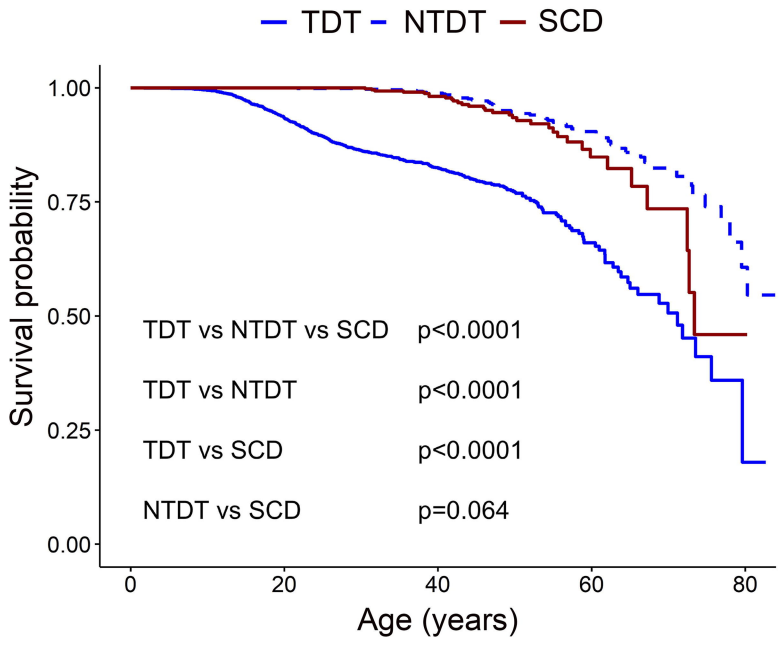
Abbreviations: TDT, transfusion-dependent thalassemia; NTDT, non-transfusion-dependent thalassemia; SCD, sickle cell disease; IQR, interquartile range.

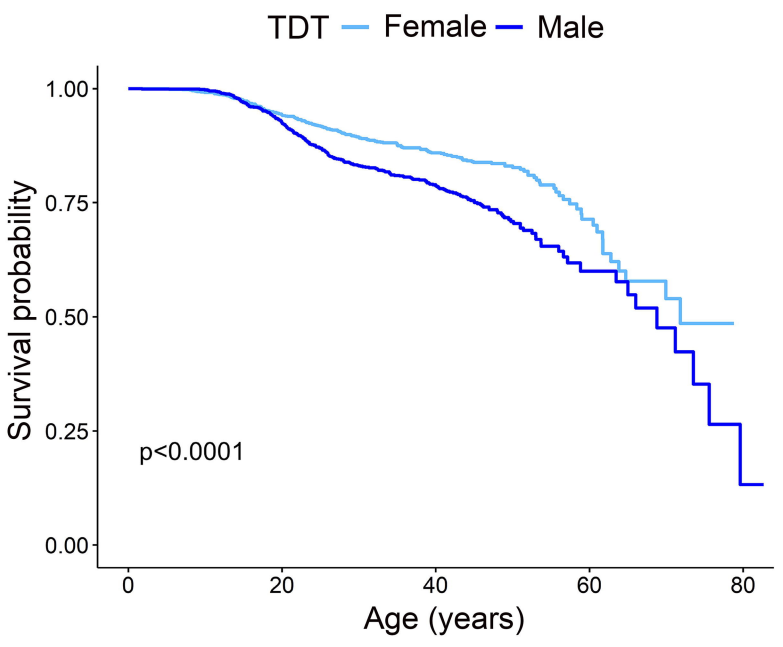
FIGURE LEGENDS

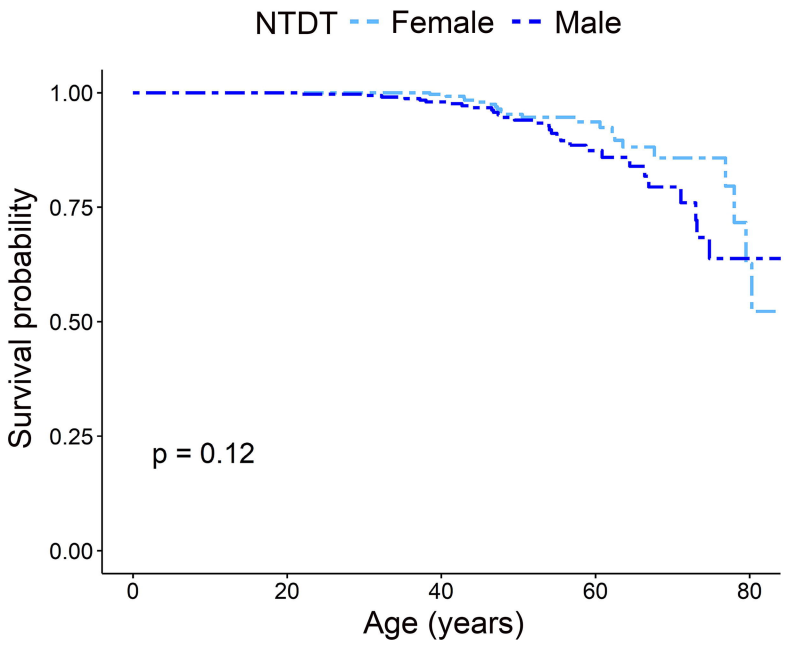
Figure 1. Hemoglobinopathies in Italy according to the national survey in 2019. **(A)** Geographical distribution of facilities included in the survey (n = 131); the black points indicate the location of the eight reference centers included in the survival cohort analyses. The administrative units shown are the 20 regions (administrative 1 level) of Italy. **(B)** Distribution of patients per 100,000 inhabitants by region in Italy. **(C)** Distribution of patients by age and sex for TDT, NTDT and SCD patients with light grey bars reflecting age distribution of the general Italian population in 2019. Abbreviations: TDT, transfusion-dependent thalassemia; NTDT, non-transfusion-dependent thalassemia; SCD, sickle cell disease.

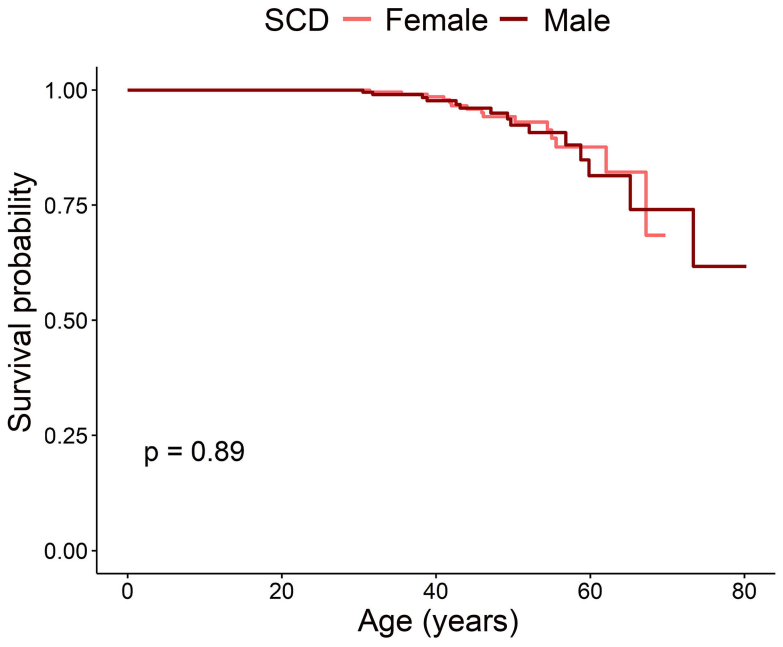
Figure 2. Kaplan-Meier survival curves for the survival cohort with comparisons by hemoglobinopathy type and sex. Abbreviations: TDT, transfusion-dependent thalassemia; NTDT, non-transfusion-dependent thalassemia; SCD, sickle cell disease.


A
Facilities surveryed (n = 131)
5 10 15 20
1
20
10
2
3
7
7
4
17
3
4
9
1
1
4
3
9
7
5
14
B
Patients/100,000 inhabitants
Hemoglobinopathies
20 40 60
Patients/100,000 inhabitants
TDT
10 20 30 40 50
Patients/100,000 inhabitants
NTDT
0 5 10 15 20
Patients/100,000 inhabitants
SCD
2 4 6 8
C
Male
Age (years)
Female
≥ 66
51-65
36-50
19-35
6-18
0-5
30 20 10 0
0 10 20 30
Percentage of TDT
Male
Age (years)
Female
≥ 66
51-65
36-50
19-35
6-18
0-5
20 10 0
0 10 20
Percentage of NTDT
Male
Age (years)
Female
≥ 66
51-65
36-50
19-35
6-18
0-5
20 10 0
0 10 20
Percentage of SCD


TDT
NTDT
SCD
Survival probability
1.00
0.75
0.50
0.25
0.00
0
20
40
60
80
Age (years)
TDT vs NTDT vs SCD p<0.0001
TDT vs NTDT p<0.0001
TDT vs SCD p<0.0001
NTDT vs SCD p=0.064


TDT
Female
Male
Survival probability
1.00
0.75
0.50
0.25
0.00
0
20
40
60
80
Age (years)
p<0.0001


NTDT
Female
Male
Survival probability
1.00
0.75
0.50
0.25
0.00
0
20
40
60
80
Age (years)
p = 0.12


SCD
Female
Male
Survival probability
1.00
0.75
0.50
0.25
0.00
0
20
40
60
80
Age (years)
p = 0.89

Supplementary Appendix

Supplementary Table S1. Collaborators of the Italian Hemoglobinopathies National Survey Group.

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S. Cesaro	Oncoematologia Pediatrica, Verona
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L. Cimminelli	Divisione di Pediatria, Biella
V. Coha	DH Ematologia, Pinerolo
G. Colarusso	SOC Pediatria e Neonatologia/TIN - Ambulatorio Ematologia Pediatrica, Prato
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Supplementary Table S2. Standardized mortality ratio estimates for the general Italian population and hemoglobinopathies.

General population*			TDT		NTDT		SCD	
Age group	**Population**	**Deaths**	**Observed Deaths#**	**Expected Deaths**	**Observed Deaths#**	**Expected Deaths**	**Observed Deaths#**	**Expected Deaths**
0-4	2338752	1239	1	5.6	0	1.3	0	1.6
5-9	2691273	149	12	0.6	0	0.2	0	0.2
10-14	2841862	210	55	0.8	0	0.2	0	0.2
15-19	2873676	550	85	2.0	0	0.6	0	0.6
20-24	2962307	814	88	2.7	1	0.9	0	0.7
25-29	3175599	995	64	2.8	0	1.0	0	0.8
30-34	3320500	1231	33	2.9	2	1.1	3	0.8
35-39	3654733	1915	33	3.6	4	1.5	4	0.9
40-44	4372031	3743	36	4.3	7	2.0	6	1.2
45-49	4785280	6675	17	3.9	10	2.5	5	1.3
50-54	4900974	11105	18	2.9	6	3.0	4	1.4
55-59	4387417	16499	12	2.2	4	3.3	4	1.3
60-64	3819054	22919	10	1.8	6	3.4	1	1.0
65-69	3468709	32725	3	10.2	3	17.2	2	5.6
≥ 70	10224506	533648	5	6.1	8	17.5	3	2.1
Total	**59816673**	**634417**	**472**	**52**	**51**	**56**	**32**	**20**
			SMR: 9.0 (95% CI: 8.2-9.8)		**SMR: 0.9 (95% CI: 0.7-1.2)**		**SMR: 1.6 (95% CI: 1.1-2.2)**	

*Data of 2019 from Istat.
#In the period of observation (1970-2019).
Abbreviations: TDT, transfusion-dependent thalassemia; NTDT, non-transfusion-dependent thalassemia; SCD, sickle cell disease; SMR, standardized mortality ratio; CI, confidence interval.

Supplementary Figure S1. PMR for hemoglobinoplathies (entire period of observation) compared to the general Italian population (2019) by age group. The main causes of death at higher proportion than the general population in TDT were diseases of the circulatory system in the 0-19 age group (PMR =11.5, 95%CI: 10.2-12.9,) and hematological diseases in patients under 40 years (PMR = 8.9, 95%CI: 7.4-10.4, in 0-19 years; PMR = 7.3, 95%CI: 6.2-8.3, in 20-39 years). Mortality from infections in TDT was higher in all age groups: 4.9 (95%CI: 4.0-5.7) in 0-19 years, 5.4 (95%CI: 4.7-6.2) in 20-39 years, 5.9 (95%CI: 4.6-7.2) in 40-59 years, and 12.2 (95%CI: 7.1- 17.3) in ≥60 years. In NTDT, increased mortality was largely related to infections in patients aged 20-59 years (PMR = 12.5, 95%CI: 4.8-20.2, in 20-39 years; PMR = 7.6, 95%CI: 4.7-10.5, in 40-59 years) and hematological diseases in the age group 40-59 yeas (PMR = 8.7, 95%CI: 3.9-13.4). In SCD, we observed an increased PMR for hematological diseases in the age group 20-39 years (PMR = 41.1, 95%CI: 15.7-66.5) and 40-59 years (PMR = 24.6, 95%CI: 12.0-37.3). Causes of death were ordered according to ICD-10. The use of ICD-10 coding for causes of death may not be ideal since many causes of death attributed to thalassemia or sickle cell disease complications may be labelled as 'hematological disease', but this was necessary to allow comparisons with the general population. Abbreviations: PMR, proportionate mortality ratio; CI, confidence interval; TDT, transfusion-dependent thalassemia; NTDT, non-transfusion-dependent thalassemia; SCD, sickle cell disease.