Association between eosinophilia and lymphocytosis with functional outcomes of patients with Hirschsprung disease following transabdominal Yancey–Soave pull-through

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ABSTRACT

Introduction: Hirschsprung disease (HSCR) is a disorder caused by the failure of neural crest migration leading to an aganglionic colon and functional obstruction. Transabdominal Yancey–Soave pull-through is one of the definitive therapies for this condition. Prognostic factors, including sex, aganglionosis type, age at definitive surgery, nutritional status, eosinophilia and lymphocytosis, might influence the outcomes of the pull-through. We evaluated the functional outcomes of HSCR patients after Yancey-Soave surgery and associated them with the prognostic factors.

Materials and Methods: The study included Hirschsprung patients aged ≥3 and <18 years who underwent Yancey-Soave surgery at our hospital. The functional outcomes were evaluated using the Krickenbeck classification to determine voluntary bowel movement (VBM), constipation and soiling.

Results: Most (82.6%) patients showed VBM, 26.1% had constipation and 4.3% suffered from soiling. Among 23 patients who received Yancey–Soave surgery, 8 (34.8%) had eosinophilia and 5 (21.7%) had lymphocytosis. However, no significant differences were observed between eosinophilia and non-eosinophilia groups for VBM (p=1.0), constipation (p= 0.621) or soiling (p=0.738). Similarly, no significant differences were found between lymphocytosis and non-lymphocytosis groups for VBM (p=1.0), constipation (p=0.545) or soiling (p=0.973). Moreover, no other prognostic factors affected the functional outcomes after Yancey–Soave surgery (p>0.05).

Conclusion: Our study shows that eosinophilia and lymphocytosis might not affect the functional outcome of patients with HSCR following Yancey-Soave surgery. In addition, sex, aganglionosis type, age at definitive surgery and nutritional status might not influence the functional outcome after definitive surgery. Further, a more extensive study is essential to clarify our findings.

KEYWORDS:
Eosinophilia; functional outcomes; Hirschsprungdisease; lymphocytosis; Yancey–Soave pull-through

INTRODUCTION

Hirschsprung disease (HSCR) is a disease characterised by the absence of ganglion cells. It is the most common cause of functional obstruction in children,[1] with an incidence of 1 in 5000 live births[2] and a total male-to-female ratio of 1:4. The incidence of HSCR in Indonesia reaches 1 in 3250 births.[3]

One of the definitive therapies for HSCR is transabdominal Yancey–Soave pull-through which is aimed at removing the aganglionic colon and pulling the normal colon down to the anus while preserving sphincter function.[4] Several postoperative outcomes, such as Hirschsprung-associated-enterocolitis (HAEC), soiling and constipation, might be found and can lead to morbidity and mortality in HSCR patients, thus requiring evaluation.[5,6] Some prognostic factors, including eosinophilia, might influence the outcomes of the pull-through; however, they show conflicting findings.[7,8] Therefore, we evaluated the functional outcomes of HSCR patients after Yancey–Soave surgery and associated them with the prognostic factors.

MATERIALS AND METHODS

Patients

Following approval by the Institutional Review Board of the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito Hospital, Indonesia (KE/FK/110/EC/2020), we conducted a cross-sectional study involving HSCR patients ≥3 and <18 years old who underwent Yancey–Soave surgery between 2013 and 2020 in our hospital. Patients who had incomplete medical records data were excluded.

Prognostic Factors

Patients who met the criteria were classified into some characteristics, including sex (male and female), aganglionosis (short and long), age at surgery (<3 years and ≥3 years) and nutritional status (well- and undernourished). Nutritional status was divided into well- and undernourished and assessed based on weight-for-age z-score for patients aged <5 years, where undernourished was defined as a condition in which the patient's z-score value was below –2.9 For patients aged 5–18 years, nutritional status was evaluated using body mass index.[9]

This article was accepted: 19 February 2024
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Serum Eosinophilia and Lymphocytosis
In previous studies, eosinophilia was determined by histopathology that needs rectal biopsy.[7,8] Therefore, we chose a non-invasive, more accessible and routine method to determine the association between eosinophilia and lymphocytosis and functional outcomes using their serum level.

In this study, peripheral blood samples were collected 1–8 days before definitive surgery. Eosinophilia is described as an elevation of eosinophils >0.5 ×109/L, and lymphocytosis is characterised by an increase in lymphocytes >7 $\times 10^9$/L.

Functional Outcomes
Functional outcomes were evaluated with Krickenbeck classification to determine voluntary bowel movement (VBM), constipation and soiling. Constipation is further divided into three categories, namely grade 1 (managed through dietary patterns), grade 2 (requires laxative use) and grade 3 (resistant to dietary changes and laxative use). Meanwhile, soiling is categorised into grade 1 (1–2×/week), grade 2 (every day, without social disturbances) and grade 3 (constant and causing social disturbances).[10]

Statistical Analysis
Data were presented in numbers/percentages and analysed using the Fisher Exact or Chi-square test to examine the association between prognostic factors and functional outcomes.

RESULTS

Baseline Characteristics
In this study, HSCR patients were identified based on the International Classification of Disease Tenth Revision (ICD-10) with diagnosis coding ICD-10-CM Q43.1 and Soave procedure based on the International Classification of Disease Ninth Revision with code ICD-9-CM 48.41.[11] The patient clinical characteristics are shown in Table I. Twenty-three HSCR patients had complete data for final analysis. Most patients were male (78.3%), had short-segment HSCR (91.3%) and were well nourished (65.2%) (Table I).

Functional Outcomes
Among 23 patients, most (82.6%) showed VBM, 26.1% had constipation, and 4.3% suffered from soiling (Table II).

Association Between Prognostic Factors and Functional Outcomes
Subsequently, we determined the association between the patient's characteristics, including sex, age of pull through, aganglionosis type, nutritional status, eosinophilia and lymphocytosis and functional outcomes, i.e., VBM, soiling and constipation. None of the prognostic variableswere significantly associated with the functional outcomes: VBM, soiling and constipation following Yancey–Soave pull-through (Tables III, IV and V, respectively).

DISCUSSION

Our study reveals that most HSCR patients have VBM following the Yancey-Soave pull-through. Only a few HSCR patients show abnormal VBM. Abnormal VBM might be associated with abnormalities in anal canal function and sphincter control, as well as hypomotility.[12] Abnormalities in anal canal function and sphincter control can be associated with the location of the anastomosis. An anastomosis closer to the dentate line increases the risk of abnormal VBM and incontinence as it can damage the nerve endings at the dentate line, which are essential for holding back the urge for defecation.[13,14]

Furthermore, constipation found in this study was ~26% of cases. In HSCR patients following Yancey-Soave pull-through, the incidence of constipation is relatively high, possibly due to anastomotic strictures in the muscular cuff.[15] In the Yancey-Soave pull-through, this muscular cuff remains contracted and can lead to compression and disruption of the normal colonic peristaltic movement. This becomes a cause of functional obstruction, which can result in constipation.[16]

Interestingly, only one case of soiling was noted in our study. Soiling can be caused by injuries to the sphincter muscles, damage to the anal canal, and the presence of overflow incontinence due to constipation. However, these phenomena are rarely observed in the transabdominal pull-through technique[17,18] as our study.

Mucosal eosinophilia has been investigated to be associated with the functional outcomes of HSCR patients following pull-through; however, studies reveal conflicting findings and scarce.[7,8,19] Our study failed to show the association between serum eosinophilia and lymphocytosis and functional outcomes of HSCR patients after definitive surgery. Our findings support a current study.[7] However, we utilised a different method, i.e., serum eosinophilia vs. histopathology.[7] Another novelty of our study is that we also used another variable, i.e., serum lymphocytosis vs. eosinophilia.[7,19] In addition, we chose the serum approach due to its minimal invasiveness, less harmful to patients,routine assessment in daily practice, and ease of monitoring the changes. Our study provides new evidence that eosinophilia is not significantly associated with the functional outcomes of HSCR patients after pull-through from a specific developing country.

Interestingly, a previous study analysed rectal biopsies in non-HSCR patients and found that patients with mucosal eosinophilia were at a higher risk of experiencing constipation and growth failure.[20] Furthermore, a high incidence of recurrent abdominal pain, diarrhoea, and constipation was observed in patients with eosinophilic colitis.[21] Constipation in patients with eosinophilia is suspected to occur because eosinophils disrupt gastrointestinal motility and might have a negative impact on myenteric ganglion cells. There is also evidence that mast cells and eosinophils are critical cells in the development of dysmotility by releasing granules.[20]

In contrast, one found that despite findings of eosinophil infiltration in the myenteric plexus of HSCR patients, no gastrointestinal complications were observed.[8] It is also noted that eosinophil infiltration in the myenteric plexus of HSCR patients does not lead to a poor prognosis after surgery.[8] These findings were similar to a current study showing no significant differences in postoperative outcomes, feeding issues, and stooling issues between patient groups with and without mucosal eosinophilia.[7]

Table I: Clinical characteristics of HSCR patients who underwent Yancey–Soave pull-through in our institution

Characteristic	n=23	Percentage (%)
Sex		
Male	18	78.3
Female	5	21.7
Aganglionosis type		
Long	2	8.7
Short	21	91.3
Age at surgery		
< 3 years old	11	47.8
≥ 3 years old	12	52.2
Nutritional status		
Well-nourished	15	65.2
Undernourished	8	34.8
Eosinophilia		
Yes	8	34.8
No	15	65.2
Lymphocytosis		
Yes	5	21.7
No	18	78.3

Table II: Functional outcomes in HSCR patients after Yancey-Soave pull-through in our institution

Functional outcomes	n (%)
Voluntary bowel movement (VBM)	19/23 (82.6)
Soiling	1/23 (4.3)
√ Grade 1	1 (100)
√ Grade 2	-
√ Grade 3	-
Constipation	6/23 (26.1)
√ Grade 1	2 (33.3)
√ Grade 2	3 (50)
√ Grade 3	1 (16.7)

Table III: Association between patients' characteristics and VBM in HSCR patients after Yancey–Soave pull-through

Variables	VBM		OR (95% CI)	p-value
	Yes (n, %)	No (n, %)		
Sex				
• Male	14 (77.8)	4 (22.2)	3.41 (0.16–74.44)	0.435
• Female	5 (100)	0		
Aganglionosis type				
• Long	2 (100)	0	1.06 (0.04–27.11)	0.973
• Short	18 (85.7)	3 (14.3)		
Age at surgery (yo)				
• <3	10 (90.9)	1 (9.1)	0.3 (0.03–3.43)	0.59
• ≥3	9 (75)	3 (25)		
Nutritional status				
• Well-nourished	13 (86.7)	2 (13.3)	1.08 (0.08–14.08)	1.0
• Undernourished	7 (87.5)	1 (12.5)		
Eosinophilia				
• Yes	7 (87.5)	1 (12.5)	0.57 (0.05–6.61)	1.0
• No	12 (80)	3 (20)		
Lymphocytosis				
• Yes	4 (80)	1 (20)	1.25 (0.1–15.5)	1.0
• No	15 (83.3)	3 (16.7)		

HSCR, Hirschsprung disease; VBM, voluntary bowel movement; yo, years old

Table IV: Association between patients' characteristics and constipation in HSCR patients after Yancey-Soave pull-through

Variables	Constipation		OR (95% CI)	p-value
	Yes (n, %)	No (n, %)		
Sex				
• Male	4 (22.2)	14 (77.8)	0.43 (0.05–3.52)	0.576
• Female	2 (40)	3 (60)		
Aganglionosis type				
• Long	0	2 (100)	0.48 (0.02–11.37)	0.647
• Short	6 (28.6)	15 (71.4)		
Age at surgery (yo)				
• <3	4 (36.4)	7 (63.6)	2.86 (0.41–20.14)	0.37
• ≥3	2 (16.7)	10 (83.3)		
Nutritional status				
• Well-nourished	2 (13.3)	13 (86.7)	0.15 (0.02–1.18)	0.131
• Undernourished	4 (50)	4 (50)		
Eosinophilia				
• Yes	3 (37.5)	5 (62.5)	2.4 (0.36–16.21)	0.621
• No	3 (20)	12 (80)		
Lymphocytosis				
• Yes	2 (40)	3 (60)	3.33 (0.38–29.39)	0.545
• No	3 (16.7)	15 (83.3)		

HSCR, Hirschsprung disease

Table V: Association between patients' characteristics and soiling in HSCR patients after Yancey–Soave pull-through

Variables	Soiling		OR (95% CI)	p-value
	Yes (n, %)	No (n, %)		
Sex				
• Male	1 (5.6)	17 (94.4)	0.94 (0.03–26.63)	0.973
• Female	0	5 (100)		
Aganglionosis type				
• Long	0	2 (100)	2.73 (0.09–86.93)	0.569
• Short	1 (4.8)	20 (95.2)		
Age at surgery (yo)				
• <3	0	11 (100)	0.33 (0.01–9.07)	0.515
• ≥3	1 (8.3)	11 (91.7)		
Nutritional status				
• Well-nourished	1 (6.7)	14 (93.3)	1.76 (0.06–48.2)	0.738
• Undernourished	0	8 (100)		
Eosinophilia				
• Yes	0	8 (100)	0.57 (0.02–15.58)	0.738
• No	1 (6.7)	14 (93.3)		
Lymphocytosis				
• Yes	0	5 (100)	1.07 (0.04–29.96)	0.973
• No	1 (5.6)	17 (94.4)		

HSCR, Hirschsprung disease.

To our knowledge, the association between serum lymphocytosis and HSCR patients' outcomes has not been extensively reported. One study found that lymphocyte infiltration in the myenteric plexus of HSCR patients.[8] Lymphocyte infiltration can damage the myenteric plexus, lead to aganglionosis, and result in the loss of inhibitory anorectal responses,[22] leading to symptoms of pseudoobstruction[12] and constipation.[13] Our study was unable to reveal the association between lymphocytosis and functional outcomes of HSCR patients after pull-through. These discrepancies might be due to different approaches: histopathology8 vs. serum (our study).

Our study did not find any association between length of aganglionosis, sex, nutritional status, and age at pull-through with functional outcomes of HSCR patients following pull-through, including VBM, constipation and soling (Tables III, IV and V, respectively). Most of our patients are male, short-aganglionosis, well-nourished and undergoing definitive surgery at ≥3 years old. It is postulated that female patients may have an elevated susceptibility to experiencing constipation due to hormonal factors.[15] In addition, postoperative functional problems arise, in part, from the lack of coordinated function in the aganglionic colon.[23] The lengthening of the aganglionic colon corresponds to a more proximal site of obstruction, leading to increased intraluminal pressure and consequently exacerbating the severity of dysmotility.[24] The correlation between long-segment HSCR and worse functional outcomes is conflicting.[25-28] Some studies showed that patients with long-segment HSCR had higher soiling and incontinence rates,[25-26] whereas other reports failed to reveal the association,[27,28] Notably, older HSCR patients were observed to experience more severe intestinal obstruction.[29]

The lack of significance in the results of this study might be attributed to the postoperative functional outcomes in HSCR patientsare possibly more related to mucosal eosinophilia and lymphocytosis rather than serum eosinophilia and lymphocytosis. The association between mucosal and serum eosinophilia is controversial. One study showed that no correlation was found between serum eosinophils count and mucosal eosinophils in tissue biopsies, suggesting that peripheral eosinophilia might not imply eosinophil infiltration in tissues,[30] while another revealed that serum eosinophilia was found in 35% of patients with eosinophilic colitis.[31] It is interesting and important to perform a further study to determine: 1) the association between mucosal and serum eosinophilia specifically in HSCR patients; and 2) how mucosal and serum eosinophil interact and affect each other.

Furthermore, the absence of a statistically significant association between prognostic factors and functional outcomes within this study might also be attributed to the small sample size. The limited sample size might be due to the rarity of the transabdominal pull-through Yancey-Soave at our hospital. We currently prefer performed transanal endorectal[32] and Swenson-like pull-through due to the establishment of early diagnosis of HSCR in our institution.

CONCLUSION

Our study shows that eosinophilia and lymphocytosis might not affect the functional outcome of patients with HSCR following Yancey–Soave surgery. In addition, sex, aganglionosis type, age at definitive surgery and nutritional status might not influence the functional outcome after definitive surgery. Further, a more extensive study is essential to clarify our findings.

ACKNOWLEDGMENTS

We thank all those who provided excellent technical support and assistance during the study.

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