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Original Article

Clinical outcomes and risk factors for postoperative complications in children with Hirschsprung's disease

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Abstract: Objective: To explore and analyze the risk factors for postoperative complications in patients with Hirschsprung's disease (HD). Methods: Patients with HD admitted to the hospital from 2015 to 2020 were reviewed in this retrospective study. Follow-up data collected included constipation, fecal incontinence, anastomotic fistula, Hirschsprung's-associated enterocolitis (HAEC), and readmission. The putative risk factors for postoperative complications in patients with HD were as follows: clinical classification, gender, operative age, hemoglobin and serum albumin levels and preoperative HAEC. A follow-up survey was conducted for all patients by telephone. Data were analyzed statistically using SPSS version 23.0. Results: A total of 154 patients were included in the study, of whom 119 patients were followed up successfully. 53 patients who had complications postoperatively were compared to 66 patients who had no related complications. Among patients with complications: 8 had constipation, 22 had fecal incontinence and 33 had HAEC. The gender, operative age, hemoglobin levels and preoperative HAEC did not differ significantly between the two groups. However, significant differences were observed between the 2 groups in clinical classification, surgical method, serum albumin level, and whether or not a one-stage operation was performed ($P<0.05$). Conclusion: Clinical classification, surgical method, preoperative albumin level and whether or not a one-stage operation was performed emerged as risk factors affecting the postoperative complications of patients with HD. Therefore, the prognosis in HD can be improved by strengthening the preoperative nutritional support and selecting appropriate surgical methods according to the clinical subtype.

Keywords: Hirschsprung's disease, risk factors, complications, Hirschsprung's-associated enterocolitis, surgery

Introduction

Hirschsprung's disease (HD) is one of the most common congenital gastrointestinal abnormalities in infants, occurring in approximately 1 in 5000 births. It is caused by a congenital developmental defect of the enteric nervous system (ENS). The bowel movement is impaired because of the malfunctioning ENS. Therefore, abdominal distension, delayed passage of meconium, and intractable constipation are typical clinical symptoms of HD [1-3]. Currently, resection and anastomosis of the bowel is the most widely accepted method for managing HD. The common operations include Swenson, Duhamel, Rehbein, and Soave. Operations for HD are complex, giving rise to many postoperative complications, including but not limited to constipation, fecal incontinence, anastomotic fistula, and enterocolitis. Although the surgical technique for HD has dramatically improved over the years, the incidence of postoperative complications remains high at 20-40% [4, 5]. The prevalence of fecal incontinence was 20% (range: 3-48%) and that of constipation was 14% (range: 1-56%) in a meta-analysis of HD patients >10 years-old [6]. Studies demonstrated that impaired bowel function with fecal incontinence, soiling, and constipation, has a negative influence on the generic health-related quality of life (HrQoL) of HD patients. A meta-analysis reported a lower HrQoL in HD patients >10 years-old compared to the general population with regard to fecal incontinence or constipation [6, 7].

Importantly, fecal incontinence, soiling, and constipation are short- and long-term issues in patients with HD, that alter the HrQoL [8]. Several studies have reported bowel function,

QoL and postoperative complications in patients with HD over the last few years, but the results were varied [9-11]. Therefore, exploring and analyzing the risk factors associated with postoperative complications in patients with HD is an urgent need. The present study aimed to identify the risk factors for postoperative complications by a retrospective analysis of patients with HD at our center from 2015 to 2020 in order to reduce future complications and consequently improve their QoL.

Materials and methods

Patients

Patients from the Department of General Surgery of Shanghai Children's Hospital, Shanghai, China who presented and had symptoms varying from neonatal intestinal obstruction to intractable constipation and enterocolitis were recruited for this study. These patients also showed a delayed passage of meconium.

A retrospective analysis of clinical outcomes and risk factors related to postoperative complications was conducted. Data collected from patients included: clinical classification, gender, age at operation, preoperative Hirschsprung's-associated enterocolitis (HAEC), hemoglobin and serum albumin levels, and whether or not a one-stage operation was performed. All patients were followed up by phone. The follow-up survey asked for information regarding postoperative constipation, fecal incontinence, anastomotic fistula, HAEC, and readmission.

HD diagnosis and treatment

The diagnosis of HD was based on symptoms, barium enema, and biopsy results. The biopsy methods included full-thickness rectal biopsy and rectal submucosal biopsy. According to the extent of aganglionosis, the clinical classification of HD included:

1. Short segment: narrow segment located in the mid to distal rectum.

2. Ordinary: narrow segment located in the anus to proximal rectum or rectosigmoid junction, even up to the distal sigmoid colon.

3. Long segment: narrow segment extending from the anus to the descending colon or even transverse colon.

4. Total colon aganglionosis: refers to the ileum within 30 cm from the ileocecal valve in the narrow segment of the ascending colon.

5. Total intestinal aganglionosis: refers to stenosis involving the whole colon and small intestine that is >30 cm away from the ileocecum, or the duodenum.

All patients were operated on after diagnosis. Soave, improved Soave, laparoscopic surgery and modified Duhamel were the primary treatment of HD at our center.

Statistical analysis

SPSS 23.0 statistical software was used for data collation and analysis. The counted data were expressed as a percentage, and χ^2 test was used.

Univariate model analysis and multivariate conditional logistic regression analysis of risk factors for postoperative complications in patients with HD were performed to assess the risk factors for the occurrence of complications. The possible risk factors included clinical classification, gender, operative age, preoperative HAEC, hemoglobin and serum albumin level, and whether or not one-stage operation was performed. $P<0.05$ indicated a significant difference. The area under the ROC curve (AUC) was used to determine the diagnostic performance, and values >0.7 were considered to represent good performance.

Results

Patient characteristics

A total of 154 patients with HD were enrolled in this study, of whom 119 were successfully followed up over the phone. The age of the patients conducted in the follow-up ranged from 1-6 years, (average: 37) months. The median age at operation was 11 (range: 1 month-7 years). Most of the patients were males, and most were >3 months-old. In clinical classification, the ordinary type was the primary type, and Soave was the primary surgical method. Almost all patients had an enema before the operation. In addition, most patients underwent a one-stage operation (**Table 1**). Patients who underwent reoperation at other hospitals

Table 1. Demographics and characteristics of patients

Total number		119 (%)
Age at operation	≤3 month	36 (30.2%)
	>3 month	83 (69.8%)
Gender	male	98 (82.4%)
	female	21 (17.6%)
Clinical classification	Short segment	10 (8.4%)
	Ordinary	74 (62.2%)
	Long	22 (18.5%)
	Total colonic	13 (10.9%)
Surgical approach	Soave	40 (33.6%)
	Improved Soave	10 (8.4%)
	Laparoscopic-assisted Soave	50 (42.0%)
	Laparoscopic-assisted improved soave	9 (7.6%)
	modified Duhamel	10 (8.4%)
HAEC before operation	Yes	27 (22.7%)
	No	92 (77.3%)
Enema before operation	Yes	113 (95.0%)
	No	6 (5.0%)
Primary surgery	Yes	91 (76.5%)
	No	28 (23.5%)
Albumin level	Normal	93 (78.2%)
	Low	26 (21.8%)
Hemoglobin level	Normal	70 (58.8%)
	Low	49 (41.2%)

or did not undergo a radical operation after diagnosis were excluded from this study.

Clinical outcomes

53/119 (44.5%) patients with HD had postoperative complications, such as constipation, fecal incontinence, and HAEC. Constipation occurred in 8 (6.7%), fecal incontinence in 22 (18.5%) and enterocolitis in 33 (27.7%). Intriguingly, 10 (8.4%) patients had two complications and the remaining 66 patients had no related complications.

Univariate analysis was conducted according to the age at operation, gender, clinical classification, surgical approach, preoperative HAEC, and preoperative hemoglobin and albumin levels. Analysis of postoperative HAEC patients showed that clinical classification, surgical method, and whether one-stage radical surgery was performed caused complications ($P< 0.05$). These results also showed that there were no significant complications of constipation or fecal incontinence (**Table 2**).

In addition, clinical classification, surgical method, and one-stage radical surgery were statistically significant in causing complications ($P<0.05$) (**Table 3**). Furthermore, multivariate logistic regression analysis showed that clinical classification and preoperative albumin level were independent risk factors for postoperative complications (**Table 4**).

Receiver operating characteristic (ROC) curve analysis revealed that the area under the ROC curve (AUC) of the combination of clinical classification, surgical approach, and albumin level for predicting postoperative complications was 0.70 (**Figure 1**). Thus, the combination of clinical classification, surgical approach, and albumin level may have a predictive value.

Discussion

Hirschsprung's disease (HD) is a congenital defect due to an abnormality in migration, proliferation, differentiation, and preservation of enteric neural crest derived cells (ENCCs) [3, 13]. This alteration causes aganglionosis in the

Table 2. Univariate analysis of risk factors related to complications

		Constipation		Fecal incontinence		HAEC	
		number	*P*-Value	number	*P*-Value	number	*P*-Value
Age at operation	≤3 month	1	0.432	8	0.608	9	0.824
	>3 month	7		14		24	
Gender	male	6	0.630	20	0.357	24	0.109
	female	2		2		9	
Clinical classification	Short segment	2	0.099	1	0.880	2	0.014
	Ordinary	3		14		15	
	Long	3		4		8	
	Total colonic	0		3		8	
Surgical approach	Soave	4	0.655	8	0.980	10	0.040
	Improved Soave	0		2		3	
	Laparoscopic-assisted Soave	3		9		11	
	Laparoscopic-assisted improved soave	1		1		2	
	modified Duhamel	0		2		7	
HAEC before operation	Yes	1	0.683	4	0.435	25	1.000
	No	7		18		8	
Enema before operation	Yes	8	1.000	22	0.590	31	0.664
	No	0		0		2	
Primary surgery	Yes	4	0.090	18	0.589	22	0.014
	No	4		4		11	
Albumin level	Normal	8	0.196	18	0.779	27	0.803
	Low	0		4		6	
Hemoglobin level	Normal	4	0.717	15	0.346	18	0.531
	Low	4		7		15	

Table 3. Univariate analysis of risk factors of complications in patients with HD

		Complications	No complications	*P*-Value
Age at operation	≤3 month	15	21	0.694
	>3 month	38	45	
Gender	male	41	57	0.232
	female	12	9	
Clinical classification	Short segment	3	7	0.007
	Ordinary	27	47	
	Long	12	10	
	Total colonic	11	2	
Surgical approach	Soave	18	22	0.042
	Improved Soave	4	6	
	Laparoscopic-assisted Soave	18	32	
	Laparoscopic-assisted improved soave	4	5	
	modified Duhamel	9	1	
HAEC before operation	Yes	11	16	0.655
	No	42	50	
Enema before operation	Yes	51	62	0.695
	No	2	4	
Primary surgery	Yes	34	57	0.005
	No	19	9	
Albumin level	Normal	45	48	0.124
	Low	8	18	
Hemoglobin level	Normal	32	38	0.853
	Low	21	28	

Table 4. Logistic regression analysis of risk factors for complications

	β	SE	χ^2	OR	95% CI	*P*-Value
Age at operation	0.562	0.509	1.219	1.754	0.647-4.754	0.270
Gender	0.172	0.573	0.090	1.188	0.386-3.656	0.764
Clinical classification	-.765	0.340	5.072	0.465	0.239-0.906	0.024
Surgical approach	-.218	0.197	1.223	0.804	0.546-1.184	0.269
HAEC before operation	0.361	0.507	0.509	1.435	0.532-3.874	0.476
Enema before operation	0.153	0.989	0.024	1.165	0.168-8.093	0.877
Primary surgery	-.830	0.627	1.753	0.436	0.128-1.490	0.186
Albumin level	1.168	0.591	3.898	3.214	1.009-10.244	0.048
Hemoglobin level	-.210	0.451	0.217	0.811	0.335-1.961	0.642

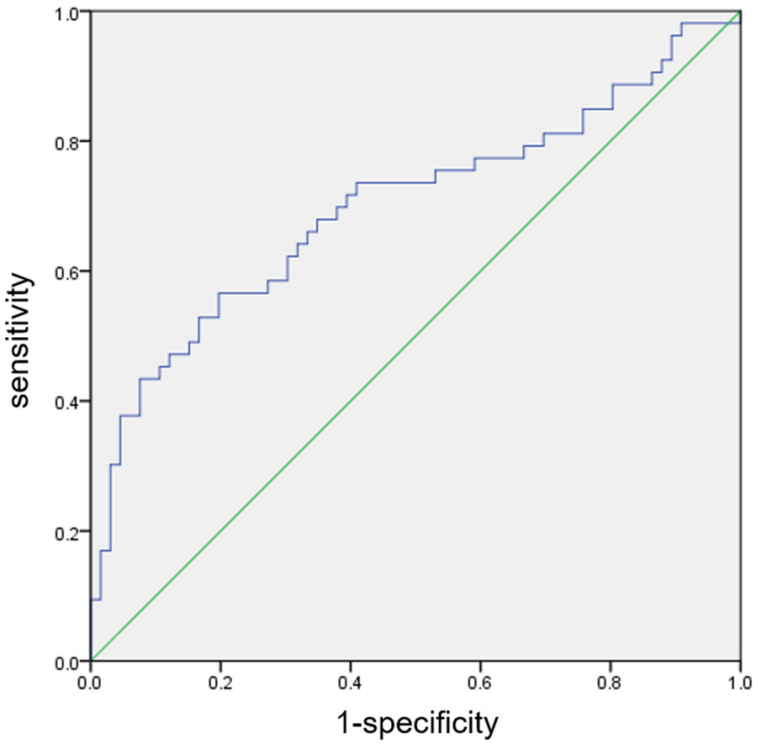

Figure 1. Predictive efficacy of clinical classification, surgical approach, and serum albumin level. AUC: 0.7.

distal intestine, resulting in intestinal obstruction. Surgery is the primary treatment causing several postoperative complications that severely affect the QoL of patients, and some patients even need reoperation [10]. Therefore, it is crucial to analyze and explore the risk factors for postoperative complications in patients HD. According to the results, we can formulate corresponding preventive measures to reduce the incidence of postoperative complications and improve the overall treatment.

Over the last few decades single-center and multi-center studies have mainly focused on postoperative complications in children with HD. The incidence of postoperative complications in patients who underwent Soave surgery ranged from 14.7-67% [12]. Various factors including the age of the child at the time of operation, the duration of the disease, associated anomalies, and the type of surgical procedure, contributed to the occurrence of complications [13, 14].

In this retrospective study, 119 patients diagnosed with HD who underwent radical surgery were analyzed. HAEC, constipation, and fecal incontinence were the most common postoperative complications in this study. We also observed that clinical classification, surgical method, and whether a one-stage operation was performed were significant risk factors related to postoperative complications in children with HD.

In this study, HAEC was the main postoperative complication in patients, with an incidence of 27.7%. 20/33 patients were readmitted to the hospital. The occurrence of HAEC varies according to different reports. Le-Nguyen et al. [15] reported that the incidences of HAEC before and after surgery were 25% and 19%

respectively. Chung et al. [16] reported that the incidence of HAEC after 1 year of surgery was 20.8%. Addtionally, Neuvonen et al. [17] reported postoperative recurrent enterocolitis in 44%.

Some studies indicate that common risk factors for HAEC include low weight, low IgA, the length of intestine involved in HD, preoperative enteritis, and other congenital diseases [18]. However, only a few studies have analyzed the effect of age, pathologic typing, and surgical method on HAEC, although the conclusions were varied [16]. In the current study, the risk factors included clinical classification, surgical method, and whether or not one-stage radical surgery was performed. The incidence of enterocolitis in the long segment (36.4%), and total colon aganglionosis (61.4%) was significantly higher than that in the common type and short segment aganglionsis. The longer the aganglionic segment, the greater the intestinal ENS defect, and the more severely impaired the intestinal barrier and immune function. Moreover, fecal stasis and intestinal microflora disorder also increased intestinal susceptibility. Some studies reported that oral probiotics reduce the incidence and severity of postoperative HAEC [19]. Some researchers used different cuff lengths for the Soave technique and found that the incidence of enterocolitis was lower in patients with short cuff lengths (9% *vs* 30%) [20, 21].

In addition to HAEC, constipation and fecal incontinence are also common postoperative complications in patients with HD. Constipation and fecal incontinence have been recognized as chronic problems in a large proportion of patients with HD [5, 22, 23]. In this study, the incidence of these complications was 6.7% and 18.5%, respectively. Widyasari et al. [5] reported constipation in 24% of patients who underwent Soave's procedure. Wang et al. showed that the probability of early postoperative fecal contamination in HD children is 30-40% [24], which is caused by intraoperative injury of the internal sphincter and the pelvic floor nerves. The major contributors to fecal continence are the anal sphincters, colonic motility, anorectal sensation, and the sub-epithelium of the anal canal [25, 26]. All these factors can be effectuated during transanal surgery, causing soiling. In this study, the surgical approach was one of the main risk factors for complications in patients with HD. Typically, constipation occurs in patients undergoing Soave surgery, which might be caused by simple mucosal stripping and large residual muscle sheaths lacking ganglion cells. Then these patients required a prolonged duration for anal expansion.

Conversely, the modified Soave method excised a part of the muscle sheath, and our analysis showed that the incidence of postoperative constipation in such patients was extremely low. Early intervention such as dietary adjustment and defecation training, may improve the patient's defecation control ability, thereby improving their QoL [23, 27].

Furthermore, primary or staged surgery for HD remains controversial. Presently, most doctors adopt the one-staged operation for HD patients due to the safety and efficacy of the procedure. In a multicenter, large-sample retrospective study [28], the surgical complications not including anastomotic stenosis, HAEC incidence, and reoperation rate were lower than those for the secondary surgery. A meta-analysis by Zimmer et al. [29] showed that there were neither significant differences in the rate of good bowel function after the first and second-stage operation nor in the incidence of fecal fouling and fecal incontinence. However, the incidence of constipation in the first-stage was lower than that of the second-stage operation (P=0.006) in this analysis, indicating that the early radical surgery was beneficial to the recovery of the bowel function of patients. Additionally, the incidences of constipation and HAEC were lower after primary surgery than after secondary surgery, while the incidence of fecal contamination was higher after secondary surgery. Notably, most patients who underwent staged surgery in our study were in an unstable condition or presented with severe complications. The outcome of such patients may not be ideal for primary surgery. Thus, we hypothesize that primary surgery would be most feasible for patients with HD in a stable condition when not diagnosed with HAEC. Conversely, staging surgery would be recommended for patients who have severe complications such as HAEC, bowel perforation, malnutrition, or severe proximal bowel expansion.

The current study was carried out using an extensive data analysis and the results provid-

ed a reliable theory. Nonetheless, these findings were not in agreement with those from previous studies, which might be related to the patient's characteristics, the number of patients, and time of follow-up. Therefore, in future studies, a large sample size with data from multiple centers should be used to evaluate the risk factors related to postoperative complications in patients with HD.

Conclusion

This study shows the clinical outcomes and risk factors of complications after surgery for HD. Postoperative complications such as fecal incontinence, constipation, and enterocolitis severely affect the quality of life of patients with HD. Clinical classification, surgical method, preoperative albumin level, and one-stage operation, if performed are related risk factors affecting the postoperative complications of patients with HD. Therefore, the prognosis of HD can be improved by strengthening preoperative nutritional support and selecting appropriate surgical methods according to different clinical types and the preoperative condition of the patients.

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The procedures mentioned in the present study have been approved by the Ethics Committee of Shanghai Children's Hospital (approval No. 2020RY023-E01).

Disclosure of conflict of interest

None.

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