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ORIGINAL RESEARCH ARTICLE

Mortality, Clinical Complications, and Healthcare Resource Utilization Associated with Managing Transfusion-Dependent β-Thalassemia and Sickle Cell Disease with Recurrent Vaso-occlusive Crises in Italy

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Abstract

Objective To examine the clinical burden and healthcare resource utilization (HCRU) among patients with transfusion-dependent β-thalassemia (TDT) and patients with sickle cell disease (SCD) with recurrent vaso-occlusive crises (VOCs) in Italy.

Methods Eligible patients were identified from an administrative claims database from 1 January 2010 and 1 February 2019. Patients with TDT had ≥ 1 iron chelation treatment, ≥ 8 red blood cell transfusions (RBCTs) during any 12-month period, and ≥ 12 months of available data pre- and post-index (i.e., first RBCT claim). Patients with SCD with recurrent VOCs had ≥ 2 VOCs/year in ≥ 2 consecutive years and ≥ 12 months of available data pre- and post-index (second VOC claim in the second of 2 consecutive years). Patients were propensity score matched to five controls by age, sex, geographic area, and index year. Clinical and HCRU outcomes were evaluated post-index.

Results In total, 214 patients with TDT and 111 patients with SCD with recurrent VOCs were matched to 1070 and 555 controls, respectively. Both patient groups had substantially higher mortality rates than controls (TDT: 4.8 versus 0.8 deaths per 100 person-years; SCD: 1.6 versus 0.4 deaths per 100 person-years). Clinical complications were prevalent in both patient groups. Compared with controls, both patient groups had significantly higher mean rates of all-cause hospitalizations (TDT: 1.4 versus 0.1; SCD: 2.0 versus 0.1) and outpatient services (TDT: 21.9 versus 1.6; SCD: 6.2 versus 1.0) per patient per year (all: $p < 0.05$).

Conclusions Management of TDT and SCD in Italy is associated with significant clinical and health system burden, highlighting the need for new treatments that eliminate RBCTs and VOCs.

1 Introduction

Thalassemias and sickle cell disease (SCD) are common monogenic disorders globally [1, 2]. β-thalassemia and SCD are natively endemic to Italy [1, 3], and their prevalence has risen due to increased migration from other endemic regions (e.g., Africa, the Eastern Mediterranean, and Southeast Asia) [3–6]. In 2023, the Italian Society of Thalassemia and Haemoglobinopathies (SITE) reported approximately 7200 cases of β-thalassemia in Italy, among which 5200 cases were transfusion-dependent β-thalassemia (TDT) [7], increased from approximately 6300 β-thalassemia and 3000 TDT cases in 2019 [8]. In addition, the SCD Global Burden of Disease Study estimated approximately 2600 prevalent cases of SCD in Italy in 2021 [9], which aligned with estimates from SITE (2385) [7] and the RADeep program (1850–4000) [10]. These numbers may be underestimated, as registry data are incomplete [11, 12], and some contemporaneous studies have approximated nearly 6000 patients with TDT and 2000–8000 patients with SCD in Italy [6, 12, 13].

β-thalassemia and SCD are caused by β-globin gene (*HBB*) mutations [2, 14, 15]. In β-thalassemia, reduced or absent β-globin production leads to excess α-globin and

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Key Points for Decision Makers

Few studies have measured the real-world clinical and health system impact of transfusion-dependent β-thalassemia and sickle cell disease with recurrent vaso-occlusive crises in Italy.

Italian patients with these diseases have elevated mortality and healthcare resource utilization (e.g., hospitalizations and prescriptions) compared with the general population, as well as a high prevalence of clinical complications associated with the diseases.

Novel therapies are needed to mitigate the burden of managing transfusion-dependent β-thalassemia and sickle cell disease.

inefficient red blood cell production [2]. Clinical features of β-thalassemia include hemolytic anemia and iron overload [2]. Patients with the most severe presentation of the disease, TDT, must receive regular red blood cell transfusions (RBCTs) to survive and iron chelation therapy to manage iron-overload-related complications from frequent RBCTs [2, 14]. In SCD, abnormal hemoglobin polymerizes within red blood cells on deoxygenation to disrupt cell flexibility [15, 16]. Resultant vaso-occlusion, infarction, and hemolytic anemia contribute to progressive damage to multiple organ systems [15, 16]. Notably, recurrent vaso-occlusive crises (VOCs) associated with SCD are a predominant cause of early mortality and morbidity among patients with this disease [17]. In line with the clinical consequences of managing frequent RBCTs and VOCs, recent studies support considerable healthcare resource utilization (HCRU) among the subset of patients affected by TDT or SCD with recurrent VOCs in high-resource countries [18–24].

Despite strategies (e.g., screening policies, awareness campaigns, and clinical guidelines) that have improved the prevention, early diagnosis, and management of hemoglobinopathies in Italy [3, 4, 6, 25], further efforts are needed to better understand and address these national health priorities [26, 27]. Few Italian studies have described the health system impact of β-thalassemia and SCD, especially the most severe forms. Perrone et al. and De Franceschi et al. recently reported high annual mean rates of hospitalizations, outpatient services, and outpatient prescriptions among patients with TDT and patients with SCD, respectively [12, 28]. However, Perrone et al. collected data only from 2010 to 2016 [28], and De Franceschi et al. did not evaluate resource utilization associated with the management of recurrent VOCs [12]. Given the limited available data on and ever-growing relevance of severe hemoglobinopathies in Italy, this retrospective claims analysis aimed to comprehensively measure real-world mortality, clinical complications, and HCRU among Italian patients with TDT and Italian patients with SCD with recurrent VOCs.

2 Methods

2.1 Study Design and Data Source

This longitudinal, observational, retrospective cohort study identified patients with TDT and patients with SCD with recurrent VOCs using an administrative claims database that includes approximately 12 million Italian residents served by the National Health Service (NHS)/Local Health Units (LHU).[29] The database includes demographic, pharmaceutical, hospitalization, outpatient specialist service, and payment exemption data and excludes emergency department (ED) data. The overall study period was 1 January 2010–1 February 2020.

2.2 Study Population

2.2.1 Patients with TDT

Patients with TDT who had ≥ 1 iron chelation therapy anatomical therapeutic chemical (ATC) claim code(s) from 1 January 2010 to 1 February 2019, received ≥ 8 RBCTs during any 12-month period, and had ≥ 12 months of available data before and after the index date (i.e., the date of their first RBCT claim) were included. Patients were excluded if they had evidence of congenital anemias, iron deficiency anemia, myelodysplastic syndrome, myelofibrosis, myelophthisis, or SCD; evidence in their medical records of hematopoietic stem cell transplantation (HSCT) at any time; or ≥ 1 erythropoietin prescription claim from 1 January 2010 to 1 February 2019.

2.2.2 Patients with SCD with Recurrent VOCs

Eligible patients with SCD with recurrent VOCs had an SCD international classification of diseases (ICD) claims code between 1 January 2010 and 1 February 1 2019, ≥ 2 VOCs per year in ≥ 2 consecutive years, and ≥ 12 months of available data before and after the index date (i.e., the date of the second VOC claim in the second of 2 consecutive years). A VOC was defined as acute pain crisis, acute chest syndrome, priapism, or splenic sequestration. Patients whose medical records showed evidence of HSCT at any time were excluded.

2.2.3 Matched Controls

Given the observational nature of the study, non-random assignment can result in groups that are not equivalent on a number of baseline characteristics. Propensity score matching was performed to reduce potential imbalance in baseline characteristics when identifying matched controls (i.e., individuals from the general population without TDT or SCD with recurrent VOCs) for each eligible patient with TDT or SCD with recurrent VOCs. The propensity score was estimated by logistic regression model (considering the confounding variables: age at index date, sex, geographic area of residence, and index year). Propensity scores were divided in quintiles, and patients were stratified in each quintile on the basis of their propensity score. A 1:5 matching algorithm was used to match patients in each quintile in the two groups to identify two balanced cohorts of patients to compare. To evaluate the balance between the relevant cohorts (i.e., (1) TDT and matched general population controls and (2) SCD with recurrent VOCs and matched general population controls) *p*-values for each covariate before and after matching were calculated. An adequate balance was defined as p-value > 0.05. The index date was assumed to be from the same index year as for the matched patient. Matched controls were required to have ≥ 12 months of available data before and after the index date.

All eligible patients and matched controls were followed for ≥ 12 months from the index date to the earliest occurrence of a censoring event (i.e., death or deregistration from the database) or the study period end date, whichever came first.

2.3 Study Outcomes

Baseline demographics (i.e., age, sex, and geographic area of residence) were calculated at the index date. Mean follow-up time was also reported. Mortality proportions, mortality rates per 100 person-years, and clinical complication proportions were assessed during follow-up. HCRU during follow-up was summarized as rates per patient per year (PPPY).

2.4 Statistical Analysis

Demographic, mortality, clinical complication, and HCRU data were analyzed descriptively. Values associated with patient numbers < 4 were blinded to ensure patient privacy. Numbers (proportions) of patients or events are reported for categorical variables and means (standard deviations [SDs]) are reported for continuous variables.

Descriptive analyses were performed for mortality and HCRU for patients with TDT, patients with SCD with recurrent VOCs, and matched controls. Descriptive analyses were also performed for clinical complications for patients with TDT and SCD with recurrent VOCs.

Comparative analyses were performed for mortality and HCRU outcomes between patients with TDT, patients with SCD with recurrent VOCs, and matched controls. Statistical significance (i.e., $p < 0.05$) was determined by a *Z*-test for mortality proportion differences and a *t*-test for HCRU rate differences.

Subgroup analyses were used to evaluate mortality, clinical complications, and HCRU by age at the index date among patients with TDT (0–11, 12–35, 36–64, and ≥ 65 years) and patients with SCD with recurrent VOCs (0–11, 12–35, and ≥ 36 years). Age groups were aligned with pediatric (0–11 years), adolescent and young adult (12–35 years), older adult (36–64 years), and geriatric (≥ 65 years). Given sample size limitations for patients with SCD, older adults and geriatric individuals were combined (i.e., ≥ 36 years). HCRU was also assessed by number of RBCTs during follow-up (< 8, 8–16, and > 16 PPPY) among patients with TDT.

3 Results

3.1 Demographics

A total of 214 patients with TDT were included in the study (Fig. 1) and matched to 1070 controls. The mean age was 46.7 (SD 20.2) years, and 45.8% of patients were aged 36–64 years (Table 1). Approximately half (54.2%) of the patients with TDT were female, and 69.6% resided in South Italy (Table 1).

Of the patients with SCD with recurrent VOCs identified from the claims database, 111 fulfilled the eligibility criteria (Fig. 1) and were matched to 555 controls. The mean age was 24.5 (SD 18.6) years, and similar proportions of patients with SCD with recurrent VOCs composed each age group (0–11 years: 36.1%; 12–35 years: 29.7%; and ≥ 36 years: 34.2%; Table 1). Most patients with SCD with recurrent VOCs were female (50.5%) and resided in South Italy (53.2%; Table 1).

The demographics of patients with TDT and patients with SCD with recurrent VOCs were similar to those of matched controls (Table 1).

3.2 Mortality

The proportion of deaths and mortality rate during follow-up were higher among patients with TDT than among matched controls (22.0% versus 4.5%, $p < 0.001$, and 4.8 versus 0.8 deaths per 100 person-years, respectively; Table 2).

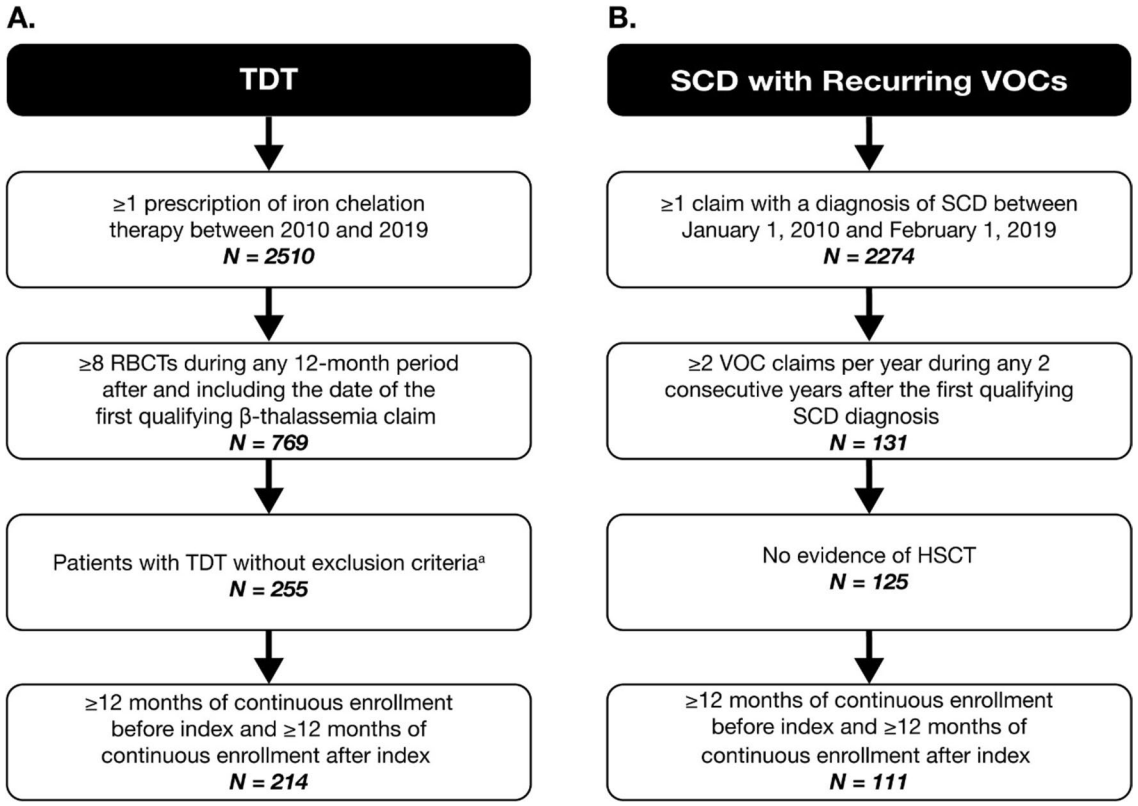

Fig. 1 Patient attrition for **A** TDT and **B** SCD with recurrent VOCs. *HSCT* hematopoietic stem cell transplantation, *RBCT* red blood cell transfusion, *SCD* sickle cell disease, *TDT* transfusion-dependent β-thalassemia, *VOC* vaso-occlusive crisis. [a]Exclusion criteria included patients with congenital anemias, iron deficiency anemia, myelodysplastic syndrome, myelofibrosis, myelophthisis, or SCD; evidence of HSCT at any time in their medical records; or ≥ 1 erythropoietin prescription claim during the inclusion period

Similarly, the proportion of deaths during follow-up was higher among patients with SCD with recurrent VOCs than among matched controls (8.1% versus 2.3%, $p < 0.001$), as was the mortality rate (1.6 versus 0.4 deaths per 100 person-years; Table 2). Mortality rates per 100 person-years increased with age for both patients with TDT (0–11 years: 0; 12–35 years: 0.7; 36–64 years: 1.8; ≥ 65 years: 27.1) and patients with SCD with recurrent VOCs (0–11 years: 0; 12–35 years: 1.2; ≥ 36 years: 3.7; Tables 1 and 2 of the Electronic Supplementary Material [ESM]).

3.3 Clinical Complications

Among patients with TDT, endocrine complications (19.2%), liver complications (14.5%), malignancies (13.1%), cardiopulmonary complications (12.1%), and musculoskeletal complications (10.3%) were the most prevalent (Table 3). The most common clinical complications among patients with SCD with recurrent VOCs were chronic pain (17.1%), liver complications (13.5%), avascular bone necrosis (10.8%), and gallstones (10.8%; Table 4). Generally, clinical complications were more common in older patients (i.e., aged ≥ 36 years) with TDT (e.g., malignancies [18.1%] and endocrine complications [23.5%]; Table 3 of the ESM) or SCD with recurrent VOCs (e.g., liver complications [23.7%] and gallstones [21.1%]; Table 4 of the ESM).

3.4 Healthcare Resource Utilization

Patients with TDT received a mean of 18.2 (SD 12.2) RBCTs PPPY during follow-up. Mean HCRU rates PPPY were significantly higher among patients with TDT than among matched controls (all-cause hospitalizations [1.4 versus 0.1], outpatient services [21.9 versus 1.6], and outpatient prescriptions [20.3 versus 4.9]; Table 5). Mean outpatient prescription rates PPPY increased with age among patients with TDT (0–11 years: 8.2; 12–35 years: 14.5; 36–64 years: 20.2; ≥ 65 years: 28.8), and mean outpatient service rates PPPY increased with the number of RBCTs PPPY (< 8: 13.5; 8–16: 17.8; > 16: 27.4; Table 5 of the ESM).

Patients with SCD with recurrent VOCs versus matched controls had significantly higher mean rates of all-cause

Table 1 Demographics of patients with TDT, patients with SCD with recurrent VOCs, and matched controls

	Patients with TDT (*N* = 214)	Matched controls[a] (*N* = 1070)	Patients with SCD with recurrent VOCs (*N* = 111)	Matched controls[a] (*N* = 555)
Age in years, mean (SD)	46.7 (20.2)	45.0 (19.4)	24.5 (18.6)	26.5 (21.7)
Age group in years, *n* (%)*				
0–11	7 (3.3)	58 (5.4)	40 (36.1)	186 (33.5)
12–35	58 (27.1)	255 (23.8)	33 (29.7)	173 (31.2)
36–64	98 (45.8)	542 (50.7)	38 (34.2)[b]	196 (35.3)[b]
≥ 65	51 (23.8)	215 (20.1)		
Sex, *n* (%)*				
Male	98 (45.8)	461 (43.1)	55 (49.5)	269 (48.5)
Female	116 (54.2)	609 (56.9)	56 (50.5)	286 (51.5)
Geographic area, *n* (%)*				
North Italy	40 (18.7)	186 (17.4)	33 (29.7)	171 (30.8)
Central Italy	25 (11.7)	106 (9.9)	19 (17.1)	83 (15.0)
South Italy	149 (69.6)	778 (72.7)	59 (53.2)	301 (54.2)
Follow-up time (years), mean (SD)	4.6 (2.5)	5.6 (2.4)	5.1 (2.2)	6.5 (2.3)

SCD sickle cell disease, *SD* standard deviation, *TDT* transfusion-dependent β-thalassemia, *VOC* vaso-occlusive crisis

*p-Values for patients with SCD with recurrent VOCs and TDT were $p > 0.05$ compared with respective matched controls (SCD with recurrent VOCs: age $p = 0.875$, sex $p = 0.835$, and geographic area $p = 0.845$; TDT: age $p = 0.216$, sex $p = 0.465$, and geographic area $p = 0.619$).

[a]Individuals from the general population were propensity score matched, without replacement, by age at the index date, sex, geographic area of residence, and index year to patients with SCD with recurrent VOCs and patients with TDT

[b]Individuals aged ≥ 36 years of age (includes individuals 36–64 years and ≥ 65 years)

Table 2 Mortality among patients with TDT, patients with SCD with recurrent VOCs, and matched controls

	Patients with TDT (*N* = 214)	Matched controls[a] (*N* = 1070)	Patients with SCD with recurrent VOCs (*N* = 111)	Matched controls[a] (*N* = 555)
Deaths, *n* (%)*	47 (22.0)	48 (4.5)	9 (8.1)	13 (2.3)
Person-years	973	5941	569	3083
Overall mortality rate (per 100 person-years)	4.8	0.8	1.6	0.4

SCD sickle cell disease, *SD* standard deviation, *TDT* transfusion-dependent β-thalassemia, *VOC* vaso-occlusive crisis

*$p < 0.001$ for rates in patients with SCD with recurrent VOCs versus matched controls and patients with TDT versus matched controls

[a]Individuals from the general population were propensity score matched, without replacement, by age at the index date, sex, geographic area of residence, and index year to patients with SCD with recurrent VOCs and patients with TDT

hospitalizations (2.0 versus 0.1), outpatient services (6.2 versus 1.0), and outpatient prescriptions (12.2 versus 2.5) PPPY during follow-up (Table 5). Older patients with SCD with recurrent VOCs had higher mean all-cause hospitalization rates PPPY (0–11 years: 1.6; 12–35 years: 2.0; ≥ 36 years: 2.4; Table 6 of the ESM). Similarly, as age increased, so did mean outpatient service rates PPPY (0–11 years: 5.7; 12–35 years: 5.8; ≥ 36 years: 7.2) and mean outpatient prescription rates PPPY (0–11 years: 7.1; 12–35 years: 11.1; ≥ 36 years: 18.4; Table 6 of the ESM).

4 Discussion

Here, we report clinical outcomes and HCRU among patients with TDT and patients with SCD with recurrent VOCs in Italy, derived from real-world administrative claims data. Elevated mortality, high prevalence of clinical complications, and significant HCRU were observed among these patient groups during follow-up. Older age was associated with greater clinical burden and HCRU; frequent RBCTs were also a driver of HCRU for patients with TDT.

Table 3 Clinical complications during follow-up in patients with TDT

Complication, *n* (%)[a]	Patients with TDT (*N* = 214)
Endocrine complications[b]	41 (19.2)
Diabetes	36 (16.8)
Hypothyroidism	7 (3.3)
Liver complications[c]	31 (14.5)
HBV/HCV	20 (9.3)
Hepatic fibrosis/cirrhosis	13 (6.1)
Malignancies[d]	28 (13.1)
Leukemia	21 (9.8)
Lymphoma	5 (2.3)
Solid malignancies	4 (1.9)
Cardiopulmonary complications[e]	26 (12.1)
Heart failure	13 (6.1)
Atrial fibrillation	12 (5.6)
Musculoskeletal complications	22 (10.3)
Osteoporosis	20 (9.3)
Osteopenia	4 (1.9)
Depression	20 (9.3)
Infections[f]	12 (5.6)

HBV hepatitis B virus, *HCV* hepatitis C virus, *TDT* transfusion-dependent β-thalassemia

[a]Inclusive of complications that were not blinded (i.e., affecting < 4 patients) or 0 in the overall cohort. Individual patients could have more than one clinical complication.

[b]Inclusive of diabetes, hypothyroidism, and hypoparathyroidism

[c]Inclusive of HBV/HCV, hepatocellular carcinoma, hepatomegaly, and hepatic fibrosis/cirrhosis

[d]Inclusive of leukemia, lymphoma, solid malignancies, and myeloma

[e]Inclusive of heart failure, pericarditis, atrial fibrillation, and pulmonary hypertension

[f]Inclusive of sepsis/septicemia, bacteremia, pneumococcal sepsis, and osteomyelitis

Table 4 Clinical complications during follow-up in patients with SCD with recurrent VOCs

Complication, *n* (%)[a]	SCD with recurrent VOCs (*N* = 111)
Chronic pain[b]	19 (17.1)
Liver complications[c]	15 (13.5)
Hepatitis	11 (9.9)
Hepatic fibrosis	8 (7.2)
Avascular bone necrosis	12 (10.8)
Gallstones	12 (10.8)
Cardiopulmonary complications[d]	8 (7.2)
Heart failure	8 (7.2)
Cardiomegaly	4 (3.6)
Infections	8 (7.2)
Hypersplenism	8 (7.2)
Hypercoagulable state	8 (7.2)
Pulmonary embolism	4 (3.6)
Deep vein thrombosis	4 (3.6)
Depression	7 (6.3)
Renal complications[e]	4 (3.6)
Biliary complications[f]	4 (3.6)

SCD sickle cell disease, *VOC* vaso-occlusive crisis

[a]Inclusive of complications that were not blinded (i.e., affecting < 4 patients) or 0 in the overall cohort. Individual patients could have more than one clinical complication.

[b]Identified by patients receiving ≥ 2 opioid prescriptions

[c]Inclusive of portal hypertension, hepatic insufficiency, hepatitis, and hepatic fibrosis/cirrhosis

[d]Inclusive of pulmonary hypertension, heart failure, and cardiomegaly

[e]Inclusive of nephrolithiasis and renal insufficiency

[f]Inclusive of indirect hyperbilirubinemia and biliary sludge

We observed a substantially higher mortality proportion and rate among patients with TDT than among the general population (22.0% versus 4.5% and 4.8 versus 0.8 deaths per 100 person-years) [20, 30]. Although one recent Italian study reported a lower mortality proportion (13.1%) among patients with TDT who were optimally managed at specialized centers [31], our results highlight the unmet need of TDT patient populations in Italy, inclusive of those who might not be managed at specialized centers. We also observed a substantially higher mortality proportion and rate among patients with SCD with recurrent VOCs than among the general population (8.1% versus 2.3%, corresponding to 1.6 versus 0.4 deaths per 100 person-years). Patient outcomes were consistent with a recent study that observed a mean age of death of 49.5 years and mortality proportion of 9.4% in 534 Italian patients with SCD [32]. Additionally, the SCD-associated mortality observed in this study was largely similar to that observed in studies conducted in other European countries [18, 33]. The increased mortality rates as patients age are consistent with those observed in other studies of patients with TDT and SCD, representing the progressive nature of both diseases and the need for additional treatments that mitigate their substantial clinical burden [25, 31, 34–37].

In this study, patients with TDT and patients with SCD with recurrent VOCs experienced prevalent clinical complications that impacted diverse organ systems, as previously shown in studies conducted in other high-resource countries [18, 23, 24]. Endocrine, liver, and musculoskeletal complications have been reported among Italian patients with TDT [28, 38, 39], as have frequent hepatobiliary and musculoskeletal complications among Italian patients with SCD [12]. Although other published analyses of Italian patients with TDT observed a higher prevalence

Table 5 Annual HCRU among patients with TDT, patients with SCD with recurrent VOCs, and matched controls

HCRU, mean rate PPPY (SD)[a]	Patients with TDT (*N* = 214)	Matched controls[b] (*N* = 1070)	Patients with SCD with recurrent VOCs (*N* = 111)	Matched controls[b] (*N* = 555)
All-cause hospitalizations	1.4 (3.4)	0.1 (0.3)	2.0 (1.5)	0.1 (0.3)
Ordinary	0.7 (2.0)	0.1 (0.3)	0.9 (1.1)	0.1 (0.3)
Day-hospital	0.6 (1.8)	0 (0.2)	1.1 (0.8)	0 (0.2)
Outpatient services	21.9 (17.0)	1.6 (3.4)	6.2 (10.3)	1.0 (2.8)
Visits	11.4 (13.7)	0.5 (1.4)	3.4 (6.1)	0.3 (1.1)
Diagnostic tests/laboratory visits	10.5 (8.0)	1.1 (2.4)	2.8 (5.0)	0.8 (2.2)
Outpatient prescriptions	20.3 (12.5)	4.9 (7.7)	12.2 (10.9)	2.5 (5.7)

HCRU healthcare resource utilization, *PPPY* per patient per year, *SCD* sickle cell disease, SD standard deviation, *TDT* transfusion-dependent β-thalassemia, *VOC* vaso-occlusive crisis

[a] $p < 0.001$ for rates in patients with SCD with recurrent VOCs versus matched controls and patients with TDT versus matched controls

[b] Individuals from the general population were propensity score matched, without replacement, by age at the index date, sex, geographic area of residence, and index year to patients with SCD with recurrent VOCs and patients with TDT

of clinical complications than we observed in our analysis, potentially due to the difference in study design (i.e., self-reporting survey methodology), the substantial overall clinical burden observed was largely similar [39]. The high proportion of patients with TDT-related malignancies (13.1%) is a novel finding that should be interpreted with caution and replicated in future studies; nonetheless, the differences between age groups (0–11 years: 0%; 12–35 years: blinded; 36–64 years: 4.1%; ≥ 65 years: 35.4%) are consistent with heightened malignancy risk as individuals age [34, 40]. Overall, the increased prevalence of clinical complications with age shown in this study aligns with the known progressive nature of these hemoglobinopathies and reinforces the importance of effective early intervention and management of disease [16, 34, 41].

The extensive HCRU associated with managing TDT and SCD with recurrent VOCs in Italy observed in this study was similar to that observed in studies conducted in other high-resource countries [18, 20–24]. A recent retrospective administrative data analysis in Italy also found high mean HCRU among patients with TDT (RBCTs: 11.9 PPPY; outpatient prescriptions: 23.4 PPPY; hospitalizations: 2.2 PPPY; outpatient services: 103.7 PPPY) [28]. Our study results for SCD were generally comparable to those from a recent retrospective assessment of SCD-associated HCRU in Italy conducted by De Franceschi et al. [12]. However, we observed a twofold higher mean all-cause hospitalization rate (1.10 versus 1.96 PPPY), a disparate finding that may have emerged from our focus on patients with the most severe disease, despite their younger mean age (24.5 versus 43.8 years) [12]. The increase in HCRU with age seen here is consistent with previous studies in patients with TDT and SCD from the USA [41, 42] and other countries [43, 44]. These data underline the health system impact of severe hemoglobinopathies in Italy and the relevance of patient age to their treatment and management.

This study provides new and comprehensive data on both the clinical and health system burden of TDT and SCD with recurrent VOCs in Italy. Compared with previous studies, this study focused on patients with the most severe form of these diseases and included more recent data. A key difference was that our study targeted the subset of patients with SCD with recurrent VOCs (i.e., ≥ 2 VOCs per year in ≥ 2 consecutive years). Moreover, we defined VOC more broadly (i.e., acute pain crisis, acute chest syndrome, priapism, or splenic sequestration) than SCD, with crisis requiring hospitalization only, and were therefore able to more completely capture HCRU associated with severe SCD [12]. Our dataset was also more recent than other published Italian HCRU datasets for TDT and SCD, with a cut-off in 2020 versus 2016−2017 [12, 28].

The results presented here should be interpreted in the context of certain limitations. First, the analysis was conducted using a sample corresponding to 20% of the total Italian population; thus, our findings may not fully capture the diversity of patient populations in clinical practice settings. Moreover, there was potential for misclassification bias arising from our use of administrative claims data obtained for reimbursement, which could have also led to incomplete information on possible cofounders (e.g., disease severity and comorbidities) that may have influenced the results [12, 45]. In addition, while propensity score matching reduced potential confounding between cases and controls, there is risk of matching dissimilar patients who have similar scores but have differences in key variables. Disease burden and HCRU were most likely under-reported, as the database we

used did not capture ED data, which is particularly relevant for patients with SCD. As such, we expect that the number of patients who met our definition of SCD with recurrent VOCs and VOC-related outcomes was underestimated. De Franceschi et al. similarly noted the likelihood that they underestimated the frequency of VOCs and extent of HCRU, as ED admissions data for this patient group were missing [12]. Furthermore, we may have underestimated HCRU, as we excluded patients who did not fulfill the minimum 12-month pre- and post-index date periods (e.g., due to death or non-continuous enrollment). Interpretation of clinical complication outcomes by age was limited by small sample sizes and substantial blinding. Lastly, we are unable to directly compare our findings with those of prior studies of severe SCD, given that they did not use a standardized definition of recurrent VOCs. Comparison is further challenged by varied VOC definitions across studies, including our use of a novel and more inclusive composite definition [45].

5 Conclusions

Italian patients with TDT or SCD with recurrent VOCs have considerable mortality, clinical complications, and HCRU, despite the current standard of care. Elevated HCRU is driven by older age in both hemoglobinopathies and by RBCTs in TDT. Strategies to reduce the dependence on RBCTs in TDT and incidence of VOCs in SCD, such as new treatment options, are required to potentially alleviate the growing burden of illness and HCRU associated with these severe hemoglobinopathies in Italy.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s41669-024-00532-4.

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Declarations

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Conflicts of Interest Chuka Udeze, Nanxin Li, and Thi Xuan Mai Patricia Dang are employees of Vertex Pharmaceuticals Incorporated and may hold stock or stock options in the company. Gian Luca Forni reports advisory board participation for Agios, Bristol Myers Squibb, and Vertex. Melania Dovizio, Chiara Veronesi, and Luca Degli Esposti do not have conflicts of interest to disclose.

Availability of Data and Material This study used data available from Clicon. Restrictions apply to the availability of these data, which were used under a licensing agreement.

Ethics Approval The Declaration of Helsinki is not applicable to this study. The study was conducted in accordance with ethical standards, submitted, and approved by the local ethics committees of the participating healthcare entities as follows: Authorization of the Ethics Committee "BAT (Barletta-Andria-Trani) Comitato etico interprovinciale Area I" (protocol number 68/CE/20, approval date 3 December 2020). Authorization of the Ethics Committee "Berica Comitato Etico per le Sperimentazioni Cliniche (CESC) della Provincia di Vicenza" (protocol number 1627, approval date 28 October 2020). Authorization of the Ethics Committee "Foggia Comitato etico interprovinciale Area I" (protocol number 63/CE/20, approval date 3 December 2020). Authorization of the Ethics Committee "Frosinone Comitato Etico Lazio 2" (protocol number 0179046/2020, approval date 28 October 2020). Authorization of the Ethics Committee "Genova Comitato Etico Regionale Liguria" (protocol number 0179046/2020, approval date 14 June 2021). Authorization of the Ethics Committee "Comitato Etico ASL Lecce" (protocol number 34, approval date 04 July 2019). Authorization of the Ethics Committee "Napoli 3 Comitato Etico Interaziendale Campania Sud" (protocol number 51, approval date 02 September 2020). Authorization of the Ethics Committee "Pedemontana Comitato Etico per le Sperimentazioni Cliniche (CESC) della Provincia di Vicenza" (protocol number 0036999, approval date 28 April 2021). Authorization of the Ethics Committee "Comitato Etico delle Province di Chieti e Pescara" (protocol number 07, approval date 18 March 2021). Authorization of the Ethics Committee "ASREM Azienda Sanitaria Regione Molise" (protocol number 101125, approval date 27 October 2020). Authorization of the Ethics Committee "Roma 4 Comitato Etico Lazio 1" (protocol number 1079/CE Lazio 1, approval date 23 September 2020). Authorization of the Ethics Committee "Roma 5 Comitato Etico Lazio 1" (protocol number 1166/CE Lazio 1, approval date 12 October 2020). Authorization of the Ethics Committee "Roma 6 Comitato Etico Lazio 2" (protocol number 0216084/2020, approval date 15 December 2020). Authorization of the Ethics Committee "Salerno Comitato Etico Inter-aziendale Campania Sud" (protocol number 64, approval date 03 November 2020). Authorization of the Ethics Committee "Serenissima Comitato Etico per la Sperimentazione Clinica della provincia di Venezia e IRCCS S. Camillo" (28/07/2020). Authorization of the Ethics Committee "Comitato Etico per le province di L'Aquila e Teramo" (protocol number 11, approval date 24 March 2021). Authorization of the Ethics Committee "Umbria 2 Comitato Etico Regionale Umbria" (protocol number 19414/20/ON, approval date 16 September 2020). Authorization of the Ethics Committee "Vercelli Comitato Etico Interaziendale A.O. SS. Antonio e Biagio e Cesare Arrigo – Alessandria" (protocol number 0008668, approval date 20 April 2021).

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