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

Data on the global burden of hemoglobinopathies, including the thalassemias and sickle cell disease (SCD), are mostly derived from modeling 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 changed considerably due to advances in management, patient mobility, and migration fluxes.[6,8,9] Here, we 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 at reference centers for over 50 years.

In December 2019, following the constitution of the National Network of Thalassemia and Hemoglobinopathies (Law 205/17, art. 1, subsection 437), we conducted a cross-sectional national survey 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 8 of the regional reference centers from 1970 onwards who were followed until death, loss to follow up, or December 2019; the 8 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 log-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 Italian National Institute of Statistics database (http://dati.istat.it/). To allow comparisons with the general population, causes of death were classified according to the primary cause based on the ICD-10 code recorded on death certificates. For each cause of death, we calculated the proportionate mortality ratio (PMR) between hemoglobinopathies and the general population considering 4 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 fifteen 5-year 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; 23 of these (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. Distribution was heterogeneous across the country with the highest prevalence of TDT in Sardinia, Sicily, and Calabria (Southern Italy) (55.5, 27.5, and 16.6 patients / 100,000 inhabitants, respectively), of NTDT in Sardinia, Liguria (in the 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) (Table 1, Figure 1B). 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) (χ^2 test, 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) (χ^2 test, *P*=0.14) (Figure 1C). There was higher patient clustering under 50 years of age for both males and females compared to the general population (Figure 1C). We observed aging of thalassemia due to a decrease in 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 this is not reflected in age distribution due to recent migration fluxes. Approximately 80% of the SCD population under 30 years of age 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 shown 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). In TDT, females had better survival rates

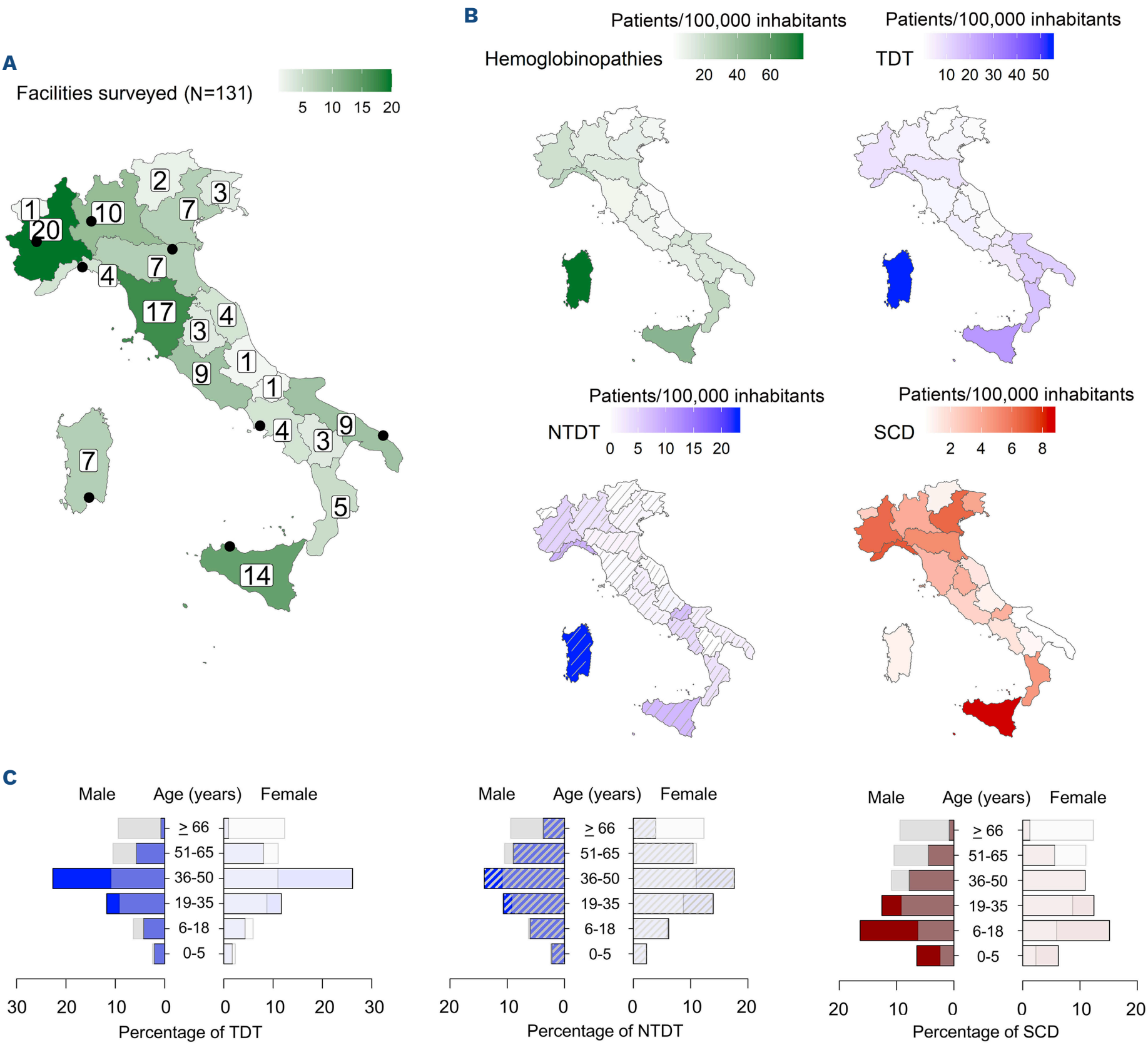

Figure 1. Hemoglobinopathies in Italy according to the national survey in 2019. (A) Geographical distribution of facilities included in the survey (N=131); black points indicate the location of the 8 reference centers included in the survival cohort analyses. The administrative units shown are the 20 regions (administrative level 1) of Italy. (B) Distribution of patients per 100,000 inhabitants by region in Italy. (C) Distribution of patients by age and sex for transfusion-dependent thalassemia (TDT), non-transfusion-dependent thalassemia (NTDT), and sickle cell disease (SCD) patients, with light gray bars reflecting age distribution of the general Italian population in 2019.

than males (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. SMR for NTDT was 0.9 (95% CI: 0.7-1.2) (*Online Supplementary Table S2*). Using 2019 data from the general population to inform on 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. *Online 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 differs for NTDT and SCD, especially those with mild phenotypes, who are not continuously followed at specialized centers, with sporadic access to emergency departments for acute events. This is also supported by a

Table 1. Distribution of patients across Italy.

Region	Geographical location	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 across Italy		16.0	8.7	3.3	3.9

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

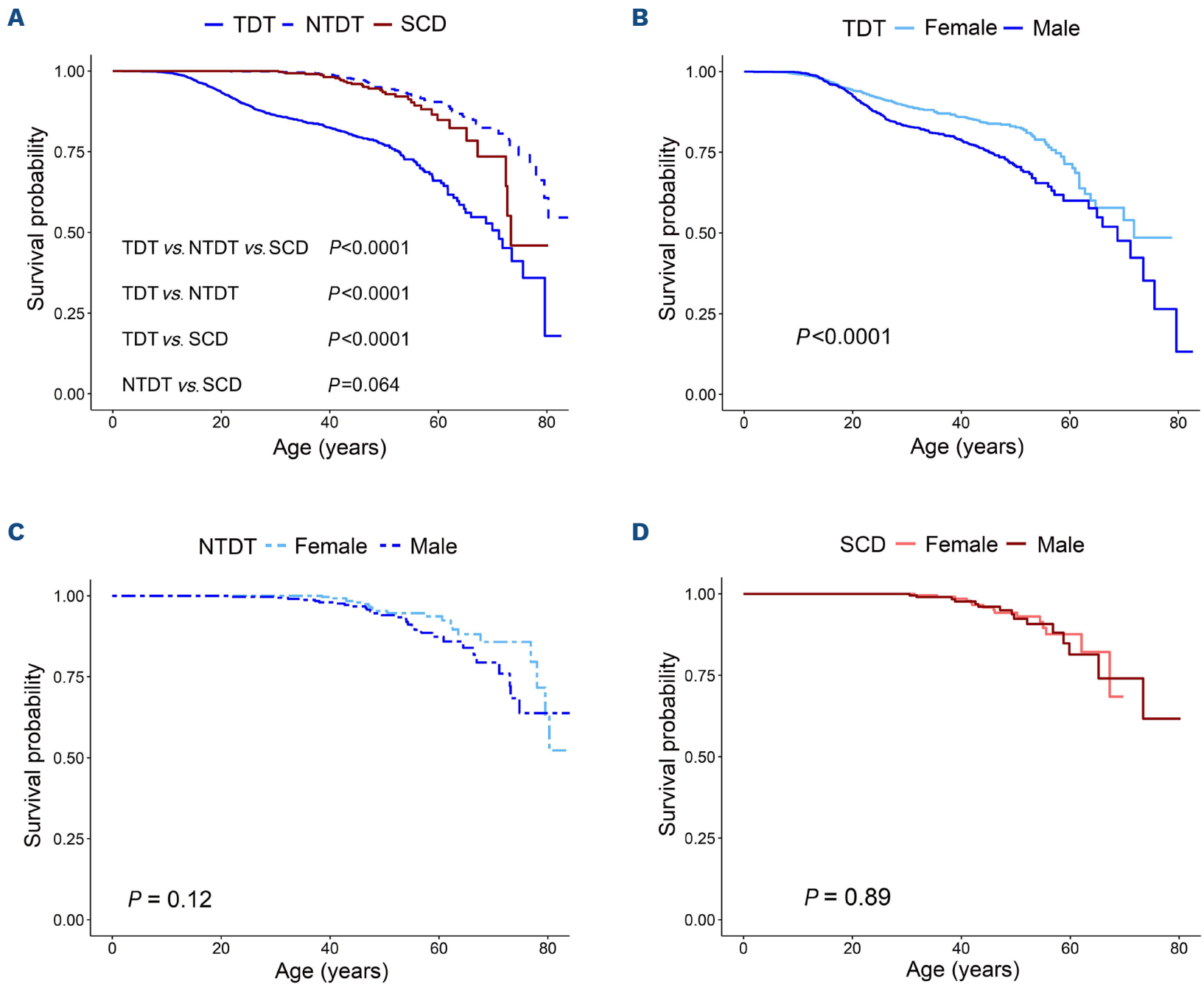

Figure 2. Kaplan-Meier survival curves for the survival cohort with comparisons by hemoglobinopathy type and sex. (A) Survival comparisons for transfusion-dependent thalassemia (TDT), non-transfusion-dependent thalassemia (NTDT), and sickle cell disease (SCD). (B) Survival in TDT females and males. (C) Survival in NTDT females and males. (D) Survival in SCD females and males.

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, figures for Italy were 6,497 (95% CI: 5,432-7,602) for thalassemia (compared with 7,169 TDT/NTDT patients in this survey) and 2,675 (95% CI: 2,354-3,015) for SCD (compared with 2,348 SCD patients in this survey).[3,15] Our data reflect 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. However, 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. 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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Disclosures

No conflicts of interest to disclose.

Contributions

BG, AG and GLF are responsible for study conception and design. BG, SB, MC, EC, RDM, AG, MRG, GG, RL, FL, AM, RO, AP, SP, AGP, VMP, RR, GRo, GRu and MZ collected the data. BG and FBP are responsible for statistical analysis. FBP, KMM, LDF and GLF reviewed the analysis and interpreted the results. BG, FBP, LDF and KMM drafted the manuscript. All authors reviewed the manuscript for important intellectual content and approved the final version for submission.

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Data-sharing statement

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

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