

## Sickle cell disease in Germany: results from a national registry

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**HEMATOLOGY: RESEARCH ARTICLE****Sickle cell disease in Germany: Results from a national registry**

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Abbreviations: EBV, Epstein-Barr virus; GPOH, German Society of Pediatric Oncology and Hematology; HbS, hemoglobin S; HbS  $\beta^{0/+}$ thal, compound heterozygosity for HbS and  $\beta^0$ thal or  $\beta^+$ thal, respectively; HbSC, compound heterozygosity for HbS and HbC; HbSS, homozygosity for HbS; HLA, human leukocyte antigen; HPFH, hereditary persistence of fetal hemoglobin; ICD, International Classification of Diseases; SCD, sickle cell disease; SD, standard deviation; TCD, transcranial Doppler ultrasonography.

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#### Abstract

**Background:** Limited data on the prevalence and medical care of sickle cell disease (SCD) in Germany are available. Here, we make use of a patient registry to characterize the burden of disease and the treatment modalities for patients with SCD in Germany.

**Procedure:** A nationwide German registry for patients with SCD documents basic data on diagnosis and patient history retrospectively at the time of registration. A prospective annual documentation provides more details on complications and treatment of SCD. For the current analyses, data of 439 patients were available.

**Results:** Most patients had homozygous SCD (HbSS 75.1%, HbS/ $\beta$ -thalassemia 13.2%, and HbSC 11.3%). The median age at diagnosis was 1.9 years (interquartile range, 0.6–4.4 years), most patients were diagnosed when characteristic symptoms occurred. Sepsis and stroke had affected 3.2% and 4.2% of patients, respectively. During the first year of observation, 48.3% of patients were admitted to a hospital and 10.1% required intensive care. Prophylactic penicillin was prescribed to 95.6% of patients with homozygous SCD or HbS/ $\beta$  thalassemia below the age of six and hydroxycarbamide to 90.4% of patients above the age of two years. At least one annual transcranial Doppler ultrasound was documented for 74.8% of patients between 2 and 18 years.

**Conclusion:** With an estimated number of at least 2000, the prevalence of SCD in Germany remains low. Prospectively, we expect that the quality of care for children with SCD will be further improved by an earlier diagnosis after the anticipated introduction of a newborn screening program for SCD.

#### KEYWORDS

epidemiology, Germany, registry, sickle cell disease

## 1 | INTRODUCTION

Sickle cell disease (SCD) is a multiorgan disorder resulting in significant morbidity and mortality.<sup>1,2</sup> Through prophylactic and therapeutic interventions such as parent education,<sup>3</sup> vaccinations,<sup>4</sup> antibiotic prophylaxis,<sup>5</sup> hydroxycarbamide treatment<sup>6</sup> and red blood cell transfusion,<sup>7</sup> survival during childhood has continuously improved.<sup>8</sup>

In Germany, SCD exclusively affects immigrants from endemic areas and their descendants, especially from Africa and the Middle East.<sup>9,10</sup> Admission diagnosis data provide an estimate of the increasing frequency of SCD and of its complications in Germany.<sup>10</sup> However, more detailed epidemiological data are required to document the burden of disease, to identify shortcomings in patient management, and to improve patient care. In addition, health policy decision-making, e.g., on the implementation of a newborn screening for SCD or on the licensing of hydroxycarbamide for infants, needs to be supported by "real-world evidence." Several patient registries worldwide have already answered many clinical questions concerning SCD.<sup>8,11–14</sup> However, these data

cannot be directly transferred to patients living in Germany, who likely differ from those living elsewhere with regard to the genetic and social background. For these reasons, a registry for patients with SCD was established by the German Society of Pediatric Oncology and Hematology (GPOH). Here, we report the first results from this registry.

## 2 | METHODS

### 2.1 | Registry design

The nationwide SCD registry records retrospective and prospective data on patients with SCD across multiple centers. Primarily, all pediatric centers organized in the German Society for Pediatric Oncology and Hematology and three internal medicine centers were invited to join the registry. In total, 61 centers were approached, 38 committed to participate and 22 were actively recruiting at the time of data cutoff. New centers may join the registry at any time. Key inclusion criterion

was the diagnosis of SCD (both homozygous and compound heterozygous). Heterozygous carriers of the HbS trait were excluded. The study was approved by the institutional review board of the Medical Faculty of Heidelberg University (S-416/2014) and performed according to the Declaration of Helsinki. Written informed consent from patients or legal guardians, respectively, was obtained. The first patient was registered in November 2015. Data cutoff for this publication was July 4, 2019. Apart from the registry, the SCD consortium mandated by the GPOH coordinates several other activities in support of the registry. These include treatment guidelines for SCD,<sup>15</sup> creation of a reference network to offer advice to physicians with limited experience with SCD, pilot projects in newborn screening for SCD, and educational events. The registry is filed with ClinicalTrials.gov (NCT03327428).

## 2.2 | Care for SCD

The registry is a purely observational study that does not regulate patient treatment. However, national treatment guidelines<sup>15</sup> recommend basic health care measures for SCD, such as parental education, vaccinations, the use of antibiotic prophylaxis or TCD screening as do international treatment guidelines.<sup>16,17</sup> In Germany, everybody is covered under an obligatory health insurance system, regardless of their employment status. New immigrants who are asylum seekers have access to medical treatment for acute conditions as well as vaccinations. After a waiting period of 15 months, they become eligible for the obligatory health insurance coverage, which includes free access to approved medications. Currently, 60 centers with expertise in pediatric hematology offer care for patients with SCD, but not all centers are equipped for TCD screening. Adults with SCD are frequently taken care of by general practitioners, most hematologists follow few patients only.

## 2.3 | Data collection

The registry continues collecting data prospectively without fixed end date. Participating centers enter data via "remote data entry" into electronic case report forms that have been designed using the electronic data capture software Marvin (XClinical GmbH, Munich, Germany). At the time of registration, basic data including date of birth, date and circumstances of diagnosis, genotype, country of origin, blood group, and patient's past medical history are reported. Starting from the date of registration, annual follow-ups prospectively document details of SCD-related complications (see Supporting Information Table S1), laboratory parameters, and treatment that have been collected in the previous 12 months. Data verification was by plausibility check but not by source data verification. The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

## 2.4 | Statistical analysis

Periodic analysis and reporting are conducted annually and include analyses specified by a cutoff date. The present report is based on an

interim analysis with all available data until the cutoff date of July 4, 2019.

In this observational study, no formal statistical hypothesis was specified in the study protocol. The sample size is not statistically powered for hypothesis testing, and the statistical analysis focuses on descriptive and exploratory techniques.

## 3 | RESULTS

Until the cutoff date, 22 centers in Germany registered a total of 439 patients with SCD. Two centers (Hamburg, Berlin) contributed each at least 50 patients, ten more centers at least 10, thus documenting that SCD patients are widely distributed across the country. Two-hundred twenty-four patients (51%) were female, and 215 (49%) were male. Genotypes, countries of origin, age at diagnosis, and age at registration are presented in Table 1. One-hundred seventy-two (90.1%) of 191 patients with SCD aged 6 to 16 years attend regular schools.

### 3.1 | SCD results in relevant morbidity

As expected, at the time of registration, more than two thirds of patients had already experienced at least one pain crisis requiring hospitalization, more than one quarter had suffered from acute chest syndrome (Table 2). These numbers were lower in patients with HbSC disease compared with homozygous SCD. Stroke and sepsis were reported in the history of 4.2% and 3.2% of all patients, respectively.

During the first year of observation (Table 3), 201 (48.4%) of 415 evaluable registry patients with SCD were treated as inpatients, 20 (10.2%) of 196 evaluable patients required intensive care. The totals of evaluable patients vary because the number of missing values differs, leaving room for a reporting bias if the number of evaluable patients is considerably lower than the total of 439. The most frequent reason for hospitalization was acute pain (154 of 413 patients, 37.3%), followed by acute chest syndrome. These numbers did not change during the second and third years of follow-up (Supporting Information Table S2). On average, patients were admitted 0.7 times per year for pain (range, 0-20). Hospital admissions for pain crisis documented during the first annual follow-up in the SCD registry (283 in  $n = 406$  patients) represent 22.3% of the 1269 hospital admissions that have been reported by hospitals with principal diagnosis "SCD with crises" (ICD code D57.0) in 2017 according to the nationwide statistics of the German Federal Statistical Office.<sup>10,18</sup> If the number of hospitalizations in the registry was representative for all patients with SCD in Germany, the minimum total number of patients with SCD in Germany could be estimated to be at least 2000. However, in adult patients treated in hospital, SCD frequently is a secondary, not a principal, hospital diagnosis. Because adults are underrepresented in our registry, the real number of patients with SCD may considerably exceed this approximation. Further, the total number of patients may be underestimated because patients with mild disease may not be captured.

The overall incidence of acute chest syndrome (72 episodes in 679 observation years) was comparable to that in the cooperative study of

**TABLE 1** Patient and disease characteristics

Genotypes (n = 425)					
HbSS 319 (75.1%)					
HbS/ $\beta^0$ thal 27 (6.4%)					
HbS/ $\beta^+$ thal 29 (6.8%)					
HbSC 48 (11.3%)					
Others: HbS/OArab 1 (0.2%), HbS/HPFH 1 (0.2%)					
Region/country of origin*					
(for each patient, country of origin of both parents is reported; n = 824)					
Africa (66.8%)	Nigeria	170	(20.6%)		
	Ghana	140	(17.0%)		
	Togo	48	(5.8%)		
	Angola	42	(5.1%)		
	Cameroon	34	(4.1%)		
	Guinea	23	(2.8%)		
	Congo	21	(2.6%)		
	Sierra Leone	12	(1.5%)		
	Other	60	(7.3%)		
Asia (21.9%)	Lebanon/Palestine	61	(7.5%)		
	Syria	41	(5.0%)		
	Turkey	32	(3.9%)		
	Iraq	25	(3.0%)		
	Other	21	(2.5%)		
Europe (without Turkey)		19	(2.3%)		
America		14	(1.7%)		
Unknown		53	(6.4%)		
Age at diagnosis/at registration					
	<1 year	1-5 years	6-11 years	12-17 years	>17 years
At diagnosis (n = 379)	129 (34%)	189 (49.9%)	44 (11.6%)	13 (3.4%)	4 (1.1%)
At registration (n = 438)	14 (3.2%)	108 (24.7%)	155 (35.4%)	92 (21.0%)	69 (15.8%)
Circumstance of diagnosis (n = 351)					
Newborn screening	Positive family history	Routine checkup	Symptoms	Incidental finding	Others
18 (5.1%)	76 (21.7%)	5 (1.4%)	202 (57.5%)	34 (9.7%)	16 (4.6%)

\*Only countries contributing > 10 to the countries of origin.

**TABLE 2** Medical history prior to registration: SCD-associated complications by genotype

Genotype	HbSS n = 319	HbS $\beta^0$ thal n = 27	HbS $\beta^+$ thal n = 29	HbSC n = 48	Total n = 425*
Severe pain crisis**	221 (71.1%)	17 (65.4%)	21 (72.4%)	24 (53.3%)	285 (69.0%)
Acute chest syndrome	102 (33.3%)	2 (8.7%)	6 (20.7%)	8 (18.2%)	118 (29.2%)
Splenic sequestration	42 (13.8%)	7 (29.2%)	7 (25.9%)	0	56 (14.0%)
Splenectomy	40 (12.8%)	9 (36.0%)	6 (20.7%)	0	55 (13.3%)
Aplastic crisis	28 (9.4%)	3 (13.0%)	5 (17.2%)	5 (11.4%)	42 (10.6%)
Stroke	15 (5.0%)	2 (8.3%)	0	0	17 (4.2%)
Sepsis	12 (3.9%)	0	1 (3.4%)	0	13 (3.2%)
Reaction to red blood cell transfusion**	5 (1.7%)	0	0	0	5 (1.3%)

\*Two patients with genotypes HbS/OArab and HbS/HPFH were excluded from this table; percentages were calculated from nonmissing values only.

\*\*Resulting in hospital admission.

**TABLE 3** SCD-associated complications by genotype, first annual follow-up

Genotype	HbSS <i>n</i> = 304	HbS $\beta^0$ thal <i>n</i> = 26	HbS $\beta^+$ thal <i>n</i> = 29	HbSC <i>n</i> = 45	Total <i>n</i> = 406 <sup>a</sup>
Severe pain crisis <sup>b</sup>	112 (36.7%)	10 (38.5%)	14 (48.3%)	10 (22.2%)	147 <sup>c</sup> (36.1%)
Acute chest syndrome	37 (12.1%)	1 (3.8%)	3 (10.3%)	3 (6.7%)	44 (10.8%)
Splenic sequestration	4 (1.3%)	2 (7.7%)	0	0	6 (1.5%)
Splenectomy	8 (2.6%)	1 (3.8%)	0	0	9 (2.2%)
Aplastic crisis	3 (1.0)	0	1 (3.4%)	3 (6.7%)	8 <sup>c</sup> (2.0%)
Stroke	1 (0.3)	0	0	0	1 (0.2)
Sepsis	3 (1.0%)	0	0	0	3 (0.7%)
Reaction to red blood cell transfusion <sup>b</sup>	0	1 (3.8%)	1 (3.4%)	0	2 (0.5%)

<sup>a</sup>Patients with documented genotype and first annual examination, percentages were calculated from nonmissing values only.

<sup>b</sup>Resulting in hospital admission.

<sup>c</sup>One patient with genotype HbS/HPFH experienced both pain crisis and aplastic crisis; one patient with genotype HbS/OArab had not experienced complications related to SCD.

SCD.<sup>19</sup> Above the age of one year, the frequency of hospitalization for pain and acute chest syndrome did not change with age.

Three patients died of SCD-related complications, all male and genotype HbSS: one patient (age 7 years) from streptococcal sepsis, one (age 40) from heart failure with siderosis, and one (age 11) from cerebral venous sinus thrombosis, intracranial bleeding and pulmonary embolism. One additional patient (male, HbSS, age 6) died from pulmonary complications and viral infection (EBV, Boca) on day 100 after allogeneic stem cell transplantation from a matched unrelated donor.

### 3.2 | Treatment of sickle cell disease

Almost all children up to the age of five years with the genotypes HbSS and HbS  $\beta^0$ thal were prescribed antibiotic prophylaxis with penicillin V (95.6%). The only currently available disease-modifying drug hydroxycarbamide is licensed in Europe for use in children with SCD with an age of two years and older. Close to 80% of all registry patients were prescribed hydroxycarbamide, 90.4% of patients above the age of two with either HbSS or HbS  $\beta^0$ thal genotypes. These numbers by far exceed those of other recent registry cohorts.<sup>11,12</sup> Patients without hydroxycarbamide had fewer pain crises or chest syndromes (on average, 0.3/year in 111 patient years, SD 0.6) as compared with patients on hydroxycarbamide (0.8/year in 554 patient years, SD 1.6), indicating that only mildly affected patients did not receive hydroxycarbamide. The high proportion of patients prescribed hydroxycarbamide is reflected in HbF levels. Adult patients with genotype HbSS had a mean HbF level of 12.5% (SD 8.2%, *n* = 11), more than twice that reported for hydroxycarbamide-naïve patients of West African origin.<sup>20,21</sup> This relation holds true for patients of all ages both of African origin (*n* = 105, mean HbF 17.6%, SD 15.3) and of non-African origin (*n* = 48, mean HbF 19.8%, SD 16.5), indicating that due to the effect of hydroxycarbamide, the HbF levels in the registry patients are higher than in hydroxycarbamide-naïve patients from Jamaica and similar to Indian patients of a comparable age distribution.<sup>22</sup>

The high proportion of patients prescribed antibiotic prophylaxis and hydroxycarbamide documents good compliance with current guidelines.<sup>15,17</sup> However, although the rate of transcranial Doppler (TCD) ultrasounds usage (74.8% of patients with an indication) compares favorably with historic cohorts,<sup>13,23</sup> this important diagnostic procedure is still underused.

One hundred six of 413 patients (25.7%) received red blood cell transfusions, 84 (20.3%) for acute complications, 19 (4.6%) as a “chronic” transfusion program, and 3 (0.7%) had both chronic and emergency transfusions.

Twenty-three patients received 24 allogeneic stem cell transplantations. All patients transplanted from a matched sibling donor (*n* = 15) were alive without SCD and without GvHD at last contact. Ten of these had at least one year of follow-up. Of the eight patients having received allogeneic stem cell transplantation from a matched unrelated donor, one patient died and one was transplanted a second time for treatment-induced myelodysplastic syndrome after graft failure one year after his first transplant. Of the remaining six patients, follow-up is below one year in five.

### 3.3 | Patients with an early diagnosis tend to have fewer vaso-occlusive crises

Because SCD is not a target disease of the general newborn screening in Germany, most of the registered patients were diagnosed later than the first year of life after symptoms of SCD had occurred. In order to tentatively assess within the limitations of a retrospective registry whether an early diagnosis and subsequent treatment results in fewer complications, we defined two groups of patients. If patients were diagnosed within the first six months of life before the onset of symptoms (either because of positive family history, newborn screening, or incidental finding), they were categorized as being diagnosed “early” (*n* = 55). Patients diagnosed with symptoms of SCD or after the age of six months were categorized as being diagnosed “late” (*n* = 325). The proportion of patients with a history of pain crises was higher in the “late” diagnosis group compared with the “early” diagnosis group

(69.6% vs 53.7%,  $P(\text{Fisher}) = 0.03$ ). As the “early diagnosis group” was younger (mean age at registration 6.4 years) compared with the “late diagnosis group” (10.8 years), this comparison is skewed by differing age distributions. While the patients were followed in the registry, the frequency of complications (hospitalization for acute pain crises or chest syndrome) in the early diagnosis group did not differ significantly from that in the late diagnosis group (mean 0.5/year in patients with early diagnosis vs 0.8/year in patients with late diagnosis; standard deviation 1.0 and 1.6, respectively). These findings suggest that our patient registry may currently not be suitable to show the advantages of newborn screening, either because of the limited number of registered patients or, more likely, because of a bias against early and potentially fatal events in patients who have not been diagnosed early.

## 4 | DISCUSSION

We set up a nationwide registry for SCD patients living in Germany, a country that has recently accommodated a large number of immigrants from regions with high prevalence of SCD.

On the basis of the insurance data documenting the total frequency of hospital admissions<sup>10,18</sup> and the average number of admissions for pain crisis per patient documented here, we estimate the national German SCD registry to currently cover up to 25% of all patients living with SCD in the country. Further, the registry demonstrates that the contributing centers generally treat their patients according to current guidelines, which results in a profile of morbidity and mortality that is likely comparable with that of higher incidence countries in Europe and North America.

In comparison with other European countries, the German registry data reveal two unique characteristics: First, the diagnosis is made at a relatively old age and mostly related to the occurrence of symptoms. This challenge will likely be addressed by the introduction of a newborn screening for SCD in Germany, which is expected to be introduced in 2021. Second, the proportion of patients treated with hydroxycarbamide is far higher than reported in any SCD registry so far,<sup>11,12</sup> consistent with current national guidelines.<sup>15</sup> We assume that the comprehensive use of hydroxycarbamide is a characteristic of the mostly academic centers participating in the registry but may not be a nationwide phenomenon.

Our study suffers from several limitations that are inherent to the design of a voluntary registry. Although 38.2% patients admitted to German hospitals for SCD were age 20 or above,<sup>10</sup> only 15.8% of our registry patients are adults. This bias toward younger patients is due to the fact that primarily large pediatric centers contributed to the registry. Unfortunately, patients with SCD who are taken care of by family physicians or at smaller institutions are much more difficult to enroll and require further efforts until a near to complete enrollment of all patients with SCD can be achieved. Although the total number of patients with SCD in Germany is not known, we estimate the total number of patients with SCD to be at least 2000 in Germany for 2017.

With regard to severe complications of SCD, the most important limitation of our registry is the lack of a universal newborn screening for SCD. The fact that most patients were diagnosed with SCD when symptoms occurred raises the concern of lethal complications before the diagnosis of SCD is made. Children dying from complications of SCD before the diagnosis is made cannot be enrolled in the registry, thus the number of severe complications may be underestimated. Similar concerns relate to patients arriving in Germany as refugees, typically without documentation of their medical history.<sup>10,24</sup> Although we know that the number of patients with SCD has increased by more than 30% after 2013,<sup>10</sup> we do not know how many of the registry patients were born in Germany and how many arrived after having suffered from SCD in their home country or in another health care system.

Despite the obvious limitations, this registry systematically gathers nationwide data on SCD and its treatment for Germany. In comparison with a previous registry,<sup>25</sup> both the number of enrolled patients and the total of patients with SCD in Germany have approximately doubled since 2005. Although the proportion of patients treated with hydroxycarbamide has increased more than threefold compared with 2005 and antibiotic prophylaxis is offered > 95% of preschool children, TCD measurements are still not used in every patient in need. We conclude that the physicians that contributed to this registry, mostly pediatricians, are aware of current treatment guidelines. However, the incomplete availability of TCD screening due to the lack of physicians with expertise in this technique, and most importantly the late diagnosis due to the lack of a newborn screening for SCD preclude treatment according to international standards. In order to improve medical care for patients with SCD, the most important measures are a newborn screening program that is expected to be introduced in 2021<sup>26</sup> and a TCD training program for physicians.

Patient registries, together with concomitant efforts such as physician training on treatment guidelines or establishing newborn screening programs for SCD, are essential for a comprehensive national SCD management in countries where SCD has only recently been recognized as a challenge.<sup>27</sup> However, an optimal care will only be achieved if a network of both pediatric and internal medical centers is dedicated to offer routine follow-up and emergency treatment for patients with SCD.

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## CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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