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HEMATOLOGY: RESEARCH ARTICLE

Long-term hematologic and clinical outcomes of splenectomy in children with hereditary spherocytosis and sickle cell disease

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Abstract

Background: Total splenectomy (TS) and partial splenectomy (PS) are used for children with congenital hemolytic anemia (CHA), although the long-term outcomes of these procedures are poorly defined. This report describes long-term outcomes of children with CHA requiring TS or PS.

Procedure: We collected data from children ages 2-17 with hereditary spherocytosis (HS) or sickle cell disease (SCD) requiring TS or PS from 1996 to 2016 from 14 sites in the Splenectomy in Congenital Hemolytic Anemia (SICHA) consortium using a prospective, observational patient registry. We summarized hematologic outcomes, clinical outcomes, and adverse events to 5 years after surgery. Hematologic outcomes were compared using mixed effects modeling.

Results: Over the study period, 110 children with HS and 97 children with SCD underwent TS or PS. From preoperatively compared to postoperatively, children with HS increased their mean hemoglobin level by 3.4 g/dL, decreased their mean reticulocyte percentage by 6.7%, and decreased their mean bilirubin by 2.4 mg/dL. Hematologic improvements and improved clinical outcomes were sustained over 5 years of follow-up. For children with SCD, there was no change in hemoglobin after PS or TS following surgery, although all clinical outcomes were improved. Over 5 years, there was one child with HS and five children with SCD who developed postsplenectomy sepsis.

Conclusions: For children with HS, there are excellent long-term hematologic and clinical outcomes following either PS or TS. Although hemoglobin levels do not change after TS or PS in SCD, the long-term clinical outcomes for children with SCD are favorable.

KEYWORDS
congenital hemolytic anemia, outcomes, sickle cell, spherocytosis, splenectomy

1 | INTRODUCTION

For severely affected children with congenital hemolytic anemia (CHA) such as hereditary spherocytosis (HS) or sickle cell disease (SCD), surgical treatment with total splenectomy (TS) is often required.[1,2] There is continued interest in partial splenectomy (PS) due to risks of overwhelming postsplenectomy sepsis, venous thromboembolism, and pulmonary hypertension from TS.[3–7] However, the long-term outcomes of TS and PS remain poorly defined, as most reports are from single institutions, retrospective, and limited by several biases.[8–12]

For many clinical practices, there is great value using data from clinical and administrative datasets to predict expected health outcomes.[5,8] However, the use of common datasets for the study of less frequent conditions is difficult, as these datasets often do not record outcomes considered most important by clinicians and families. In particular, research on spleen surgery in CHA is challenged by

Abbreviations: ACS, acute chest syndrome; AE, adverse event; CHA, Congenital Hemolytic Anemia; HS, hereditary spherocytosis; IQR, Interquartile Range; IRB, Institutional Review Board; NCATS, National Center for Advancing Translational Sciences; NIH, National Institutes of Health; PS, Partial Splenectomy; REDCap, Research Electronic Data Capture platform; SCD, sickle cell disease; SE, Standard Error; SICHA, Splenectomy in Congenital Hemolytic Anemia; TS, Total Splenectomy.

the heterogeneity of diseases, small number of subjects, variations in surgical technique, and use of nonstandardized data.[8,9] In these settings, a patient registry is a powerful tool to collect high-quality, standardized data.[11]

To improve the care of children with CHA, we have operated the Splenectomy in Congenital Hemolytic Anemia (SICHA) consortium, a research consortium composed of pediatric surgeons and hematologists across North America. Our group has operated a web-based, prospective, patient registry using standardized data to better understand the outcomes of children with CHA undergoing TS or PS. We previously have shown excellent clinical outcomes as well as hematologic results following TS or PS over short-term (1 year) follow-up.[13] The objective of this current report is to summarize the long-term outcomes (5 years) after TS or PS in children with HS and SCD.

2 | METHODS

2.1 | SICHA consortium

The SICHA consortium was formed to improve the care of children with CHA, with participation from 16 sites across North America. Our consortium has operated a combined retrospective and prospective, observational, web-based patient registry for children with CHA requiring splenectomy using the Research Electronic Data Capture (REDCap) platform. The design, data variables, outcome definitions, and operations of this patient registry have been described previously.[13,14] This report fulfills STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) criteria outlined for observational studies.[15]

2.2 | Study population

Children were offered enrollment in the SICHA registry if they were aged 2-17 years and underwent either a TS or PS for congenital hemolytic anemia at any SICHA site between January 1, 1996 and December 31, 2016. All clinical management, including the decision to perform a TS or PS, was conducted locally by the surgeon, hematologist, and family. In addition to children with HS or SCD, patients with other type of CHA such as thalassemia or pyruvate kinase deficiency were included in the registry, but were excluded from this analysis due to low patient numbers. Patients undergoing splenectomy for trauma or reasons other than CHA management were not included in this registry.

From January 1, 1996 to December 31, 2008, we collected data retrospectively for 36 patients, and from January 1, 2009 to December 31, 2016, we collected data prospectively for 171 (83%) patients. This study was approved by the Institutional Review Board at each site in the SICHA consortium, with written informed consent obtained from the parent or guardian of all participants prior to participation. Each clinical site retained all identifying information, with only deidentified data collected centrally as previously described.[13] We included data from 14 sites in this current analysis due to limited data from two sites.

2.3 | Data abstraction

We collected 68 variables, including patient demographics, diagnosis, hematologic outcomes, clinical outcomes, imaging, surgical details, and adverse events (AEs) (see previous publication for all variable definitions).[13] Hematologic outcomes, clinical outcomes, and AEs were collected at baseline, 1 month, 6 months, and then annually at 1, 2, 3, 4, and 5 years after surgery.

The primary hematologic outcomes were hemoglobin (g/dL), total bilirubin (mg/dL), and reticulocyte level (percentage). The primary clinical outcomes included events of splenic sequestration, hypersplenism, aplastic crises, splenomegaly, gallstones, and completion splenectomy. Short-term (within 30 days postoperatively) AEs included infection, reoperation for total splenectomy after previous partial splenectomy, acute chest syndrome (ACS) (for SCD patients only), and death. Long-term (from 30 days to 5 years postoperatively) AEs included infection, ACS (for SCD patients only), thrombotic events, reoperation, and death. Infections captured included sepsis, bacteremia, meningitis, or other infection requiring ED admission or hospitalization.

We defined clinical outcomes and AEs as follows: transfusion dependence as participation in regular transfusion program over at least a 3-month interval; hypersplenism as chronic splenomegaly associated with thrombocytopenia (platelet counts $< 150\,000 \times 10^9$/L with or without associated neutropenia or abdominal pain); splenic sequestration as an acute increase in spleen size and firmness;and reduction of hemoglobin ≥ 2 g/dL that may include drop in platelet or white counts.[16,17] As we were interested in the longitudinal risk of AEs in all children following surgery, we summarized the cumulative incidence of any AE during the entire follow-up period for each child as a binary variable (yes/no). Patient age at time of splenectomy was not consistently reported across sites and therefore excluded from analysis. In addition to data management and quality assurance operations described previously, we performed manual data checks to review data for unexpected discrepancies.[13,14]

2.4 | Statistical analysis

We summarized hematologic outcomes, clinical outcomes, and AEs based on diagnosis (HS vs SCD) as well as by type of procedure (PS vs TS). We expressed categorical variables as frequency and percentage, and continuous variables by mean and interquartile range. We compared preoperative and postoperative clinical outcomes using McNemar's test for children with available matched data. All clinical events (infections, thrombosis, and ACS) were summarized as risk of events.

To analyze hematologic outcomes over time, we summarized values with available data at each follow-up period. To account for loss to follow-up, we applied a mixed-effects model stratified by disease type, operation (total vs partial), pre- and postsurgery, and time point after surgery. Trends in hematologic values over time were used to assess durability of changes after surgery. An interaction term between surgery and operation type (total vs partial) was used to evaluate the association of partial splenectomy on changes in hematologic values.

TABLE 1 Characteristics of children with hereditary spherocytosis or sickle cell disease undergoing total splenectomy (TS) or partial splenectomy (PS)

Patient characteristics	Overall	Hereditary spherocytosis (n = 110)		Sickle cell disease (n = 97)	
		TS	PS	TS	PS
N	207	59	51	73	24
Demographics					
Sex					
Male	110	30	26	39	15
Female	96	29	25	33	9
Race					
White	95	50	41	3	1
Black	96	5	3	66	22
American Indian/Alaska Native	2	1	1	0	0
Asian	1	0	0	0	1
More than one race	1	0	0	1	0
Not reported	12	3	6	3	0
Ethnicity					
Hispanic	10	4	1	2	3
Not Hispanic	197	55	50	71	21
Indication for surgery					
Splenic sequestration	82	NA	NA	61	21
Hypersplenism	25	16	9	NA	NA
Transfusion dependence	46	5	13	24	4
Splenomegaly	32	14	16	2	0

Demographic and indication for surgery characteristics illustrated by disease and operative approach. In reference to indication for surgery, numbers represent number of patients at baseline. NA, not applicable. Data are based on standard data definitions.[13,14]

TABLE 2 Operative characteristics of children with hereditary spherocytosis or sickle cell disease undergoing total splenectomy (TS) or partial splenectomy (PS)

Operative characteristics	Overall	Hereditary spherocytosis (n = 110)		Sickle cell disease (n = 97)	
		TS	PS	TS	PS
N	207	59	51	73	24
Initial approach					
Open	45	5	17	6	17
Laparoscopic	161	54	34	66	7
Laparoscopic converted to open	11	1	5	3	2
Additional procedure	60	20	15	21	4
Length of stay (days)	3 (2, 4)	2 (0, 6)	4 (1.5, 5.5)	3 (0,7)	3 (0.4,7.4)
Postoperative blood transfusion	10	0	3	4	3

Data expressed as number of subjects in each cohort. Continuous data (length of stay) represented by median (with interquartile range). Data are based on standard data definitions.[13,14]

An interaction term between operation type and time from surgery was used to evaluate the durability of hematologic changes over the follow-up period. The study was not powered to detect differences in long-term outcomes by type of splenectomy (TS vs PS) or by surgical approach (laparoscopy vs laparotomy). We summarized unadjusted hematologic data graphically as mean ± standard error (SE). All analyses were performed using R version 3.5.3.

3 | RESULTS

3.1 | Patient and operative characteristics

A total of 236 children were enrolled across 16 sites. Twenty-nine subjects were excluded from analysis, including 18 children with thalassemia or other CHA, 10 subjects with incomplete data, and one

subject who withdrew from the study. The final analysis cohort was composed of 207 children enrolled from 14 sites (mean 14.7 subjects/site, median 11 subjects/site). Children had a diagnosis of HS (n = 110) or SCD (n = 97), with subtypes of SCD including hemoglobin (Hgb) SS, Hgb SC, and combined Hgb S/β-thalassemia (Table 1). There were a greater number of males than females, with an expected racial and ethnic distribution by disease type. Patients were followed to 5 years after surgery, although there was relatively large attrition due to loss to follow-up, with follow-up of 133 subjects (64%) at 6 months, 103 (50%) at 1 year, 124 (60%) at 2 years, 105 (51%) at 3 years, 66 (32%) at 4 years, and 44 (21%) at 5 years. Patients were lost to follow-up because they either did not show up to their clinic appointment within the specified time range, or they moved away and established care elsewhere.

Of the 110 children with HS, 59 received a TS and 51 received a PS. For the 97 children with SCD, 73 received a TS and 24 received a PS. Indications for surgery included splenic sequestration (in SCD) or hypersplenism (in HS) (51.7%), splenomegaly (15.5%), and transfusion dependence (22.2%). Almost all (91.8%) children received preoperative vaccines, and 98.5% of children received early postoperative (within 30 days of surgery) antibiotic prophylaxis, although we did not collect the long-term antibiotic usage rate. Most children (91%) undergoing a TS had an initial laparoscopic approach compared to 55% of children with PS (Table 2).

3.2 | Hematologic outcomes

3.2.1 | Hereditary spherocytosis

Children with HS undergoing TS or PS showed improvement in all hematologic outcomes over the follow-up period (Figure 1). By unadjusted analysis, children who underwent TS increased their mean hemoglobin levels postoperatively, with levels sustained to 5 years after surgery (baseline 10.3 ± 0.2 g/dL, 5 years 13.5 ± 1.9 g/dL; mean ± SE) (Figure 1A). Hemoglobin levels also increased following PS and were sustained to 5 years after surgery (baseline 10.1 ± 0.2 g/dL, 5 years 11.9 ± 0.8 g/dL; mean ± SE) (Figure 1A).

Other hematologic outcomes improved after TS or PS in children with HS and were sustained to 5 years after surgery. Mean reticulocyte percentages decreased in TS and PS cohorts, although the long-term reticulocyte percentages were lower in TS (baseline 9.3 ± 0.7%, 5 years 2.9 ± 0.8%; mean ± SE) compared to PS (baseline 11.3 ± 0.9%, 5 years 4.8 ± 1.0 %; mean ± SE) (Figure 1B). Mean bilirubin values decreased following either TS or PS, and remained less than 2 mg/dL over 5 years of follow-up (Figure 1C).

By adjusted analysis, HS children increased their mean hemoglobin level by 3.4 g/dL after surgery (95% CI: 3.1-3.7) at 5 years of follow-up. Similarly, mean reticulocyte percentage decreased by 6.7% (5.6-7.7%, $P < .001$) after surgery. Mean bilirubin levels decreased by 2.4 mg/dL (2.0-2.8) after surgery.

For children with HS, TS had more substantial hematologic improvements than PS. The increase in mean hemoglobin at 5 years after surgery was 0.6 g/dL greater following TS compared to PS (0.2-1.0 g/dL). The decrease in mean reticulocyte percentage was similar in PS compared to TS. Mean bilirubin levels decreased by 0.7 mg/dL less in PS than TS (0.3-1.2).

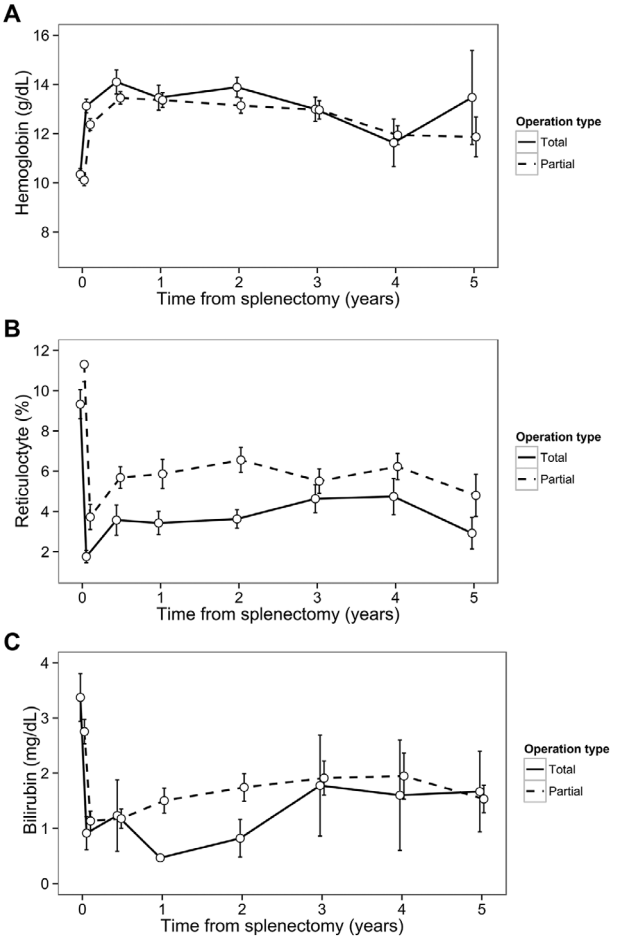

FIGURE 1 A-C, Unadjusted hematologic outcomes after partial or total splenectomy in children with hereditary spherocytosis. Data represent hemoglobin (A), reticulocyte percentage (B), and serum bilirubin (C) at baseline, 4 weeks, 24 weeks, 1 year, 2 years, 3 years, 4 years, and 5 years. Circles and error bars represent average and standard error

3.2.2 | Sickle cell disease

For children with SCD, there was no change in mean hemoglobin levels at 5 years after either PS or TS (Figure 2A). Mean reticulocyte percentages decreased compared to baseline (Figure 2B). Mean bilirubin decreased by at least 1.0 mg/dL in children with PS and TS (Figure 2C). Mixed model adjusted analysis confirmed that mean hemoglobin levels in both cohorts were unchanged after surgery. Reticulocytes decreased 2.0% (0.8-3.2%) and bilirubin decreased 0.9 mg/dL (0.5-1.3) after PS or TS.

3.3 | Clinical outcomes

Almost all children with HS or SCD had improvement of clinical outcomes after TS or PS (Table 3). For children with HS, there was a

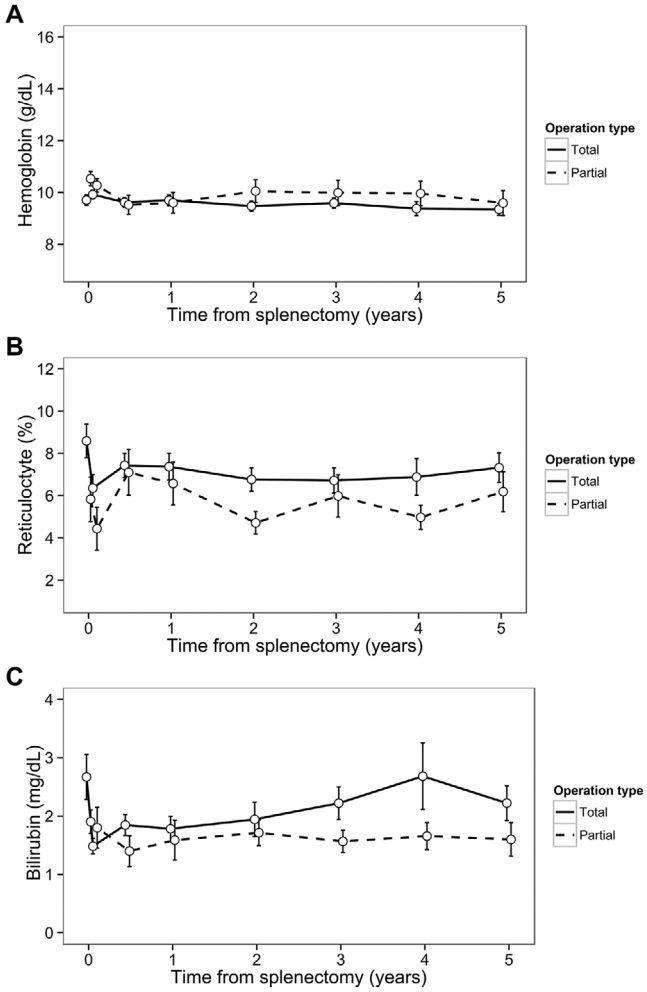

FIGURE 2 A-C, Unadjusted hematologic outcomes after partial or total splenectomy in children with sickle cell disease. Data represent hemoglobin (A), reticulocyte percentage (B), and serum bilirubin (C) at baseline, 4 weeks, 24 weeks, 1 year, 2 years, 3 years, 4 years, and 5 years. Circles and error bars represent average and standard error

decrease in transfusion requirement and improvement in all clinical outcomes. Most clinical outcomes in children with SCD were also favorable, although some children continued to receive blood transfusions over the follow-up period. Both PS and TS were associated with improved splenomegaly, splenic sequestration (in SCD), and hypersplenism (in HS).

3.4 | Adverse events

3.4.1 | Short-term AEs

Overall, the incidence of short-term (<30 days postoperatively) AEs was 5.5% among children with HS and 18.6% among children with SCD (Table 4). There were no deaths recorded. The most frequently reported short-term AE was infection, with a 4.5% infection risk in HS and an 8.2% risk in SCD. In children with SCD, there was a 10.3% risk of ACS.

3.4.2 | Long-term AEs

The most common long-term AE (30 days to 5 years postoperatively) was infection, predominately upper and lower respiratory tract infections. There were no deaths recorded. HS patients undergoing TS or PS had a 13.6% cumulative risk of infection, including one patient with sepsis and one with meningitis over 5 years of follow-up (Table 4). There were three HS patients (5.9%) who required a reoperation for completion splenectomy following PS. In children with SCD, there was a cumulative infection risk of 47.4%, including five patients with sepsis. Patients with SCD had a 5.2% risk of thrombotic events and a 26.8% risk of ACS. The long-term risk of ACS among children with SCD requiring TS was 31.5% and 12.5% in children with PS.

4 | DISCUSSION

Although different types of splenectomy are used for severely affected children with CHA, the long-term risks and benefits of total and partial splenectomy remain poorly understood by families and clinicians. Most existing studies are limited by use of single institution reports, absence of standardized data, or limited follow-up.[11,12] To address this research gap, our consortium developed a multisite, web-based prospective patient registry based on use of standardized data definitions for children with CHA requiring surgery. We have previously demonstrated excellent hematologic and clinical outcomes in children with HS after total and partial splenectomy over 1 year of follow-

TABLE 3 Clinical symptoms at baseline and after total splenectomy (TS) or partial splenectomy (PS) for children with hereditary spherocytosis (HS) or sickle cell disease (SCD)

	Hereditary spherocytosis (n = 110)			Sickle cell disease (n = 97)		
	Baseline	Postoperative	*P*-value	Baseline	Postoperative	*P*-value
Splenic sequestration	NA	NA		82	0	<.001
Hypersplenism	25	7	<.001	NA	NA	
Transfusions	18	1	<.001	28	27	1.00
Aplastic or anemic crisis	11	NR		1	NR	
Splenomegaly	30	6	<.001	2	0	.48

Symptoms summarized as number of children in each cohort at baseline and up to 5 year postoperatively. Any symptom reported during follow-up period was counted once, with multiple episodes of the same symptoms counted only once. *P*-values represent McNemar's for matched pair differences between baseline and postoperative follow-up. NA, not applicable; NR, not recorded. Data are based on standard data definitions.[13,14]

TABLE 4 Short-term and long-term adverse events (AE) in children with hereditary spherocytosis or sickle cell disease undergoing total splenectomy (TS) or partial splenectomy (PS)

		Hereditary spherocytosis (n = 110)		Sickle cell disease (n = 97)	
Adverse events	**Overall**	**TS**	**PS**	**TS**	**PS**
N	207	59	51	73	24
Short term (<30 days postoperative)					
Infection	13	1	4	6	2
Reoperation	1	1	0	0	0
Acute chest syndrome	10	NA	NA	5	5
Long term (30 days to 5 years)					
Thrombotic events	5	0	0	5	0
Sepsis/bacteremia	6	1	0	5	0
Meningitis	1	1	0	0	0
Other infection requiring hospitalization	54	6	7	28	13
Acute chest syndrome	26	NA	NA	23	3
Gallstones	8	0	4	3	1
Completion splenectomy	3	NA	3	NA	0

NA, not applicable. Data are summarized as overall incidence of each adverse event with all outcomes based on standard data definitions.[13,14]

up, with clinical outcomes improved in children with SCD.[13,14] In our current study, we found that these favorable outcomes are sustained to 5 years after surgery. Although our study was not designed to directly compare surgical procedures, we found that most children with HS or SCD undergoing either TS or PS have quite favorable clinical outcomes.

The patterns of hematologic outcomes differ between HS and SCD following splenectomy. For children with HS, both TS and PS result in sustained improvement of hematologic laboratory parameters, control of clinical symptoms, and a low risk of AEs to 5 years after surgery. In contrast, for children with SCD, reticulocyte and bilirubin did improve after surgery, although hemoglobin levels did not change following TS or PS. However, we found favorable clinical outcomes following surgery in children with SCD, particularly markedly decreased rates of sequestration crises. Elimination of splenic sequestration provides a substantial benefit to children with SCD, as sequestration crises are a significant cause of morbidity and mortality.[18,19] Our findings concur with most existing literature that splenectomy does not result in change in hemoglobin levels in children with SCD.[8,20] Many children with SCD continued to receive transfusions after splenectomy, although this may reflect the clinical practice in severely affected children with SCD to continue transfusion therapy throughout childhood to prevent sickling events and other morbidity.

Our report has several strengths, including its generalizability, multi-institutional design, web-based data entry, and use of standardized data definitions. This report of long-term outcomes of splenectomy should be of great value for clinicians and families to understand expected outcomes of different types of splenectomy. As well, our data provide robust baseline information to facilitate a clinical trial of TS and PS in children with CHA. As the outcomes following either TS or PS are quite favorable, we suggest that any clinical trial should focus on factors that impact the decisions related to surgery, such as patient- (or family-) preferences, quality of life assessment, and cost-effectiveness analysis.

Our analysis has several limitations, many of which are inherent to use of an observational patient registry. First, our study is not designed to compare the efficacy of different surgical procedures or surgical versus medical therapies. Comparison of treatments would require a randomized clinical trial, although the many types of CHA, small population, and rare AEs limit the feasibility of such a clinical trial. Second, our results are limited by the relatively large number of patients lost to follow-up and prone to attrition bias. We recognize that patient attrition and missing data are common challenges for patient registries, and we appreciate the diligent data collection by study sites. As well, mixed modeling allows for adjustment for missing data. Third, we did not collect several outcomes of potential interest to families and providers, such as etiologies of infections requiring hospitalization, quality of life measures, and compliance with antibiotic prophylaxis. Fourth, we did not examine how disease severity or genotype affects surgical outcomes.

In conclusion, we found favorable long-term hematologic outcomes, clinical outcomes, and rates of AEs in children with HS or SCD undergoing total or partial splenectomy. Our results add to existing literature in this area, and should provide reassurance to families and providers that TS or PS results in quite favorable outcomes. However, clinicians and families considering splenectomy should evaluate all expected risks and benefits, and individualize surgical decision-making based on disease severity and long-term goals.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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ETHICAL APPROVAL

According to the policy activities that constitute research at Duke University, the observational patient registry met criteria for operational improvement activities and was considered exempt from review by the Duke University Medical Center Institutional Review Board (IRB) (Pro00020000). The study responsible for participant enrollment and data collection was approved by the Duke University Medical Center Institutional Review Board (Pro00021114).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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