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Predictor of Hirschsprung-associated enterocolitis: A regression analysis

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ABSTRACT

Aim: To identify independent predictors for Hirschsprung-associated enterocolitis (HAEC) through regression analysis of various clinical factors.

Method: This retrospective study examined clinical, surgical, and diagnostic data of patients treated for Hirschsprung's disease (HD), evaluating the impact of various factors like aganglionic segment length and postoperative complications.

Results: We analyzed data from 161 patients with HD. Surgical interventions were split between the Rehbein procedure at 47.2% (n=76) and transanal endorectal pull-through (TEPT) at 52,8% (n=85). The median age at diagnosis was 7 [3-12.5] months. The average length of the aganglionic segment measured 25 [20-30] cm distributed as follows: ultrashort segment (16.9%, n=27), rectosigmoid (47.5%, n=76), descending colon (18.8%, n=30), splenic flexure (12.5%, n=20), transverse colon (3.7%, n=6), and ascending colon (0.6%, n=1). Preoperative enterocolitis was observed in 33.1% (n=53). Postoperative enterocolitis occurred in 28.1% (n=45). Additional interventions included rectal botox injections (2.5%, n=4), myectomies (3.1%, n=5), and re-do surgeries (3.1%, n=5). Anastomotic strictures were noted in 5.6% (n=9) of the cases. Upon analyzing patients who presented with HAEC in the preoperative period, it was determined that the length of the aganglionic segment (p=0.001, OR: 1.07) and the age at diagnosis (p=0.003, OR: 1.03) were independent risk factors for HAEC. A positive correlation was found between Length of aganglionic segment and number of preoperative HAEC (p=0.002, r=0.405).

Conclusion: In our study, it was observed that long-segment Hirschsprung's disease and a delayed age at diagnosis are risk factors for Hirschsprung-associated enterocolitis.

Key words: Hirschsprung disease, agangliosis, Hirschsprung-associated enterocolitis.

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Introduction

Hirschsprung's disease (HD) is a birth defect marked by a lack of ganglion cells in two critical areas of the lower rectum: the submucosal Meissner's plexus and the muscularis Auerbach's plexus [1]. This absence can extend upward to varying degrees. The condition occurs in approximately 1 to 1.63 cases per 10,000 live births. The primary method for diagnosing HD is through the histopathological analysis of rectal biopsy samples [2].

HD is recognized as a multi-genetic disorder with a complex etiology. The most common genetic alterations are mutations in the RET proto-oncogene and the endothelin receptor B (ENDRB). HD often presents independently but can also be associated with other conditions, such

as Trisomy 21 in about 10% of cases, and various syndromes. Familial recurrence is observed in syndromic forms of HD, notably in conditions like multiple endocrine neoplasia (MEN) 2A, caused by RET mutations, and Shah-Waardenburg (WS4) syndrome due to ENDRB mutations. Nevertheless, a significant portion of HD cases are sporadic, with no clear genetic cause [3,4].

The absence of ganglion cells is a key diagnostic marker for HD, determined through specific staining methods, including acetylcholinesterase (AChE) staining of rectal tissue samples. Anorectal manometry and contrast enema are additional diagnostic tools, with the absence of the recto-anal inhibitory reflex (RAIR) in manometry being indicative of HD. Contrast enema features such as a transition zone, altered recto-sigmoid ratio, and prolonged contrast retention also aid in diagnosis [5,6].

Surgical treatment is typically required for HD. Prior to surgery, rectal irrigation is essential, particularly in managing HAEC, which is the most serious complication of HD [7]. The surgical strategy is determined by the presence of any comorbid conditions. In cases of short-segment HD without other health issues, a single-stage surgical procedure is often suitable. However, for more complex cases, a staged surgical approach starting with a colostomy is generally recommended. The ideal timing for definitive surgery is typically 4 to 6 months post-colostomy [8,9]. Surgical techniques vary, with traditional methods like the Swenson technique and newer procedures that preserve rectal and bladder innervation, such as the Duhamel and Soave techniques. The one-stage transanal Soave procedure, performed in the neonatal period, may avoid the need for abdominal incision and colostomy [10,11]. The TEPT procedure for HD, initially described by de la Torre and Langer in the late 1990s, has demonstrated itself as a straightforward and efficient technique. It offers several notable advantages, including reduced invasiveness, decreased postoperative pain, quicker initiation of feeding, shorter hospitalization, and improved cosmetic results without the presence of an abdominal scar [1-3]. In 1953, Fritz Rehbein pioneered the intraabdominal colon resection technique for the treatment of Hirschsprung's disease at the Clinic for Pediatric Surgery in Bremen, Germany. This surgical approach offers several significant advantages: Eliminates the risk of compromising the autonomous nerve plexus in the small pelvis, which supplies the bladder, urethra, genital organs, and the rectum. Reduces stress on the continence organ and prevents incontinence. Simplifies the technical execution of the procedure. Positions the anastomosis in an extraperitoneal location [3-5].

A major postoperative challenge in HD is HAEC, an inflammatory intestinal disorder. Other complications, though less common, include anastomotic leakage, stenosis, wound infections, bleeding, and perianal excoriations. Post-surgery bowel habit changes like constipation and fecal incontinence are also observed, attributed to factors such as high anal resting pressure, poor rectal peristalsis, or surgical technique [12-15].

The aim of this study is to identify independent predictors for Hirschsprung-associated enterocolitis (HAEC) through regression analysis of various clinical factors.

Materials and metods

Population: This study was conducted over an extensive period from January 2000 to January 2023. A total of 161 patients were included in the research. The study population comprised patients diagnosed with Hirschsprung's disease who had undergone

surgical treatment. The study was retrospective in nature. We systematically reviewed patient records to collect data. The collected data included age, sex, age at the time of surgery, the extent and length of the aganglionic segment, presence of HAEC, postoperative complications, and whether the patient had undergone procedures such as myectomy or Botox injections. In addition to clinical data, we also evaluated laboratory and radiological findings for each patient. This comprehensive approach allowed for a detailed understanding of the disease's impact and treatment outcomes.

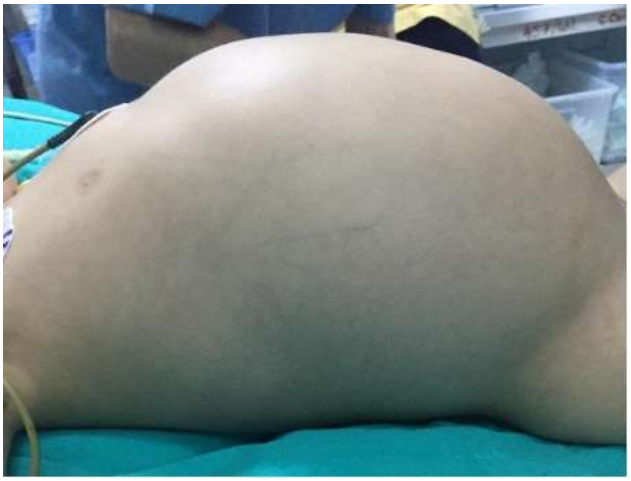

Figure 1. Severe distended abdomen.

Clinical monitoring: All patients presenting with symptoms such as inability to pass stool, abdominal distension, and vomiting underwent a detailed medical history assessment (Figure 1). This was followed by a comprehensive physical examination, including an abdominal and rectal examination. Particular attention was given to patients who, according to their medical history, had not passed meconium within the first 48 hours post-birth and/or exhibited a 'wash out' sign after rectal examination. These patients routinely underwent an abdominal X-ray (Figure 2A). If the X-ray indicated suspicion of colonic abnormalities, a contrast enema was performed (Figure 2B). Further abdominal X-rays were taken 24 and 48 hours after the contrast enema to evaluate delayed images (Figure 2C). Patients showing a transition zone on the colonography or retained contrast in the colon on delayed images were strongly suspected of having HD. All these patients were then subjected to a rectal biopsy for histopathological examination. In patients underwent laparotomy, the distended colon can be seen (Figure 3). While some patients underwent staged surgeries following rectal biopsy, others received rectal irrigation prior to

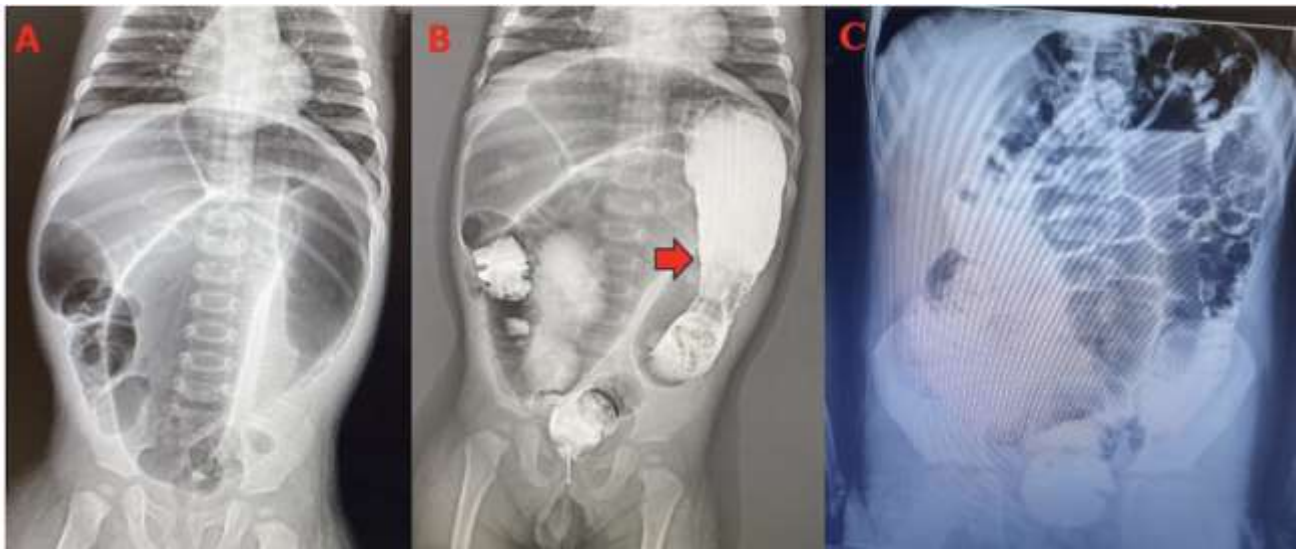

Figure 2. Radiograph. **A.** Preoperative period with distended abnormal bowel loops. **B**. Contrast enema graphy. **C.** Late graphy (at 24 h).

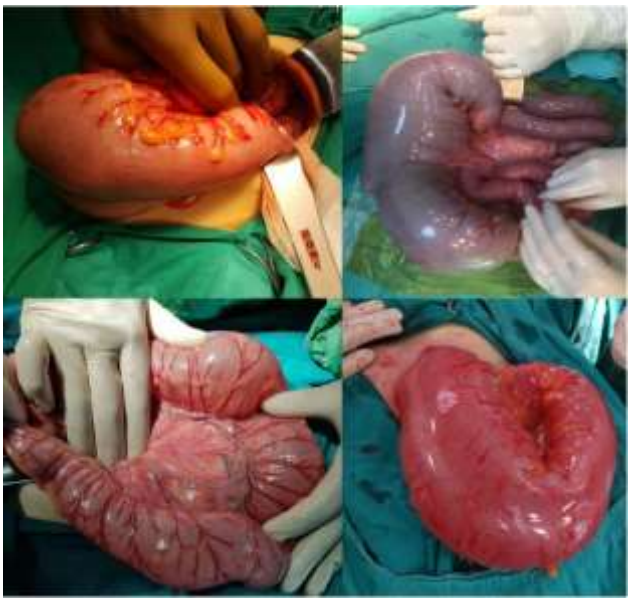

Figure 3. The images from laparotomy.

Table 1. HAEC diagnostic criteria (HAEC > 10 points).

	History
2	Diarrhea with explosive stool
2	Diarrhea with foul-smelling stool
1	Diarrhea with bloody stool
1	History of enterocolitis
	Physical examination
2	Explosive discharge of gas and stool on rectal examination
2	Distended abdomen
1	Decreased peripheral perfusion
1	Lethargy
1	Fever
	Radiologic examination
1	Multiple air fluid levels
1	Dilated loops of bowel
1	Sawtooth appearance with irregular mucosal lining
1	Cutoff sign in rectosigmoid with absence of distal air
1	Pneumatosis
	Laboratory
1	Leukocytosis
1	Shift to left
20	Total score

biopsy. Patients who tolerated rectal irrigation and gained adequate weight were scheduled for surgery once they reached a suitable weight. During this period, the possibility of HAEC was considered. Follow-up evaluations included assessments for HAEC, with diagnostic criteria summarized in Table 1 [16]. Patients diagnosed with HAEC were hospitalized and started on appropriate HAEC treatment, primarily comprising antibiotic therapy and rectal irrigation. The study included patients who underwent either Rehbein surgery or Transanal Endorectal Pull-Through (TEPT) procedures (Figure 4). The surgical interventional of these patients was performed by 5 different surgeons.

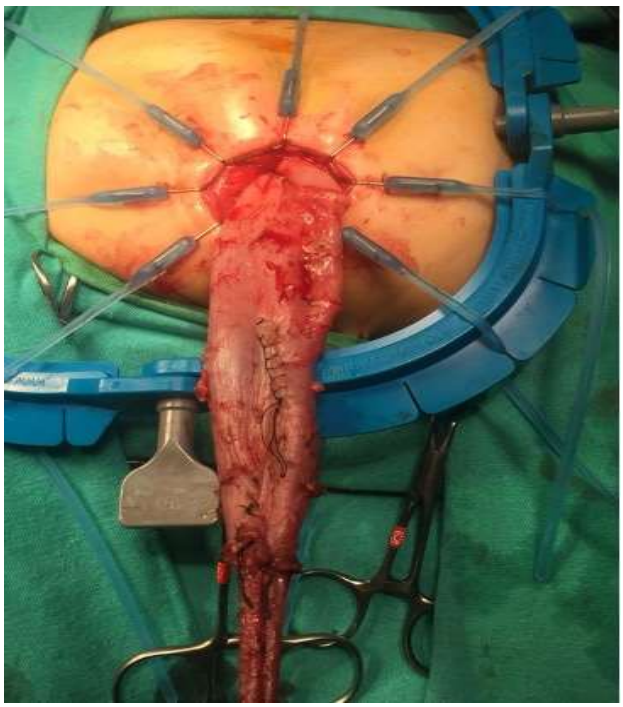

Figure 4. Image of transanal endorectal pull-through.

Eligibility criteria: In the retrospective data review, we included patients whose records were accessible, complete, and consistent. A key inclusion criterion was that the patients must have undergone either Rehbein or TEPT surgery. Exclusion criteria were set as follows: patients aged 18 years or older, those who had been operated on using a different surgical technique,

and patients whose retrospective data were inconsistent or incomplete. These criteria ensured a focused and reliable analysis of the targeted patient group.

Ethical approval: The study was approved ethically by non-interventional ethics committee of Başakşehir Çam and Sakura City Hospital (KAEK/2023.11.617). Written informed consents were obtained from all patients and/or their guardians.

Statistical analysis: Patient data were analyzed using descriptive statistical methods, encompassing the calculation of frequencies and specific characteristics for each variable. For continuous variables, we computed the mean and standard deviation (or median [IQR]) to summarize the data. We assessed the normality of these continuous variables using Shapiro-Wilk and Kolmogorov-Smirnov tests. In instances where continuous data were not normally distributed, non-parametric methods were applied instead of the t-test, which is typically used for analyzing continuous variables that follow a normal distribution. For categorical variables, the chi-square test was the primary method of analysis, supplemented by Fisher's exact test when necessary. The risk factor analysis was performed by using binary logistic regression analysis. The cut-off value of total aganglionic bowel length for HAEC was calculated by ROC analysis. The data processing and analysis were conducted using the SPSS Statistics software, Version 26.0 (IBM Corp., Armonk, NY, USA). $p<0.05$ was deemed to be statistically significant.

Results

A total of 161 patients were analyzed during study period. In the analyzed cohort, a range of comorbidities were identified alongside the primary condition under study. Urinary system pathologies were the most prevalent, affecting 20.5% of the patients (n=9). Hypothyroidism and Down Syndrome were observed in an equal proportion of participants, each accounting for 13.6% (n=6). Inguinal pathologies were present in 11.4% (n=5) of cases, while hypospadias and major cardiac diseases were reported in 9.1% of patients (n=4 for each). Diabetes and hydrocephaly had an incidence rate of 4.5% (n=2 for each), the same prevalence as autism. Rarer conditions included Mowat Wilson Syndrome, cerebral palsy, muscular dystrophy, and polydactyly, each constituting 2.3% of the sample population (n=1 for each) (Table 2).

Table 2. Comorbidities.

Comorbidities	n	%
Urinary system pathologies	9	20.5
Hypothyroidism	6	13.6
Down Syndrome	6	13.6
Inguinal pathologies	5	11.4
Hypospadias	4	9.1
Major cardiac diseases	4	9.1
Diabetes	2	4.5
Hydrocephaly	2	4.5
Autism	2	4.5
Mowat-Wilson Syndrome	1	2.3
Cerebral Palcy	1	2.3
Muscular dystrophy	1	2.3
Polydactili	1	2.3

In this study, the median age at diagnosis was 7 [3-12.5] months. Patients underwent surgery at a median age of 11 [5-15] months. The cohort predominantly consisted of male patients, accounting for 83.2% (n=134), while female patients represented 16.8% (n=27). Regarding the surgical technique employed, the Rehbein procedure was used in 47.2% (n=76) of cases, whereas TEPT was utilized in 52.8% (n=85) of instances. The length of the aganglionic segment averaged 25 [20-30] cm. The distribution of the

Table 3. Demographic.

Parameters	n or median	% or IQR
Age at diagnosis (month)*	7	3-12.5
Age at surgery (month)*	11	5-15
Gender		
Male	134	83.2%
Female	27	16.8%
Technique		
Rehbein	76	47.2%
TEPT	85	52.8%
Length of aganglionic segment (cm)*	25	20-30
Segment		
Ultrashort	27	16.9%
Rectosigmoid	77	47.5%
Descending colon	30	18.8%
Splenic flexura	20	12.5%
Transverse colon	6	3.7%
Ascending colon	1	0.6%
Preoperative enterocolitis	53	33.1%
Number of preoperative enterocolitis		
Once	28	52.8%
Twice	17	32.1%
>2 times	8	15.1%
Postoperative enterocolitis	45	28.1%
Number of postoperative enterocolitis		
Once	35	77.7%
Twice	9	20%
>2 times	1	2.3%
Anastomotic stricture	9	5.6%
Rectal botox application	4	2.5%
Myectomy	5	3.1%
Re-do surgery	5	3.1%
The follow-up period (month)*	48	4-98

Table 4. Predictor of HAEC in preoperative period.

Predictor	Estimate	SE	Z	*P*	Odds ratio (OR)
Intercept	-4.0891	0.9174	-4.46	*<0.001*	0.0168
Gender	0.6096	0.5150	1.18	*0.237*	1.8397
Age at diagnosis	0.0368	0.0124	2.98	*0.003*	1.0375
Comorbidity	0.8667	0.4917	1.76	*0.078*	2.3790
Length of aganglionic segment (cm)	0.0736	0.0229	3.21	*0.001*	1.0763

aganglionic segment was as follows: ultrashort segment in 16.9% (n=27) of cases, rectosigmoid region in 47.5% (n=77), descending colon in 18.8% (n=30), splenic flexure in 12.5% (n=20), transverse colon in 3.7% (n=6), and ascending colon in 0.6% (n=1) of the cases. Preoperative enterocolitis was noted in 33.1% (n=53) of patients. Among these, 52.8% (n=28) experienced enterocolitis once, 32.1% (n=17) twice, and 15.1% (n=8) more than two times. Postoperative enterocolitis occurred in 28.1% (n=45) of cases, with the majority (77.7%, n=35) experiencing it once, 20% (n=9) twice, and a small minority (2.3%, n=1) more than two times. Anastomotic stricture occurred in 5.6% (n=9) of patients. Rectal botox (2.5%, n=4), myectomy (3.1%, n=5), and re-do surgery (3.1%, n=5) were performed on patients. The median follow-up period was 48 [4-98] months (Table 3).

Upon analyzing patients who presented with HAEC in the preoperative period, it was determined that the length of the aganglionic segment (p=0.001, OR: 1.07) and the age at diagnosis (p=0.003, OR: 1.03) were independent risk factors for HAEC (Table 4).

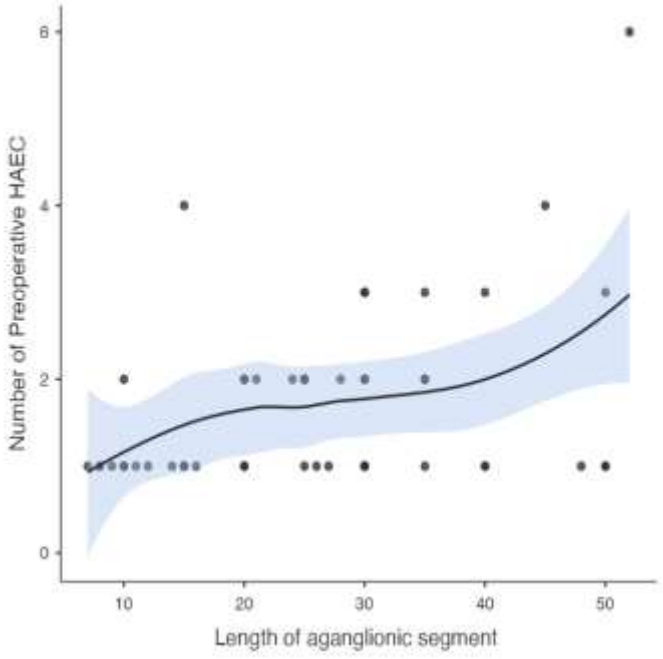

Figure 5. Correlation graph.

A positive correlation was found between Length of aganglionic segment and number of preoperative HAEC (p=0.002, r=0.405) (Figure 5).

The cut-off value of total aganglionic bowel length for HAEC was calculated by ROC analysis. As a result of the ROC analysis, sensitivity 55% and specificity 74%, negative predictive value 79% and area under curve (AUC) 0.620 were determined at the cut-off value of 28 cm of the total agognglionic segment length for HAEC (Figure 6).

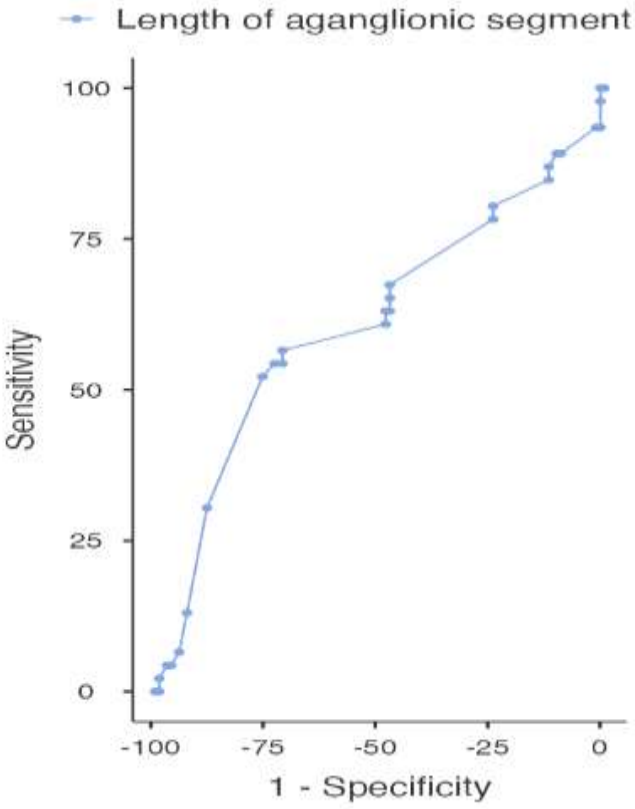

Figure 6. ROC analysis.

Discussion

The elucidation of independent predictors for HAEC is vital given its frequent occurrence and the considerable morbidity associated with it. In this extensive retrospective analysis, spanning from 2000 to 2023 with a cohort of 161 patients, the length of the aganglionic segment and the age

at diagnosis emerged as significant independent risk factors for the development of HAEC in the preoperative period. The association between the length of the aganglionic segment and HAEC susceptibility aligns with the pathophysiological understanding of the disease. A longer aganglionic segment may correlate with a more severe disruption in normal bowel motility, thereby increasing the risk of enterocolitis. This is further substantiated by our findings, which reveal a positive correlation between the length of the aganglionic segment and the number of preoperative HAEC episodes. These observations suggest that the extent of the aganglionic bowel segment could serve as a quantitative marker for the risk stratification of HAEC.

Similarly, the age at diagnosis being an independent risk factor is insightful. Delays in diagnosis can lead to prolonged periods of bowel dysfunction, which could potentially increase the risk of enterocolitis. This emphasizes the importance of early detection and intervention in Hirschsprung disease to mitigate the risk of HAEC.

The range of risk factors associated with HAEC is characterized by a variety of perspectives and research outcomes in the scientific literature. According to Pastor et al., certain factors, including preoperative enterocolitis and short-segment Hirschsprung's disease, appear not to be linked to the development of HAEC. Conversely, they suggest that the age at which surgery is undertaken is a significant factor in HAEC development [16]. This stands in contrast to findings by Gao et al. and others who have identified surgical methods and preoperative enterocolitis as associated with HAEC [17]. The protective role of the Soave procedure is also debated, with some studies affirming and others negating its benefits [18,19].

Our study adds to this ongoing discussion by identifying a number of factors linked to the development of HAEC. These findings underscore the complexity of managing HD and the importance of a multidisciplinary approach when multiple risk factors for HAEC are present. In particular, the analysis supports the notion that preoperative malnutrition, respiratory infections, and hypoproteinemia are indications for delaying surgery until these conditions are managed, thereby not exacerbating the underlying disease [20].

Other factors such as anastomosis technique, distance from the ganglion site to the incision margin, and low IgA levels have been suggested as potential risk factors for HAEC, though these were not analyzed in our study due to limited data [20-23]. Similarly, associations between HD complications with other congenital malformations, maternal age, and preterm birth are reported in the literature but could not be included in our analysis for the some reason.

Our findings differ from previous research, like the study conducted by Mao et al., which indicated a reduced occurrence of HAEC in patients undergoing the Duhamel procedure compared to TEPT [24]. However, our more extensive comparative study revealed no notable difference in the incidence of HAEC across different surgical methods. This is in agreement with the conclusions drawn by Ruttenstock et al., who identified TEPT as a safe, minimally invasive option with a low rate of postoperative HAEC [25].

Our study's retrospective design limits the ability to establish causation for HAEC risk factors. The reliance on accessible and consistent records may introduce selection bias, potentially overlooking relevant data. Additionally, the focus on Rehbein and TEPT surgeries may not fully represent the spectrum of surgical interventions for HD.

Conclusions

Our study identifies the length of the aganglionic segment and age at diagnosis as key independent risk factors for HAEC in Hirschsprung disease. These insights enhance our understanding of HAEC and can inform clinical vigilance and tailored management strategies to improve patient outcomes in HD.

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Ethical statement: *The study was approved ethically by non-interventional ethics committee of Başakşehir Çam and Sakura City Hospital (KAEK/2023.11.617). Written informed consents were obtained from all patients and/or their guardians.*

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