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Cost of health care for paediatric patients with sickle cell disease: An analysis of resource use and costs in a European country

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Abstract

Background: While multiple studies have examined the cost of health care for one aspect of sickle cell disease care, few have focussed on the overall cost of comprehensive care for sickle cell disease.

Methods: We conducted a retrospective cohort study of children with sickle cell disease treated in a comprehensive care centre from 1 January 2015 to 31 December 2016. Health care utilisation of included patients was based upon data from two main sources. The clinical practice guideline was used to determine the expected resource use of routine comprehensive care (planned elective care), and the financial claims database was used to estimate real-world resource use associated with acute and inpatient care (additional care).

Results: A total of 125 children with sickle cell disease were analysed. Expenditures for these patients averaged €5049 [standard deviation (SD) €1634] per child per year. Total yearly costs per patient varied considerably, ranging from €669 to €84 010, and less than 15% of patients were responsible for 50% of the health care costs. The majority (37%) of costs was associated with inpatient hospital care, which increased by age group, 27% with diagnostics, 19% with treatment, 11% with outpatients' visits and 6% with emergency care.

Conclusion: We have described real-world resource use and expenditures for children with sickle cell disease in a European comprehensive care centre. It seems that costs of a comprehensive approach with effective management in the outpatient setting is favourable when compared to episodic health care.

KEYWORDS
comprehensive care, health care costs, resource use, sickle cell disease

Abbreviations: CPG, Clinical Practice Guideline for Paediatric Sickle Cell Disease; CPI, consumer price index; HSCT, haematopoietic stem cell transplantation; WHO, World Health Organisation

1 | INTRODUCTION

1.1 | Sickle cell disease

Sickle cell disease is an autosomal, recessively inherited haemoglobinopathy characterised by chronic haemolytic anaemia, painful vaso-occlusive crises and progressive organ failure leading to decreased life expectancy. It is the most common monogenetic disease worldwide with an estimated 350 000 births annually and an important public health problem according to the World Health Organisation (WHO).[1]

Ninety percent of the global burden of sickle cell disease occurs in sub-Saharan Africa, where the majority of children with the disease do not live beyond 5 years of age.[1,2] In contrast, life expectancy in well-resourced countries has significantly improved with almost all infants surviving into adulthood.[3] Nevertheless, in these countries, life expectancy of patients with sickle cell disease is still 20 years shorter than the average life span of healthy adults.[4]

In the Netherlands, approximately 1500 individuals currently have sickle cell disease, of which half are children and the carrier incidence is 0.4%.[5,6] Most of those affected are from Surinam, Asian or African ancestry, with a minority being of Afro-Caribbean or Middle-Eastern descent.[7] More than a quarter of Dutch patients are treated in one of the largest comprehensive sickle cell centres in the Netherlands – the Erasmus University Medical Center-Sophia Children's Hospital (Erasmus MC). To ensure consistency in comprehensive care and reduce levels of morbidity and mortality,[8] all children with sickle cell disease in the Netherlands are treated according to the national 'Clinical Practice Guideline for Paediatric Sickle Cell Disease' (CPG; Table 1).[9]

1.2 | Cost of health care

Generally, sickle cell disease together with its related comorbidities and complications results in high utilisation of medical resources such as emergency room visits and hospitalisation.[10-12] Knowledge of expenditures associated with sickle cell disease can be used to serve

TABLE 1 Summary of the clinical standard treatment guideline for paediatric sickle cell disease in the Netherlands

	Frequency			
Items	**Birth-12 mths**	**12 mths-5 yrs**	**5-13 yrs**	**13-19 yrs**
Laboratory analyses				
- Complete blood count	3×	4×	4×	6×
- Red blood cell indices	3×	4×	4×	6×
- Low-density lipoprotein	2×	4×	4×	6×
- Bilirubin	2×	4×	4×	6×
- Liver and renal panel	2×	4×	4×	6×
- Iron status	NA	4×	4×	6×
- Folic acid and cobalamin	NA	4×	4×	6×
Haemoglobinopathy specific analyses				
- Haemoglobin phenotyping	2×	1×	NA	NA
- Haemoglobin genotyping	1×	NA	NA	NA
- Alpha thalassemia genetic mutations panel	1×	NA	NA	NA
- Glucose-6-phosphate dehydrogenase enzyme deficiency testing	1×	NA	NA	NA
Clinical geneticist outpatient visit	1×	NA	NA	1×
Paediatric haematologist outpatient visit	4×	8×	16×	12×
Urine analyses	NA	NA	8×	6×
- Dipstick				
- Sediment				
- Protein-creatinine ratio				
Transcranial Doppler	NA	4×	13×	6×
Chest X-ray	NA	NA	NA	1×
Electrocardiography	NA	NA	NA	1×
Abdominal ultrasound	NA	NA	NA	1×
Echocardiography	NA	NA	2×	1×
Ophthalmic screening	NA	NA	NA	4×

Abbreviations: mths, months; NA, not applicable; yrs, years.

as an incentive for further improvement of prevention and management strategies for disease symptoms and complications, resulting in both better care and reduced costs. In addition, estimating cost of care is important as it may ensure appropriate allocation of resources and reimbursement tariffs. However, most cost-of-care studies have focussed on only one or two aspects of care, such as hospitalisations and physician visits,[13-17] and few studies have examined health care expenditures exclusively for children. Moreover, the majority of studies are based on data from Northern America,[12,18-21] and due to large differences in health care systems, economic evidence of costs might not be generalizable to European countries.

1.3 | Study aims

Primary aims of this study were to (a) investigate overall cost of health care resource use for paediatric patients with sickle cell disease in a European country, and to (b) identify major cost drivers.

2 | METHODS

We retrospectively estimated health care costs of a paediatric cohort with sickle cell disease at the Erasmus MC by quantifying and valuing resource use for a period of 24 months.

2.1 | Study population

All children with sickle cell disease visiting the Erasmus MC for routine or emergency care in 2017 were included in the study cohort. Individual patient-level data were retrospectively analysed from the period 1 January 2015 to 31 December 2016 [ie, 24 months]. Patients were categorised into four age groups: (A) <1 year, (B) ≥1-5 years, (C) ≥5-13 years and (D) ≥13-19 years to reflect the categorisation of age used in the CPG. Unless patients were born during the observation period, they all contributed 24 months of follow-up time. To account for a shorter follow-up time of newborn patients and a possible switch between age groups during follow up, we calculated the weighted average of all costs. Weights were based on the patient-months-at-risk during the retrospective study period (ie 24 months).

2.2 | Resource use

Resource use per patient was quantified for five main resource use categories based on two main data sources.

The two main sources of data included the national CPG, and the Erasmus MC financial claims database. The five resource use categories included diagnostics, emergency room visits, inpatient care, outpatient care and treatment.

The CPG was used to determine the *expected resource use* of routine comprehensive care (planned elective care) for the categories of diagnostics, outpatient visits and inpatient visits. This implied that every child with sickle cell disease follows recommendations for health maintenance and monitoring of disease-modifying therapy, and therefore also uses all resources and generates all costs. Consequently, a full compliance to CPG was assumed. In addition to the resource use stated in the CPG, the Erasmus MC employs a specialised paediatric nurse practitioner (0.8 full-time equivalent) for both inpatient and outpatient care coordination of children with sickle cell disease. We assumed 45 min of working time for the nurse practitioner per planned outpatient visit for elective care (ie, CPG). Remaining costs were distributed over all non-elective outpatient (90%) and inpatient visits (10%) as obtained from the financial claims database.

The Erasmus MC financial claims database was used to estimate real-world resource use associated with acute and inpatient care for all five resource use categories. This database contained all recorded hospital procedures and visits to the Erasmus MC and all inpatient visits at local hospitals. For the latter, we had no access to detailed information about the inpatient episodes. Recorded resource use from the Erasmus MC financial claims database that exceeded the expected resource use in frequency was regarded as resource use *additional* to CPG. For instance, children below 1 year of age were expected to have five (routine) outpatient visits per year. In case a child in this age group had eight recorded outpatient visits in 1 year, only three were regarded as *additional* visits to the CPG.

The included items for CPG and financial claims database per resource use category are summarised in Table 2.

2.3 | Resource valuation

Prices for the resource use category 'diagnostics' were based on tariffs published by the Dutch Healthcare Authority (NZa) in 2019.[22] Since prices for haemoglobin phenotyping and haemoglobin genotyping were not available from this source, they were based on local, internal prices. Medication prices were acquired from the Dutch Healthcare Insurance Board.[23] Prices for surgical procedures (eg, cholecystectomy) were based on prices published in 2017 by NZa.[24] Costs for both outpatient and inpatient visits were calculated in accordance with the Dutch costing manual.[25] The salary for a specialised paediatric nurse practitioner was taken from the Dutch collective labour agreement for hospitals (CAO).[26]

Prices for the resource categories of emergency room visits, outpatient care and inpatient care are summarised in Table 3.

Where relevant, prices were indexed to 2019 euros using the pertinent consumer price index (CPI) published by Statistics Netherlands (CBS).[27] All statistical analyses were performed in R (version 3.6.1) using R Studio (version 1.2.1335) (Supporting Information S1 for loaded R packages). All variables were analysed using descriptive statistics. Categorical variables are presented in percentages and (total) numbers. Continuous variables such as resource use frequencies and costs are summarised by weighted means and standard deviations (SD). Summary statistics are presented in an aggregated way (ie, across all resource use categories) for the overall cohort.

TABLE 2 Resource use categories and included items per data source

Resource use category	Items CPG	Items financial claim database
Diagnostics	Diagnostic procedures (including laboratory and diagnostic imaging)	Additional diagnostic procedures (ie, X-rays, abdominal ultrasound)
Treatment	Standard medication and vaccinations	Additionally prescribed medication, surgery and blood transfusions
Emergency care	NA	Emergency room visits
Outpatient care	Routine visits to the outpatient clinic and care by specialised paediatric nurse practitioner	Additional visits to the outpatient clinic or medical social work and additional care by specialised paediatric nurse practitioner
Inpatient care	NA	Inpatient visits (including ICU) and day patient visits

Abbreviations: CPG, clinical practice guideline; ICU, intensive care unit; NA, not applicable.

TABLE 3 Prices of emergency room visits, outpatient and inpatient care

Resource use category[a]	Item	Average yearly resource use frequency, per age group based on CPG	Price in 2019 (€)	Source
Emergency room visits	Emergency room visit	NA	277	Dutch costing manual[25]
Inpatient care	Inpatient day at academic hospital	NA	669	Dutch costing manual[25]
	ICU visit	NA	2309	Dutch costing manual[25]
	Inpatient day at local hospital	NA	473	Dutch costing manual[25]
	Day patient visit	NA	319	Dutch costing manual[25]
Outpatient care	Outpatient clinic visit (paediatric haematology clinic)	A: 5 B: 2.5 C: 1.5 D: 1.5	108	Dutch costing manual[25]
	Medical social work visit	NA	69	Dutch costing manual[25]
	Specialised paediatric nurse practitioner visit (per 45 min)	A: 5 B: 2.5 C: 1.5 D: 1.5	25	Dutch collective labour agreement for hospitals[26]

Abbreviations: CPG, clinical practice guideline; ICU, intensive care unit.
[a]All care took place at the Erasmus MC - Sophia Children's Hospital, except for inpatient days at a local hospital.

Weighted mean costs are presented per age group and resource use category.

3 | RESULTS

A total of 125 patients were retrospectively analysed based on the Erasmus MC financial claim database. The mean age was 7.9 years (SD: 4.7 years) on 31 December 2015 (first year of observation) and 8.6 years (SD: 4.9 years) on 31 December 2016. Forty-three percent were female patients, and five patients entered the cohort as newborns in 2015 and 2016. Summary statistics for patient's age, sex and haemoglobin genotype at the end of the observation period (31 December 2016) are shown in Table 4 (see Supporting Information S2 for additional information on the distribution of genotypes across age groups).

Overall, 52 of 125 patients (43%) had inpatient care during the study period. These patients had a total of 133 admissions with an average length of stay of 5.2 days (SD: 4.6). On average, children were seen on an outpatient basis 2.1 times per year and admitted as inpatients 3.1 times per year. Patients in age groups A and B had no additional outpatient visits to the planned visits according to the CPG. For age groups C and D, the average yearly additional outpatient visits were marginal. The number of patients per age group, their mean years at

TABLE 4 Patient characteristics

Variable	Entire retrospective cohort (values on 31 December 2016)
Patients (n)	125
Mean age (SD)	8.6 (4.9)
Gender, n (%)	
Female	53 (42)
Male	72 (58)
Haemoglobin genotype, n (%)	
HbSS	76 (60.8)
HbSC	31 (24.8)
HbSβ^+ thalassemia	8 (6.4)
HbSβ^0 thalassemia	4 (3.2)
Other (ie, HbSdeltaβ^0, HbArabβ^0)	6 (4.8)

risk and summary statistics for inpatient and outpatient visits are presented in Table 5.

All patients (n = 125) accrued total cumulative costs of €1 205 919 during the 2 years observed. For patients with a full follow-up time (ie, 24 months), yearly total costs per patient varied considerably, ranging from €669 to €84 010. Of the total expenditures for all patients, approximately 50% of the costs were induced by 18 children (ie, 14% of the total patient population) and approximately 80% of the costs were induced by 65 children (ie, 52% of all patients). The distribution of HbSS and HbSC genotypes in the 18 children inducing 50% of the total costs was 83.3 and 11.1%, respectively.

Average yearly expenditures for all 125 children were €5049 (SD: €1634). The majority (37%) of costs was associated with inpatient care: 27% with diagnostics, 19% with treatment, 11% with outpatient care and 6% with emergency room visits. The average yearly costs per patient and age group are depicted in Figure 1. Again, average costs vary considerably between age groups, which is mainly related to differences in the number of inpatient days. Major cost drivers for age groups A and B were diagnostics and treatment, respectively. For age groups C and D, the major cost drivers were inpatient care, although for age group C, the average difference in costs between diagnostics (€1355) and inpatient care (€1488) could be regarded as marginal. Average yearly costs for inpatient care were higher in older age groups and nearly three times as high in age group D compared to group C. Only for age groups C and D, we observed stays at the intensive care unit (resource use category inpatient care) with a slight increase from age groups C and D. More information on the distribution of inpatient care across age groups can be found in Supporting Information S3.

4 | DISCUSSION

4.1 | Health care utilisation and expenditures

Although health care utilisation and costs among children with sickle cell disease have been studied previously,[12,18-21] studies from European comprehensive care centres are scarce and have only focussed on one aspect of care such as hospitalisations costs.[14,28] To our knowledge, this is the first study describing costs from a European comprehensive care centre combining standard treatment costs with real-world resource use.

The total yearly costs of health care for children with sickle cell disease, including inpatient care, outpatient care, diagnostics and treatment averaged €5049 (SD: €1634) per patient per year. This is much lower when compared to cost of health care for paediatric patients with sickle cell disease in other studies. Kauf et al calculated total costs of health care for children with sickle cell disease aged 0-9 years to be US $10 704 (€8906) [SD: US $24 696 (€20 548)] per year, of which more than 75% were associated with inpatient care.[12] In our study, inpatient care accounts for a much smaller proportion of total costs (ie, 37%). As a consequence, this substantially reduces health care costs as inpatient care is generally more expensive compared to comprehensive health care at specialised outpatient clinics. The study of Pizzo et al is up until now the only cost of care study in sickle cell disease performed in Europe. They retrospectively assessed the cost of inpatient care for vaso-occlusive crises in the United Kingdom between 2010 and 2011. For children aged 1-9 years, they reported mean admission costs to be GB £1732 (€2379, 2019). Their analysis underestimates the real costs

TABLE 5 Outpatient and inpatient visits per person year

Age group	Patients (n)	Mean years at risk (years)	Total number of outpatient visits (n)	Mean outpatient visits per person per year (n)	Total number of inpatient care days (n)	Mean inpatient days per person per year (n)	Total number of emergency room visits (n)	Mean emergency room visits per person per year (n)
Total[a]	125	1.9	496	2.1	749	3.1	253	1.1
A	17	0.5	47	5.0	10	1.1	32	3.4
B	49	1.4	168	2.5	122	1.8	90	1.3
C	69	1.7	194	1.7	302	2.6	67	0.6
D	29	1.6	87	1.8	315	6.6	64	1.3

[a]The sum of patients in each age group is not equal to the total number of patients studied, since children were analysed in older age groups when applicable during the 24-month observation period. The mean number of visits was calculated by dividing the total number of visits (per stratum) by the total years at risk (not the total number of patients), as some patients did not contribute an entire 2 years to each age group (due to increasing age and switching between categories).

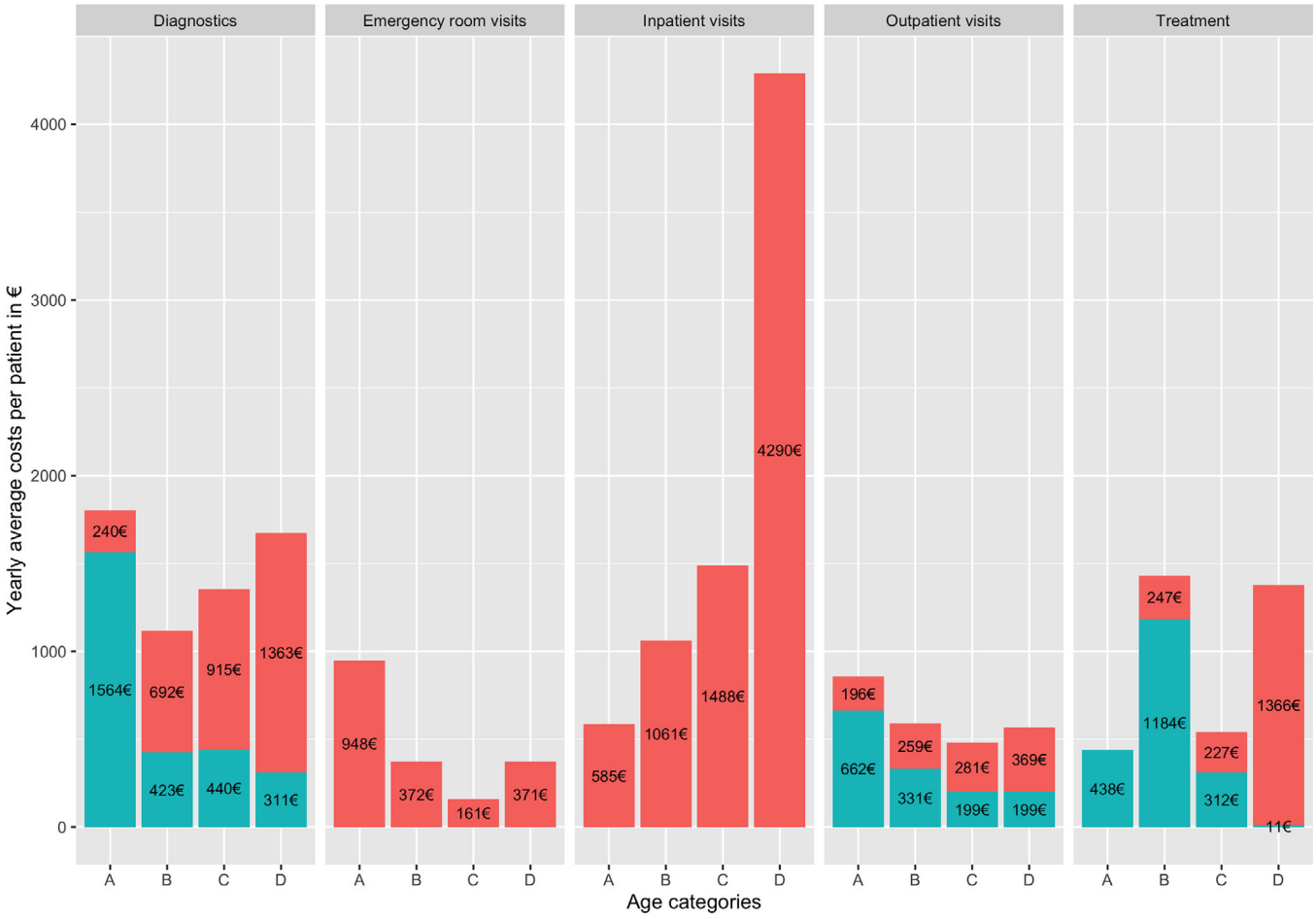

FIGURE 1 The average yearly costs per patient and age group. Green: Yearly mean costs according to the clinical practice guideline. Red: Yearly additional mean costs based on the Erasmus Medical Center financial claims database

of inpatient care, as it only considers the cases with crises as a primary diagnosis.[14] In our study, average yearly inpatient costs for children aged 1-5 (age group B) and 5-13 (age group C) years old was €1061 and €1488, respectively. However, care should be given to comparing costs, as factors such as health care financing, social and political structures as well as types of treatment regimen can vary greatly among different countries. For example, due to differences in expert opinion, the most recent guideline of the National Heart, Lung and Blood Institute advices transcranial Doppler screening every year, compared to twice a year in the Dutch CPG. Furthermore, most cost-of-care studies use the terms cost, charge and fees synonymously or confuse reimbursement with costs, making it even harder to compare international data.[29]

Sickle cell disease varies greatly in severity, with some children relatively asymptomatic while others are severely ill. As a consequence, substantial variation in health care costs is observed among children with sickle cell disease.[13,18,19,21] We also observed this variation; a relatively small fraction of patients accounted for half of the total costs (ie, 18 children generating approximately 50% of the costs). Although our study did not collect data on clinical heterogeneity (eg, organ damage), these 18 patients are most likely patients with more severe symptoms. Furthermore, the majority of these 18 patients had HbSS sickle cell disease, which is often associated with a more severe phenotype. To establish and quantify the effect of disease severity on health care costs, further studies with larger sample sizes and longer follow-up periods need to be conducted.

Although the clinical features of sickle cell disease are heterogeneous, and therefore also the associated costs both within and across age groups, yearly additional mean costs based on the financial claims database seemed to increase with age for all resource use categories. This is consistent with previous research showing that age is an important determinant of disease severity, since older patients are more likely to accumulate organ damage and dysfunction and have more frequent painful vaso-occlusive crises.[30-34] However, yearly additional mean costs for emergency room visits follow a reverse trend (ie, decrease between age groups A to C), while they increase for age group D again. A similar pattern is seen in the general paediatric population, in which young children also constitute a disproportionately high share of paediatric emergency care, mostly due to respiratory infections.[35,36] In addition, parents tend to be more anxious when their child has just been diagnosed with sickle cell disease (via the newborn screening program), possibly leading to more frequent hospital visits.

Estimating cost of care is important for appropriate allocation of resources and reimbursement tariffs. Furthermore, specific to the health care system in the Netherlands, knowledge of health care utilisation and expenditures for patients with sickle cell disease may help to establish a diagnosis treatment combination (DBC) for (paediatric) patients with sickle cell disease. DBCs describe a complete care episode and are used as the basis for remuneration negotiations between hospitals and health care insurers. Currently, haemoglobinopathies (including sickle cell disease and thalassemia) do not have a separate DBC code and are declared by the DBC 'anaemia not otherwise specified'. We hope this study will play a role in the authorisation of a DBC for paediatric sickle cell disease, by giving insight into overall cost of health care resource use for sickle cell disease patient in the Netherlands.

4.2 | Limitations

This study is not without limitations which need to be considered when interpreting the results. Firstly, it is important to note that our analyses do not aim at deriving statistical inference and therefore our results are descriptive in nature. Secondly, sample size (125 patients), information about patient characteristics, and follow-up time (24 months) were limited. A further stratification into subgroups according to potential cost predictors was therefore not possible. Thirdly, a substantial proportion of patients were admitted to local hospitals. There are more than 10 local shared care centres, all with their own medical databases, which are not linked to the financial claims database of the Erasmus MC. Although inpatient days were manually retrieved, detailed information about those care episodes, especially with regard to treatment and diagnostics, is missing. Hence, the estimated total costs reported for these items should be seen as lower limits of the actual costs. For example, although most complex care have been given at the Erasmus MC, some children may have had a blood transfusion or imaging procedures during admissions at a local hospital. These interventions remain unknown and are therefore not reflected in the total costs. Nevertheless, by including the major cost driver (inpatient days in local hospital), we believe that results will not be substantially different. The Sickle Cell Outcome REsearch (SCORE) consortium of the Netherlands is currently developing a multicentre database for (paediatric) sickle cell patients, which is an important step toward more detailed analysis of patient-related data. Fourthly, none of the patients in our cohort had a haematopoietic stem cell transplantation (HSCT) during the observed time period. Although HSCT is still a relatively uncommon treatment, median total costs for children with sickle cell disease is around US $413 000 (€343 627) for inpatient care and US $18 000 (€14 977) for outpatient care,[37] which would consequently have increased total annual costs when performed. Finally, it is important to note that we have adopted a health care perspective approach, meaning that patient's costs (ie, patient's time lost from school, transportation costs and parental loss of wage earning capacity due to caretaking of a chronically sick child) were not accounted for in calculations. Further research is warranted to determine this important cost component.

5 | CONCLUSION

In summary, we have described a detailed investigation of resource use and cost of health care for paediatric patients with sickle cell disease in the Netherlands over a 2-year period, retrospectively. Sickle cell disease is a chronic, complex and often unpredictable disease requiring life-long management. Our analyses suggest that costs of a comprehensive, multidisciplinary approach with effective management in the outpatient setting is favourable when compared to episodic health care. Lower resource use and costs were observed for acute care and inpatient facilities. However, care should be given with regard to comparing our data to other countries. Further studies including more patients with longer follow-up times are needed to confirm our findings. In addition, to enhance medical outcomes and decrease health care utilisation and costs, further investigation of the small subset of children who consume a large percentage of the resources is required.

CONFLICT OF INTEREST

Marjon H. Cnossen has received investigator-initiated research and travel grants from The Netherlands Organisation for Scientific Research (NWO)-the Netherlands Organisation for Health Research and Development (ZonMw), the Dutch 'Innovatiefonds Zorgverzekeraars', Pfizer, Baxter/Baxalta/Shire, Bayer Schering Pharma, CSL Behring, Sobi and Biogen Idec, Novo Nordisk, Novartis and Nordic Pharma, and has served as a member on steering boards of Roche and Bayer. All grants, awards and fees go to the institution. Anne P.J. de Pagter has received a grant from Rotary Foundation for the institution. All other authors declare no conflict of interest relevant to the contents of this manuscript.

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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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