National registry of hemoglobinopathies in Spain (REPHem)

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Abstract

Background: Although highly prevalent throughout the world, the accurate prevalence of hemoglobinopathies in Spain is unknown.

Procedure: This study presents data on the national registry of hemoglobinopathies of patients with thalassemia major (TM), thalassemia intermedia (TI), and sickle cell disease (SCD) in Spain created in 2014. Fifty centers reported cases retrospectively. Data were registered from neonatal screening or from the first contact at diagnosis until last follow-up or death.

Results: Data of the 715 eligible patients were collected: 615 SCD (497 SS, 64 SC, 54 SBeta phenotypes), 73 thalassemia, 9 CC phenotype, and 18 other variants. Most of the SCD patients were born in Spain (65%), and 51% of these were diagnosed at newborn screening. Median age at the first diagnosis was 0.4 years for thalassemia and 1.0 years for SCD. The estimated incidence was 0.002 thalassemia cases and 0.03 SCD cases/1,000 live births. Median age was 8.9 years (0.2–33.7) for thalassemia and 8.1 years (0.2–32.8) for SCD patients. Stroke was registered in 16 SCD cases. Transplantation was performed in 43 TM and 23 SCD patients at a median age of 5.2 and 7.8 years, respectively. Twenty-one patients died (3 TM, 17 SCD, 1 CC) and 200 were lost to follow-up. Causes of death were related to transplantation in three patients with TM and three patients with SCD. Death did not seem to be associated with SCD in six patients, but nine patients died secondary to disease complications. Overall survival was 95% at 15 years of age.

Conclusions: The registry provides data about the prevalence of hemoglobinopathies in Spain and will permit future cohort studies and the possibility of comparison with other registries.

KEYWORDS
hemoglobinopathy, registry, sickle cell disease, Spain, thalassemia

INTRODUCTION

The lack of accurate data on significant clinical hemoglobinopathies in Spain and the increasing need for standardized methods to assess preventive measures and treatment provides the rationale for developing a registry. Worldwide, about 60,000 children with thalassemia major (TM) and 300,000 with sickle cell disease (SCD) are born annually.1–5 As a result of migration from endemic areas, SCD is a new challenge to Spain, as the first cases were barely diagnosed 15 years ago. The first report of an increase in infants with sickle trait appeared in 20036 and led to the implementation of universal neonatal screening programs in specific regions and an inquiry restricted to a few centers.7 The incidence rate detected in Madrid6 was 5.57 hemoglobin variants and 0.16 patients with SCD per 1,000 births. In 2014, the Spanish...
population stood at 46,439,000 inhabitants, of whom 4,677,000 were immigrants (source: Instituto Nacional Estadística, www.ine.es). A survey in 2007 found that 5% of the population belonged to ethnic minority groups at risk for SCD, and in 2014, 33% of births were from a parent who had immigrated. The Madrid study estimated the prevalence of hemoglobin S to be 0.39%, which was in the middle of a range comprising high frequencies as reported in Albania (3%), France (0.6%), Portugal (0.57%), Greece (0.53%), the Netherlands (0.47%), England and Wales (0.47%), and Turkey (0.44%) and low frequencies encountered in Scotland (0.01%), Finland (0.02%), and Ireland (0.08%).

It might be thought that beta thalassemia is the most common inherited hematologic disease in Spain as a Mediterranean country. Although heterozygosis of beta chain mutations are frequent in clinical practice (1.5% of carriers with not homogeneous range of values from 0% to 5%), patients with TM or thalassemia intermedia (TI) are scarce in hematology units compared to figures from countries with similar characteristics. Thalassemia is more common in patients of Italian, Greek, Middle Eastern, Cypriot, Asian, and African descent. No cases of thalassemia were detected in the Madrid study.

The lack of sound epidemiological data in Spain led to the implementation of a national registry of hemoglobinopathies (Registro Español Pediatrío de Hemoglobinopatías [REPHem]) under the auspices of the Spanish Society of Pediatric Hematology and Oncology (SEHOP). Its objectives are to report the demographic and clinical features of these diseases and promote future cohort studies. The registry aims to address survival and clinical questions similar to other pioneering series worldwide. In this study, we present the data collected.

2 | METHODS

2.1 | Registry design

REPHem records data from patients with hemoglobinopathies in Spain, including TM, TI, and SCD. The study is observational, multicenter, and ambispective. The registry began in January 2014 with an annual follow-up, although the present study ended on May 31, 2015, when a cross-sectional analysis was performed. All pediatricians and hematologists caring for patients diagnosed with hemoglobinopathies, whose first consultation was at age less than 18 were invited to join the registry. Inclusion in the cohort was at birth if newborn screening was available or at the time of diagnosis if identification was delayed. Written informed consent was signed by patients or their legal guardians in accordance with the Declaration of Helsinki. For patients who died or were lost to follow-up before 2014, data were collected retrospectively. Patient information that predate the initiation of data collection was retrieved from the medical records. The registry and data processing were approved by the Ethics Committee, Government Children’s Office, and Spanish Data Protection Agency under the auspices of SEHOP. Variables were entered online by physicians and included identification items, date of birth, gender, diagnosis and date, circumstances of diagnosis, country of birth, genotype, blood test and imaging data, clinical complications, therapy, and follow-up (alive, deceased, lost). Double entries were examined and excluded by social security number when available; in selected cases, a combination of name, gender, date of birth, and personal contact with the attending physician determined whether a patient was recorded twice. The registry is based on a network that maintains personal contact with all physicians treating patients with hemoglobinopathies in order to ensure high-quality care. This collaboration generated national guidelines for the treatment of thalassemia and SCD and strengthens the acceptability of the registry.

2.2 | Definition of variables

Thalassemia results from impaired hemoglobin synthesis and ineffective erythropoiesis. TM requires more than eight transfusions per year before 4 years of age; TI requires occasional or no transfusions. SCD is a genetic hemolytic anemia characterized by a structurally different beta chain that leads to hemoglobin S. The main hemoglobinopathy-related events considered are well documented.

2.3 | Statistical analysis

Statistical analyses were performed using PASW Statistics for Windows, version 18.0 (SPSS, Inc., Chicago, IL). Quantitative variables were reported as median and range, while categorical variables were expressed as absolute value and percentage. Categorical variables were compared using the chi-square test or Fisher exact test. Continuous variables were compared using an unpaired t-test or the Mann-Whitney U-test as appropriate. Overall survival is defined as the probability of survival from birth to death or last follow-up visit. Survival curves were plotted using the Kaplan-Meier method and stratified according to various clinical and pathological variables. Differences were tested using the log-rank test. P-values are two-sided and considered statistically significant when less than 0.05.

3 | RESULTS

Fifty hospitals throughout Spain registered 760 patients with hemoglobinopathies. After checking for double records, 715 were eligible. One center was following more than 100 patients, another center more than 70, 7 centers recorded 20–40 patients each, and 14 added fewer than 5 patients. Thalassemia was reported in 73 cases and SCD in 615 cases (Table 1). The incidence in 2014 was estimated at 4 cases of thalassemia and 14 cases of SCD among 426,303 live births (0.002 per 1,000 live births and 0.03 per 1,000 live births, respectively).

3.1 | Thalassemia

According to the year of diagnosis in the last three decades, a slight increase in the incidence of thalassemia was observed from 0.3 patients per year before 1996 to 3.3 patients per year in the last quinquennium. Although thalassemia is not intentionally sought in the
### TABLE 1  Status of patients with hemoglobinopathies

<table>
<thead>
<tr>
<th>Type</th>
<th>Number of patients</th>
<th>%</th>
<th>Ratio boys/girls</th>
<th>Alive</th>
<th>Age (years)</th>
<th>Follow-up time (years)</th>
<th>Deceased</th>
<th>Lost to follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalassemia</td>
<td>73</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major: 67</td>
<td></td>
<td></td>
<td></td>
<td>10.5</td>
<td>1/1</td>
<td>57</td>
<td>8.9 (0.2–33.7)</td>
<td>8.0 (0.1–35.1)</td>
</tr>
<tr>
<td>Intermedia: 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>615</td>
<td></td>
<td></td>
<td>89.5</td>
<td>1.1/1</td>
<td>416</td>
<td>8.1 (0.2–32.8)</td>
<td>4.5 (0–28.8)</td>
</tr>
<tr>
<td>SS: 497</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SC: 64</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S-Beta thal* 2</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S-Beta thal*+ 2</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>27</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>26</td>
<td>1 (CC phenotype)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>715</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 2  Number of patients with thalassemia and secondary complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>TM, n = 67</th>
<th>TI, n = 6</th>
<th>Total, N = 73</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic hemosiderosis (MRI)</td>
<td>6</td>
<td>1</td>
<td>7 (9.6%)</td>
</tr>
<tr>
<td>Osteopaenia</td>
<td>4</td>
<td>1</td>
<td>5 (6.8%)</td>
</tr>
<tr>
<td>Weight/Height retardation &gt; 2SD</td>
<td>2</td>
<td>0</td>
<td>2 (2.7%)</td>
</tr>
<tr>
<td>Alloimmunization</td>
<td>2</td>
<td>1</td>
<td>3 (4.1%)</td>
</tr>
<tr>
<td>Extramedullary hemopoiesis (pseudotumor)</td>
<td>1</td>
<td>0</td>
<td>1 (1.3%)</td>
</tr>
<tr>
<td>Yersinia-induced colitis</td>
<td>1</td>
<td>0</td>
<td>1 (1.3%)</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>1</td>
<td>0</td>
<td>1 (1.3%)</td>
</tr>
<tr>
<td>Aplasia (parvovirus)</td>
<td>0</td>
<td>1</td>
<td>1 (1.3%)</td>
</tr>
<tr>
<td>Cholelithiasis</td>
<td>0</td>
<td>1</td>
<td>1 (1.3%)</td>
</tr>
</tbody>
</table>

*a One patient may have more than one complication. TM, thalassemia major; TI, thalassemia intermedia.

#### 3.2 Sickle cell disease

The regional distribution of patients with SCD shows that 75% of the cases were recruited in Madrid and Cataluña. Regarding the year of diagnosis, the figures increased from 1.7 cases per year before 1996 to 42.2 cases per year in the 5-year period between 2006 and 2010. Most patients were born in Spain, although 25% and 9% were born in Africa and America, respectively. Dividing the affected children by groups of year of birth, the first year in which the number of children born in Spain was higher than born abroad but living in the country was 2003 (Fig. 1). Fifty-one percent of the patients born in Spain and 30% of the entire group were detected because of universal neonatal screening. Median age at the first diagnosis was 1.0 year (0–18). The age of children diagnosed at birth was 6.2 years (0.3–18) and 13.0 years for those with a later diagnosis (0.9–34.1). Age was 7.8 years for those born in Spain and 15.1 years for those born abroad. Twenty-nine percent of the patients were lost to follow-up.

Other health impairments not related to hemoglobinopathy were reported in 6.6% of patients and included prematurity (seven cases), viral hepatitis (4 cases), and congenital liver disease (2 cases). Five percent of the patients had an associated alpha gene deletion or mutation, 1.3% had glucose-6-phosphate dehydrogenase deficiency, and 0.8% had congenital thrombotic diathesis.

Complications of SCD and age at presentation are listed in Table 3. Although 16 cases of stroke were registered (2.6%), neurological abnormalities were recorded in only 1.8%. The Kaplan–Meier
The cumulative incidence of stroke is represented in Fig. 2A, with an incidence of 8% at 15 years of age, reaching a plateau at 20 years. Five of 28 children with abnormal transcranial Doppler (TCD) findings suffered a stroke despite receiving transfusions (17%). Eleven patients had a stroke with normal TCD findings (1.8%). The P-value for presenting with a stroke in patients with previous abnormal TCD findings, silent infarcts, or vasculopathy on magnetic resonance imaging (MRI) was <0.001.

Chelation therapy was initiated in 4.5% of the patients, with a median duration of 1.1 years (0.2–7.9). Chelation therapy was first
used with deferasirox in 2009. Vitamin D3 was administered to 25% of patients at a median age of 0.5 years (0–17.5). Although the median age of initiation of vitamin D therapy was 0.2 years in the group with normal densitometry findings and 5 years in the osteopenia group, no statistically significant differences were found.

Hydroxyurea was added to standard treatment in 25% of the patients. The youngest recipient aged 8 months, and the duration of therapy was 3.8 years (0.2–18.4) at the end of the inclusion period. Prophylaxis with penicillin was reported in 49% of cases. Specifically, treatment was rejected in 9.8% of cases, 5.9% from the newborn screening group and 24.9% from the group diagnosed later (P < 0.001). The median age for starting antibiotic prophylaxis was 2.4 months (1 month to 14.3 years), and end of therapy was reported in only 4.6% cases (median, 6 years; range, 4 months to 12.1 years). The median duration of prophylaxis was 5.8 years (0.1–21.3). After their sixth birthday, 18.9% continued to receive penicillin. Sepsis or meningitis was recorded in 2% of cases, of whom only 2 of 13 were on antibiotics before the event (P < 0.001).

Chronic exchange or simple transfusions were reported in 6.1% of cases, with a median age of 5.4 years (7.2 months to 29 years) at the initiation of therapy. In this group, 39.5% had an abnormal TCD finding, and the remainder had other reasons for regular transfusions.

Four percent of the children underwent splenectomy at a median age of 5.6 years (10.8 months to 14.1 years). None of these patients had sepsis or meningitis. Cholecystectomy was performed in 5.6% at a median age of 12 years (3.7–21.7 years). Patients with the SC, Sβ0, and CC genotypes did not undergo any surgical procedures.

Hematopoietic stem cell transplants were performed in 3.7% of the cases between 2.1 and 15 years of age (median, 7.8 years). Most transplants were in 2014 (26%). One child rejected the marrow and underwent a successful second transplant. Three patients died of complications related to the procedure.

Thirty percent of the patients were lost to follow-up: 5% were followed exclusively in adult nonreporting units and 25% returned to their home country or were lost for other reasons. The median age for being considered lost was 4.9 years (birth–29.6 years). There were 18 deaths (2.9%, 17 SCD and 1 CC phenotype), 6 of which were probably not related to SCD but to conditions such as prematurity, metabolic diseases, malaria, neuroblastoma, and congenital cardiopathy. Mortality by genotype was 1 CC, 1 Sβ0, and 16 SS. Overall survival was 96.7% at 5 years of age and 95% at 10 and 15 years (Fig. 2B). The global mortality rate was 0.6/100 patient-years. The causes of death are listed in Table 4. The mean age at death was 6.4 years (median 3.4, range 0.02–18.3). No differences in mortality were recorded for origin (born in Spain or abroad), knowledge of Spanish, diagnosis by neonatal screening, or year of implementation of Spanish therapy guidelines. However, in patients with an associated condition, survival decreased to 94% and 83% at 1 and 5 years, respectively, that is, much lower than the age of death in patients who only had SCD (Fig. 2C, P < 0.001). Life expectancy was not calculated, as the results of survival analyses did not reach the medians.
TABLE 4 Causes of death in SCD (17 patients) and 1 patient with CC phenotype

<table>
<thead>
<tr>
<th>Patient</th>
<th>Genotype</th>
<th>Age at decease and year</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SS</td>
<td>8 years (1995)</td>
<td>BMT—acute GvHD</td>
</tr>
<tr>
<td>2</td>
<td>SS</td>
<td>18 years (2000)</td>
<td>Acute chest syndrome (on vacation in Africa)</td>
</tr>
<tr>
<td>3</td>
<td>SS</td>
<td>0.02 years (2004)</td>
<td>Prematurity (gestational age: 24 weeks)</td>
</tr>
<tr>
<td>4</td>
<td>SS</td>
<td>0.8 years (2006)</td>
<td>Liver metabolic congenital disease</td>
</tr>
<tr>
<td>5</td>
<td>SS</td>
<td>4 years (2008)</td>
<td>Neuroblastoma</td>
</tr>
<tr>
<td>6</td>
<td>SS</td>
<td>15 years (2008)</td>
<td>BMT—chronic GvHD, sepsis</td>
</tr>
<tr>
<td>7</td>
<td>SS</td>
<td>1 years (2008)</td>
<td>Spleen sequestration</td>
</tr>
<tr>
<td>8</td>
<td>SS</td>
<td>1 years (2008)</td>
<td>Spleen sequestration</td>
</tr>
<tr>
<td>9</td>
<td>SS</td>
<td>2 years (2009)</td>
<td>Death at home</td>
</tr>
<tr>
<td>10</td>
<td>SBeta0</td>
<td>3 years (2011)</td>
<td>Sepsis</td>
</tr>
<tr>
<td>11</td>
<td>SS</td>
<td>17 years (2011)</td>
<td>Malaria</td>
</tr>
<tr>
<td>12</td>
<td>SS</td>
<td>1 years (2011)</td>
<td>Spleen sequestration</td>
</tr>
<tr>
<td>13</td>
<td>SS</td>
<td>3 years (2011)</td>
<td>Sepsis</td>
</tr>
<tr>
<td>14</td>
<td>CC</td>
<td>6 years (2011)</td>
<td>Shock, no conclusive diagnosis at autopsy</td>
</tr>
<tr>
<td>15</td>
<td>SS</td>
<td>2 years (2012)</td>
<td>Metabolic congenital disorder (encephalopathy)</td>
</tr>
<tr>
<td>16</td>
<td>SS</td>
<td>10 years (2013)</td>
<td>BMT—acute GvHD</td>
</tr>
<tr>
<td>17</td>
<td>SS</td>
<td>2 years (2014)</td>
<td>Congenital cardiopathy</td>
</tr>
<tr>
<td>18</td>
<td>SS</td>
<td>16 years (2014)</td>
<td>Hemorrhagic stroke</td>
</tr>
</tbody>
</table>

BMT, bone marrow transplant; GvHD, graft versus host disease.

4 | DISCUSSION

We report data from the first registry of hemoglobinopathies in Spain in order to determine the number of affected children and adults who originally consulted as children. Spain is a multiethnic society. Migration of significant populations from high-prevalence areas to Europe began 60 years ago but has increased during the last 20 years. As large-scale immigration in Spain is a more recent phenomenon, it is difficult to provide accurate figures on disease prevalence. The incidence of hemoglobinopathy is lower in Spain than in other Mediterranean countries. With a prevalence of approximately 1.5 cases per 100,000 people, thalassemia and SCD are very rare diseases in Spain (0.16 thalassemia and 1.34 SCD per 100,000 inhabitants). Incidence is lower than that recorded in France, the United Kingdom, urban population in Germany, and Belgium. It is also lower than the European median (0.5 for thalassemia and 15 for SCD per 100,000 people). The incidence in Greece was reported to be 8% and 1–2% for thalassemia and sickle cell trait, respectively. An estimation of 100 thalassemia people in Spain had been attempted, although a more precise calculation revealed this number to be 83 patients in 1986. The number of cases in our study might have been higher if there have been unawareness of hematologists exclusively treating adult patients for whom they could send data if recruited before 18 years of age, specifically if the patients had already died or lost in follow-up. In Spain, the highest prevalence values recorded are 8% and 1–2% for thalassemia and sickle cell trait, respectively. An estimation of 100 thalassemia people in Spain had been attempted, although a more precise calculation revealed this number to be 83 patients in 1986. The number of cases in our study might have been higher if there have been unawareness of hematologists exclusively treating adult patients for whom they could send data if recruited before 18 years of age, specifically if the patients had already died or lost in follow-up. In Spain, the highest prevalence values recorded are 0.45% for sickle cell trait and 0.016% for SCD. Such low-prevalence values could be explained by prenatal counselling, low registration for adult patients with thalassemia, and lack of immigration or refugees until 20 years ago. Diagnoses of SCD reached a maximum of 42 per year in 2006–2010 and declined to 24 in the following 5 years. Prenatal counselling and a decrease in immigration from half a million in 2008 to a quarter of a million in 2014 could have affected this change. Most patients were born in Africa, although in Spain many patients are from Spanish-speaking countries in South and Central America.

We also provide a profile of the state of health of patients with hemoglobinopathy living in Spain. Our study shows that current clinical practice is homogeneous and based on national guidelines, which have been enriched by progress in treatments in other countries with decades of expertise.

Regarding events related to the specific diseases, we list those that were reported. Holistic free access to health care for children in Spain, independently of legal status, probably improves their prognosis. Height is nowadays barely affected in patients with thalassemia, and our results showed a low proportion of affected patients (2.7%), compared with findings from other series in which the median age was higher. Splenectomy is also rare, although this could reflect the fact that there are now fewer indications for this procedure to reduce transfusion requirements. Cardiac and hepatic MRI were routinely used; only hepatic iron overload was reported, although the range was low owing to the effectiveness of chelators. We expect that our recommendations to provide vitamin D prophylaxis will attenuate osteopenia. This tendency has been observed among patients born in Spain, with universal administration of cholecalciferol and stricter follow-up since the first days of life.

SCD-related events did not differ with respect to whether the diagnosis was made at birth or later. The incidence of stroke and abnormal findings in brain MRI scans in the newborn cohort was low (6 patients), but our interventions are similar to those reported by other groups (TCD every year and MRI every 2 years). Chronic transfusions are recommended when abnormal TCD findings or stenosis is detected,
bone marrow transplantation is performed if an identical donor is available, and hydroxyurea is prescribed for patients who experience silent infarcts or symptomatic patients. Therefore, we expect a 50% cumulative cerebral risk by age 18 when this registry has been running for a longer period as observed in other series.\textsuperscript{17}

Our mortality results cannot be compared with those of other registries because of the short follow-up of our young cohort. The previously reported shortened life expectancy\textsuperscript{22} has been lengthened by recent measures. Survival in thalassemia takes advantage of the new options of oral chelation and transplantation, although data may be underestimated because older cases may not have been included in the registry. Birth thalassemia cohorts with transfusions and comprehensive care have shown life expectancy extending into the fourth decade.\textsuperscript{33} The acceptable mortality rate in SCD seems to be the result of our knowledge of treatment approach in more experienced surrounding cohorts, the combination of therapies to prevent organ damage, and the low median age of the population registered. Mortality rates of 0.13, 0.25, 0.52, and 1.1 per 100 patient-years have been published for cohorts from East London, Belgium, Dallas, and the Cooperative Study on SCD, respectively.\textsuperscript{13–15,34,35} Even in a developing country such as Jamaica, with an outstanding cohort of children, the mortality rate for children aged less than 5 years is 0.31 per 100 person-years when managed at a comprehensive center.\textsuperscript{16} Lower rates have been attributed to a favorable genotype (SC), lower median age, and shorter total follow-up. Leading causes of death from SCD reported in other registries\textsuperscript{26} include liver failure (18%), stroke (17%), and pulmonary disease (18%), although 95% of children are expected to reach adulthood thanks to the major advances made in the last few decades.\textsuperscript{14} The improved survival detected in children under the age of 4 is concurrent with the introduction of pneumococcal conjugate vaccination\textsuperscript{36,37}; survival among adolescents is consistent with a combination of newborn screening, infection prophylaxis, stroke prevention, and comprehensive care.\textsuperscript{28} Our results show other perinatal non-hemoglobinopathy-related conditions as the leading cause of death, followed by complications of bone marrow transplantation (2 out of 3 before 2000) and 1 case of sepsis despite appropriate vaccination and antibiotic prophylaxis (the patient had not undergone splenectomy). The 13 SCD-related deaths were secondary to acute events or bone marrow transplantation-toxicity, possibly reflecting the finding that transplantation was indicated in children with more severe clinical disease. This issue should be addressed in the future. Neonatal screening could likely be associated with reduced morbidity and mortality, as suggested by well-documented cohorts in England and France.\textsuperscript{13,34} although the difference was not statistically significant in the Belgian registry.\textsuperscript{14} We expect that extensive newborn screening in high-prevalence areas will provide statistical power to the cohort.

Despite the improvements in survival in countries able to afford multidisciplinary teams, we did not find early mortality in children born before migration to Spain, who generally had delayed access to preventive measures. Nevertheless, since the age at entry to the registry for those born abroad is higher (5 years), not including those who died before migration, complications in this group are underestimated. We propose to monitor whether organ damage is greater in this cohort.

Our study is subject to methodological biases arising from the limitations of our team’s capacity: it was not population-based, the rate of loss to follow-up was high, lack of response from some centers consulted, and we assumed that patients who were lost to follow-up were alive. Nevertheless, the efforts made to maintain the cohort will expand the data retrieved from the registry. In addition, the registry will grow in the near future with universal newborn screening implemented in regions with a higher prevalence.

In conclusion, the aim of the national registry of pediatric hemoglobinopathies in Spain is to pave the way for future cohort studies and the possibility of comparison with other registries. The close association between clinicians made it relatively easy for the participants to collect data, draft the guidelines, and promote studies. Trials for drug development should consider clinical endpoints including low-frequency events that should be analyzed in the setting of cohort studies.\textsuperscript{39} Hemoglobinopathy registries are essential for raising awareness of the diseases among health authorities, and accurate data collection must ensure that the necessary resources are provided.

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CONFLICT OF INTEREST

The authors declare that they do not have any conflicts of interest.

REFERENCES


SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.