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Did Age at Surgery Influence Outcome in Patients With Hirschsprung Disease? A Nationwide Cohort Study in the Netherlands

*Daniëlle Roorda, †‡Sanne J. Verkuijl, *Joep P. M. Derikx, †Monika Trzpis, †§Rob J. Meinds, ‖Cornelius E. J. Sloots, ¶Marieke J. Witvliet, #Ivo de Blaauw, **Wim G. van Gemert, *Lodewijk W. E. van Heurn, and †‡Paul M. A. Broens

ABSTRACT

Objectives: Hirschsprung disease (HD) requires surgical resection of affected bowel, but the current evidence is inconclusive regarding the optimal age for resection. The aim of this study was to assess whether age at resection of the aganglionic segment is a determinant for surgical outcomes.
Methods: A cross-sectional cohort study was done including all consecutive patients with HD between 1957 and 2015, aged 8 years or older (n = 830), who were treated in 1 of the 6 pediatric surgical centers in the Netherlands. Outcome measures were mortality, postoperative complications, stoma rate and redo surgery rate, retrieved from the medical records. Additionally, constipation and fecal incontinence rate in long term were assessed with the Defecation and Continence Questionnaire (DeFeC and P-DeFeC).
Results: The medical records of 830 patients were reviewed, and 346 of the 619 eligible patients responded to the follow-up questionnaires (56%). There was a small increase in the risk of a permanent stoma [odds ratio (OR) 1.01 (95% confidence interval {CI}: 1.00–1.02); $P = 0.019$] and a temporary stoma [OR 1.01 (95% CI: 1.00–1.01); $P = 0.022$] with increasing age at surgery, regardless of the length of the aganglionic segment and operation technique. Both adjusted and unadjusted for operation technique, length of disease, and temporary stoma, age at surgery was not associated with the probability and the severity of constipation and fecal incontinence in long term.
Conclusions: In this study, we found no evidence that the age at surgery influences surgical outcomes, thus no optimal timing for surgery for HD could be determined.

An infographic is available for this article at: *http://links.lww.com/MPG/C871*.

Key Words: complications, constipation, fecal incontinence, patient outcome assessment

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What Is Known

- Patients with Hirschsprung disease require surgical treatment, but timing of surgical resection may vary between patients.
- There is contradicting evidence on the influence of the timing of surgical treatment in patients with Hirschsprung disease on patient outcome.

What Is New

- This study showed that higher age at surgery was associated with a higher risk of a stoma.
- This study showed that higher age at surgery was not associated with higher risk of complications, mortality, and redo surgery.
- This study showed that age at surgery was not associated with long-term functional outcome.

Hirschsprung disease (HD) is characterized by a congenital absence of ganglion cells in a distal segment of the gut (1). Initial treatment consists of irrigations or creating a stoma, after which a pull-through procedure is planned. There are various techniques for a pull-through procedure, always including resection of the affected bowel segment, but with varying techniques for restoration of bowel continuity, either by creating an end-to-end anastomosis or by creating a pouch. Over the past decades, surgical treatment has evolved from 3-staged procedures (stoma, pull-through and stoma reversal) to 1-staged procedures (2–5).

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From the *Amsterdam UMC, University of Amsterdam and Vrije Universiteit Amsterdam, Emma Children's Hospital, Department of Pediatric Surgery, Amsterdam Gastroenterology and Metabolism, Amsterdam, the Netherlands, the †Anorectal Physiology Laboratory, Department of Surgery, University of Groningen, University Medical Centre Groningen, Groningen, the Netherlands, the ‡Division of Pediatric Surgery, Department of Surgery, University of Groningen, University Medical Centre Groningen, Groningen, the Netherlands, the §Department of Gastroenterology and Hepatology, Medisch Spectrum Twente, Enschede, the Netherlands, the ‖Department of Pediatric Surgery, Erasmus Medical Centre, Sophia Children's Hospital, Rotterdam, the Netherlands, the ¶Department of Pediatric Surgery, Wilhelmina Children's Hospital, University Medical Centre Utrecht, Utrecht, the Netherlands, the #Division of Pediatric Surgery, Department of Surgery, Radboud UMC – Amalia Children's Hospital, Nijmegen, the Netherlands, and the **Department of Pediatric Surgery, University Medical Centre Maastricht, University of Maastricht, Maastricht, the Netherlands.
Address correspondence and reprint requests to Daniëlle Roorda, Amsterdam UMC, University of Amsterdam and Vrije Universiteit Amsterdam, Emma Children's Hospital, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands (e-mail: d.roorda@amsterdamumc.nl).
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Based on clinical experience, pediatric surgeons generally prefer to do a pull-through before the age of three months (6), in order to limit the time interval in which irrigations or a stoma are needed, and the risk of preoperative Hirschsprung-associated enterocolitis. Likewise, surgery can be advanced before the age of 1 month. However, pull-through surgery may also be postponed for several reasons, including total colonic aganglionosis, a delay in diagnosis, more urgent other surgical procedures for cardiac comorbidity, or as a result of the surgeon's preference (7). Some surgeons advocate 3-staged treatment and postponement of resection of the aganglionic segment, because of the risk of exposure to anesthetics and intraoperative hemodynamics, in a critical time window of brain development (8–10).

The evidence about the influence of early or late resection on surgical outcomes shows contradicting results with regard to postoperative complications (11–15), length of hospital stay (11,13), readmission rate (13), colostomy rate (16), and functional outcomes (11,12,14,16–20). Moreover, various cut-off points to define early or late surgery were used to assess the influence of age. Thus it remains unknown whether age is an important factor in determining the optimal timing for pull-through surgery.

The aim of this study was to assess the influence of age at surgery for HD on mortality rate, postoperative complication rate, stoma rate, redo pull-through rate, and on long-term functional outcomes including the rate and severity of constipation and fecal incontinence.

METHODS

Design, Setting, and Patients

A nationwide cross-sectional study was performed in 2018–2019, assessing the medical records of all patients with histopathological confirmation of HD, who were 8 years or older at the time of the study (n = 830 patients), in all of the 6 pediatric surgical centers in the Netherlands, between 1957 and 2015. Patients who were deceased, patients who had a permanent stoma, patients with intellectual disability and patients living abroad or without a known postal address were excluded from the assessment of the long-term functional outcomes. With the data collected in this study, a previous study has been published (21).

Outcome Variables

Surgical outcomes that were assessed in this study were mortality, postoperative complications, the creation of a temporary or permanent stoma, redo pull-through and long term functional outcomes. Data from the medical records of all patients were used to determine overall mortality rate at time of follow-up, postoperative complications within 30 days after surgery, a history of a temporary stoma, a history of a permanent stoma without a scheduled reversal, and a history of redo pull-through.

To assess constipation and fecal incontinence in the long-term follow-up, the Groningen Defecation and Fecal Continence (DeFeC) questionnaire was used for adults and the P-DeFeC questionnaire for patients aged 8–17 years (22). These questionnaires provide a detailed description of the occurrence of specific symptoms of constipation and fecal incontinence and the use of different strategies for bowel management. Reported symptoms were used to determine the occurrence of constipation according to the Rome IV criteria for functional constipation (23), the severity of constipation according to the Constipation Scoring System from Agachan et al (24), that is, an 8-item scoring system, resulting in a score varying from 0 for no constipation to 30 for severe constipation. The occurrence of fecal incontinence was determined according to the Rome IV criteria for functional fecal incontinence (25), the severity of incontinence according to the Continence Grading Scale of Jorge and Wexner (26), that is, a 5-item scoring system, resulting in a score varying from 0 for continence to 20 for complete fecal incontinence.

Data Analysis and Statistics

We used SPSS version 23.0 for Windows (IBM SPSS Statistics, IBM Corporation, Armonk, NY) for statistical analyses. Proportions were reported as percentages; continuous data were presented either as median with the minimum and maximum in the case of skewed data or as mean (μ) with standard deviation (SD) for normal distributions. Visual inspection of the distribution was done using Q–Q plots. Comparisons of continuous data were performed using the Mann-Whitney *U* test. To assess the effect of changes in the common practice over the time of the study period, the mean age at surgery was plotted against the year of operation and the correlation between both variables was determined with a Spearman rank test and expressed as Spearman's rank correlation rho (*r*) with 95% confidence intervals (CI).

The association between age at surgery and the odds of mortality, postoperative complications, a permanent stoma, redo pull-through and long-term constipation and fecal incontinence, was tested using univariate and multivariate logistic regression and was expressed as odds ratio (OR) with 95% CI. In multivariate analyses, the following covariates were included: length of aganglionosis (short vs long segment disease, in which long segment disease was defined as aganglionosis, extending proximal to the sigmoid including total colonic aganglionosis), operation technique (for each operation technique that was observed at least 10 times in our sample), and the presence of a temporary stoma. This variable selection was based on prior evidence that suggests differences in functional outcome between patients with rectosigmoid disease compared with long-segment disease, and studies suggesting differences in surgical and functional outcome after various operation techniques (27,28). A sensitivity analysis on the relation between age at surgery and the risk of a permanent stoma was separately done in patients without intellectual disability, to assess the bias of patients who received a permanent stoma because of intellectual disability, who may have limited possibilities for bowel management with irrigations. To assess the difference between the extremes of age at surgery, the functional outcomes of patients in the first and last percentile of age at surgery were compared to each other. The relationship between age at surgery and severity of constipation or fecal incontinence was assessed using the Spearman rank test and expressed as Spearman's rank correlation rho (*r*) with 95% CI. An alpha level of 0.05 was used as the level of statistical significance.

Ethics

This study had the approval code METc 2013/226 and was performed in compliance with the requirements of the local medical ethics review board. Written informed consent was obtained from each participant.

RESULTS

Patient Characteristics

Patient characteristics of all 830 of the included patients are listed in Table 1, Supplemental Digital Content, *http://links.lww.com/MPG/C870*. A total of 619 patients were invited to answer the questionnaires assessing long-term functional outcomes, of whom 346 responded (56%) (Figure 1, Supplemental Digital Content, *http://links.lww.com/MPG/C870*). The follow-up cohort was representative (21).

Age at Pull-Through Surgery

The median age at surgery was 6.7 months (range 0–270 months) in the total cohort, and slightly lower (6.0 months, range 0–169 months) in the follow-up cohort. Distribution across age groups is shown in Figure 2, Supplemental Digital Content, *http://links.lww.com/MPG/C870*. For 42 patients (5%) (of whom 7 responded to the follow-up questionnaire), the exact age at operation could not be reconstructed from the data in the medical records.

There was a significant correlation between the year of surgery (resection of aganglionosis) and age at surgery in all patients, showing earlier resection in the recent years ($r = -0.266$, 95% CI: −0.331 to −0.199, $P < 0.001$, Fig. 1).

Mortality, Postoperative Complications, Stomas, and Redo Pull-Through

In the total cohort, 43 patients were deceased, accounting for an overall mortality rate of 5%. However, in only 11 (26%) of these patients the mortality was related to HD. Of these 11 patients, this was a result of an enterocolitis episode in 7 patients, a bowel perforation in 2 patients, and in the remaining 2 patients the medical record reported "related to the aganglionosis," but no specific cause of death. The overall postoperative complication rate was 11%. With regard to stomas, 460 of the 830 patients (56%) had a temporary protective stoma and 31 of 830 patients (4%) a permanent stoma. In the total cohort, 51 patients (6%) underwent a redo pull-through (Table 1, Supplemental Digital Content, *http://links.lww.com/MPG/C870*). The odds of a permanent stoma increased with 1% for every additional month of the patient's age at surgery, both unadjusted and adjusted for length of disease and operation technique (Table 1). The same applied in the sensitivity analysis with patients without an intellectual disability, both unadjusted and adjusted. The odds of a temporary stoma also increased with 1% for every additional month of the patient's age at surgery, both unadjusted and adjusted for length of disease and operation technique (Table 1). Both the likelihood of a permanent stoma (OR: 0.89, 95% CI: 0.86–0.93, $P < 0.001$) and a temporary stoma (OR: 0.86, 95% CI: 0.84–0.88, $P < 0.001$) were dependent of the year in which resection of aganglionosis took place, with higher odds in earlier years of the study period. Age at surgery was not associated with increased likelihood of mortality, postoperative complications, and redo pull-through (Table 1).

Constipation

Multivariable regression analysis showed that age at surgery was not associated with the prevalence of constipation, when adjusted for the length of aganglionosis, the type of reconstruction, and a temporary stoma (Table 2). Age at surgery was also not

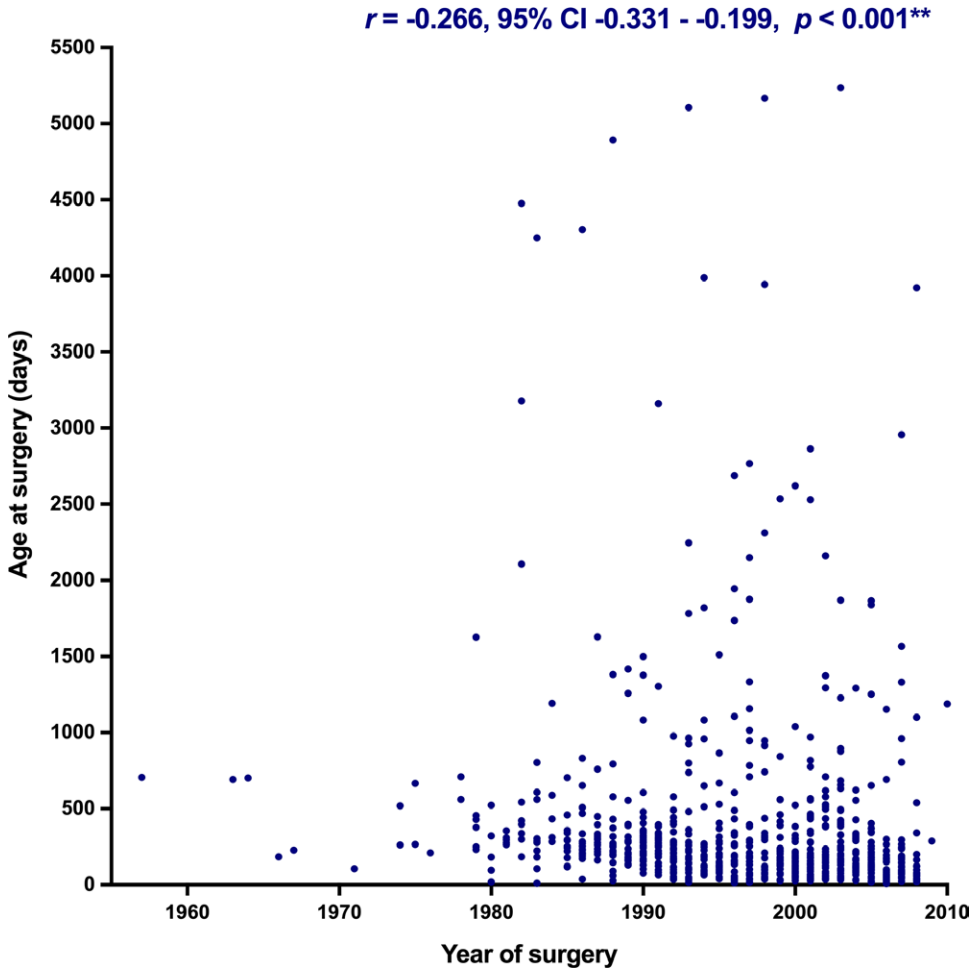

FIGURE 1. Scatterplot of age at surgery by year of surgery.

TABLE 1. Likelihood of survival, complication rate, stomas, or redo-surgery according to age at surgery (in months) within the total cohort (n = 830 patients)

	Univariable		Multivariable (adjusted for type of reconstruction and length of aganglionosis)	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Survival	0.99 (0.97–1.02)	0.513	0.99 (0.97–1.02)	0.481
Complications within 30 d	1.00 (1.00–1.01)	0.272	1.00 (1.00–1.01)	0.317
Permanent stoma	1.01 (1.00–1.02)	0.019*	1.01 (1.00–1.02)	0.014*
Temporary stoma	1.01 (1.00–1.01)	0.022*	1.01 (1.01–1.02)	0.001†
Reoperation	1.00 (0.99–1.01)	0.894	1.00 (0.99–1.01)	0.826

CI = confidence interval. *$P < 0.05$; †$P < 0.01$. The numbers in this table were rounded off to two decimal places.

TABLE 2. Likelihood of constipation and fecal incontinence by age at surgery (in months) within the follow-up cohort (n = 346 patients)

	Univariable		Multivariable (adjusted for type of reconstruction, length of aganglionosis, and temporary stoma)	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Constipation	1.00 (0.98–1.01)	0.613	0.99 (0.98–1.01)	0.356
Fecal incontinence	1.00 (0.98–1.01)	0.408	1.00 (0.99–1.01)	0.753

CI = confidence interval.

associated with the severity of constipation (Fig. 2A). The median Agachan scores of patients who were in the lowest percentile of age at surgery (eg, who underwent surgery before 1.7 months of age) were not significantly different from the median scores of patients who were in the highest percentile of age at surgery, that is, who underwent surgery after at least 31.8 months of age (5.0 vs 5.0, $U = 495.0$, $P = 0.306$).

Fecal Incontinence

Multivariable regression analysis showed that age at surgery was not associated with the prevalence of fecal incontinence, when adjusted for the length of aganglionosis, the type of reconstruction, and a temporary stoma (Table 2). Also, the age at surgery was not associated with the severity of incontinence (Fig. 2B). The median Wexner scores of patients who were in the lowest percentile of age at surgery (ie, who underwent surgery before 1.7 months of age) were not significantly different from the median scores of patients who were in the highest percentile of age at surgery, that is, who underwent surgery after at least 31.8 months of age (3.0 vs 2.0, $U = 526.0$, $P = 0.514$).

Bowel Management

Age at surgery was not related to the likelihood of the use of any of these strategies for bowel management in our follow-up sample (data are shown in Table 2, Supplemental Digital Content, *http://links.lww.com/MPG/C870*).

DISCUSSION

From this nationwide cohort study in children and adults with HD, we found no evidence that age at surgery is a risk factor for mortality, postoperative complications, redo-pull-through, and long-term functional outcomes.

In our sample, higher age at surgery was a risk factor for getting a permanent and temporary stoma. However, we also observed in our sample that the likelihood of a stoma was dependent of the year in which the surgery took place, and we thus think (as also the age at surgery was higher in earlier year of the study period) that the increased risk of a stoma actually reflects this relationship, not an actual increased risk for patients who are older at surgery. Moreover, we noticed that a relatively large number of patients had a temporary protective stoma in our cohort. This may be explained by the fact that 3-staged surgery used to be standard practice up to the late 90s, whereas nowadays single-staged surgery is more often practiced (3). It may also reflect variation in the operation techniques that have been used for restoring bowel continuity, of which some older techniques (including Rehbein) were always done under the protection of a temporary stoma. The small increased risk of a temporary stoma with higher age is therefore as expected. Nowadays patients will only receive a temporary stoma prior to surgery in case surgery is postponed because of total colonic aganglionosis, cardiac comorbidity or a delayed diagnosis.

Our findings were in line with other studies that have reported equal risk of postoperative complications and satisfactory functional outcomes after early and late surgical resection of aganglionic segment (11,14,17,18,29). However, evidence from previous studies do show some contradictory findings and often group comparisons were used to assess differences in outcomes between groups of different ages, or only patients with a delayed diagnosis were assessed. These group comparisons show large heterogeneity in the cut-off value for age at surgery that is used to compare groups, which reflects the clinical heterogeneity in approach to the age at which pull-through surgery takes place and the randomness of each cut-off value. Patients with a delay in diagnosis form a distinct group of patients with late resection of aganglionosis, in which patients often already have experienced obstructive defecation problems (without bowel management) for a long time prior to surgery, resulting in decompensated bowel, which in turn may be related to poorer functional outcomes after very late surgery (12,19). In our patients, we did not observe poorer functional outcomes after very late surgery, since the patients who underwent very late surgery (ie, who were in the highest percentile of age at surgery) did not

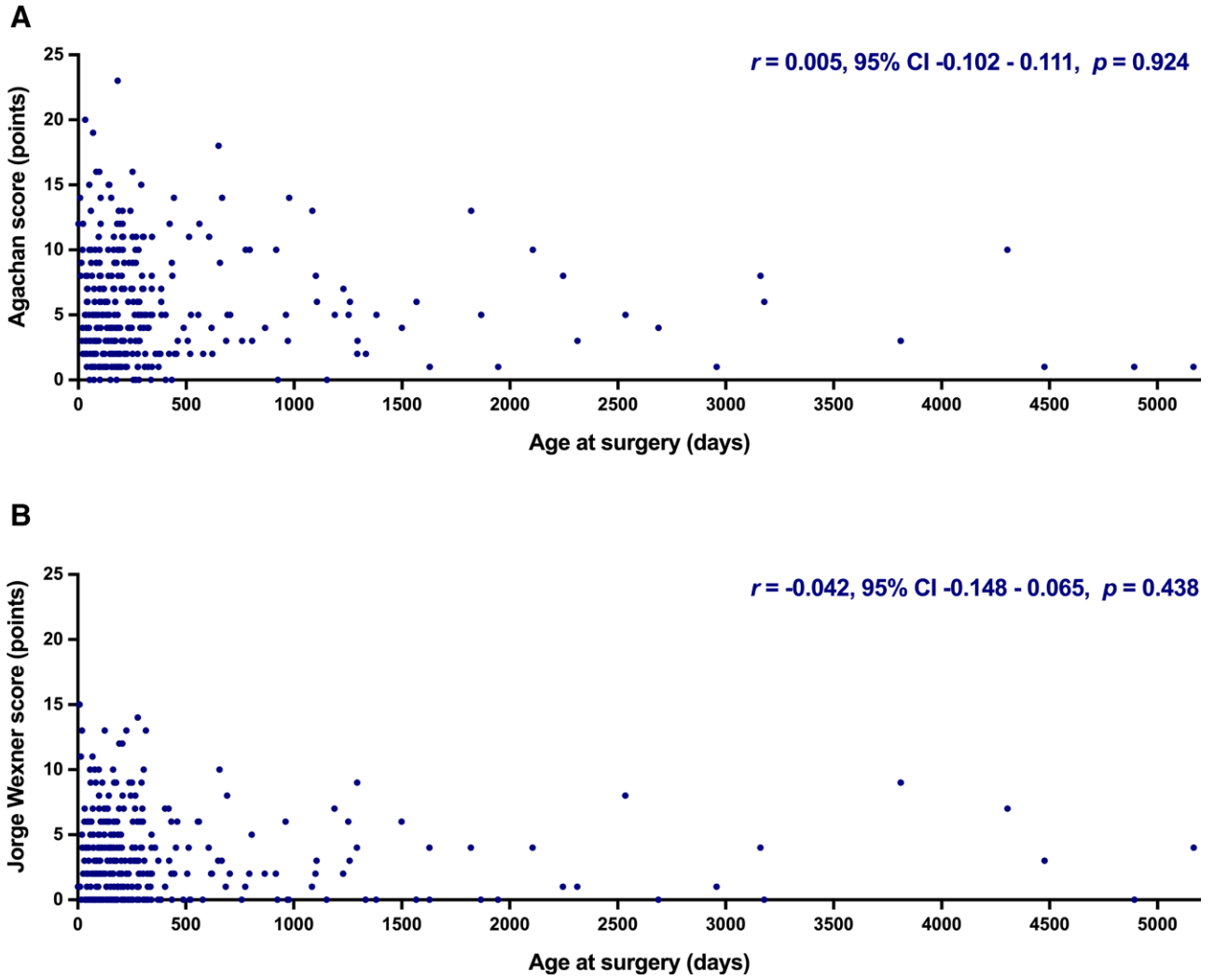

FIGURE 2. Scatterplot of (A) Achagan and (B) Jorge-Wexner scores by age at surgery.

have more severe constipation or fecal incontinence compared to patients who underwent early surgery (ie, who were in the lowest percentile of age at surgery).

Our findings suggested that age at surgery was no risk factor for any of the outcomes in this study. This indicates that there may be other clinical factors than the factors accounted for in this study that may explain earlier findings that patients with delayed surgery have worse outcomes in terms of complications and bowel function. One of these factors may be preoperative bowel management. Differences in the rate and frequency of preoperative irrigations or a temporary stoma may account for the differences in outcomes between patients with untreated HD for a longer period of time (eg, patients with recurrent constipation and an increased the risk of decompensation of the bowel), compared to patients who received adequate rectal irrigation or a stoma prior to pull-through surgery (eg, those in whom the bowel had time to recover before pull-through surgery was done). A second factor may be the perioperative technical challenges in older patients. Among the specific problems mentioned in patients with decompensated bowel is the mismatch in caliber of the dilated proximal colon and the non-dilated distal rectum, impairing the anastomosis, as well as the increased rigidness and scarring of the pelvis in older patients (30,31). A third factor explaining differences in outcomes among patients may be the hospital setting, as studies from developing countries (with often greater delays in diagnosis and lesser resources for peri-operative care and follow-up) report even worse outcomes (16). And a final factor may be, in particular for long-term functional outcome, the influence of psychosocial wellbeing on constipation or incontinence rate and severity (32,33).

A reason to postpone surgery may be the negative effects of the exposure to anesthetics on the brain, as well as the negative effects of blood loss, hypotension, decreased cerebral flow, and hypercapnia during surgical procedures (10,34–36). When patients are exposed to these negative influences during critical windows of brain development, this may result in impaired neurodevelopmental functioning (9,35–39). However, the existing evidence from the few well-designed studies with human (especially pediatric) subjects is inconclusive about the potential negative effects of anesthetics on brain development in infants and the existence of critical windows in brain development.

Strengths and Limitations

Among the strengths of this study are the large sample size, the long period of follow-up, and the statistical design that was more sensitive to assess the direct influence of age, compared to group comparisons, and the use of validated patient-reported

outcomes measures and criteria to measure long-term functional outcome. From the field of oncology, we know that patient-reported outcome measurements are more sensitive to measure symptoms than clinician-reported outcome measurements, and that clinician-reported data are often missing or heterogeneously described in medical records (40–42). The questionnaires we used to assess defecation and continence, although they may be time-consuming, are shown to have good validity and acceptable reproducibility (22).

Our findings however, have to be interpreted in the light of some limitations. The first limitation concerns the cross-sectional design of this study over a long period of time. The cross-sectional design accounted for a wide range of years, from the 1960s up till the current decade, in which improvements have been made in the process of diagnosis and surgical treatment of patients with HD. Although these improvements are believed to have resulted in improvements in survival, complication rate, and functional outcome, it might also have introduced a bias in our study. The changes in the operation techniques that were used may explain the trend toward earlier resection in our sample. There were patients in our sample who were among the first patients who underwent laparoscopic-assisted pull-through and pull-through with a completely transanal approach, as well as patients who underwent operations with techniques that are currently not used anymore in the Netherlands, including the Rehbein and Soave pull-through. Differences in experience, learning curves for new techniques, and worse outcomes after currently omitted techniques may have affected our outcome findings. However, our findings indicated no moderation by operation techniques of the tested effects on age at surgery in multivariate analysis.

A second limitation is the loss to follow-up and the risk of a response bias, a form of selection bias for which follow-up studies are always vulnerable. Patients with good clinical outcomes are more likely to be lost to follow-up and less likely to participate in research projects. Although the response rate to the questionnaires in the current study was satisfactory, a dropout analysis showed more dropout of adult patients compared to children, which might account for bias in the interpretation of problems in adulthood. Missing data in the medical records may have also introduced a small risk of a recall bias in this study.

A final limitation of this study is that we used the adult Rome IV criteria, while part of the study population consisted of children. The Rome IV criteria have originally been developed to assess constipation in the absence of physiological or anatomical abnormalities. However, as no current validated criteria for constipation in patients with anatomical abnormalities are available, the Rome IV criteria were considered to be the best available alternative. They are well-known, validated, and widely used (25,43).

CONCLUSIONS

In conclusion, we found in this study that age at surgery was no risk factor for mortality, postoperative complications, and redo pull-through, and no risk factor for constipation or fecal incontinence rate and severity.

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REFERENCES

1. Langer JC, Rollins MD, Levitt M, et al. Guidelines for the management of postoperative obstructive symptoms in children with Hirschsprung disease. *Pediatr Surg Int* 2017;33:523–6.
2. Sulkowski JP, Cooper JN, Congeni A, et al. Single-stage versus multi-stage pull-through for Hirschsprung's disease: practice trends and outcomes in infants. *J Pediatr Surg* 2014;49:1619–25.
3. Keckler SJ, Yang JC, Fraser JD, et al. Contemporary practice patterns in the surgical management of Hirschsprung's disease. *J Pediatr Surg* 2009;44:1257–60; discussion 1260.
4. Carcassonne M, Guys JM, Morrison-Lacombe G, et al. Management of Hirschsprung's disease: curative surgery before 3 months of age. *J Pediatr Surg* 1989;24:1032–4.
5. Ghoroubi J. Comparison between one and multiple stages surgery in the treatment of Hirschsprung's' disease. *Ann Pediatr Surg* 2009;5:172–76.
6. Bradnock TJ, Walker GM. Evolution in the management of Hirschsprung's disease in the UK and Ireland: a national survey of practice revisited. *Ann R Coll Surg Engl* 2011;93:34–8.
7. Kyrklund K, Sloots CEJ, de Blaauw I, et al. ERNICA guidelines for the management of rectosigmoid Hirschsprung's disease. *Orphanet J Rare Dis* 2020;15:164.
8. Sun LS, Li G, Dimaggio C, et al. Anesthesia and neurodevelopment in children: time for an answer? *Anesthesiology* 2008;109:757–61.
9. Vutskits L, Davidson A. Update on developmental anesthesia neurotoxicity. *Curr Opin Anaesthesiol* 2017;30:337–42.
10. McCann ME, Schouten AN. Beyond survival; influences of blood pressure, cerebral perfusion and anesthesia on neurodevelopment. *Paediatr Anaesth* 2014;24:68–73.
11. Xiao S, Yang W, Yuan L, et al. Timing investigation of single-stage definitive surgery for newborn with Hirschsprung's disease. *Zhonghua Wei Chang Wai Ke Za Zhi* 2016;19:1160–4.
12. Zhu T, Sun X, Wei M, et al. Optimal time for single-stage pull-through colectomy in infants with short-segment Hirschsprung disease. *Int J Colorectal Dis* 2019;34:255–9.
13. Freedman-Weiss MR, Chiu AS, Caty MG, et al. Delay in operation for Hirschsprung Disease is associated with decreased length of stay: a 5-year NSQIP-Peds analysis. *J Perinatol* 2019;39:1105–10.
14. Stensrud KJ, Emblem R, Bjornland K. Late diagnosis of Hirschsprung disease--patient characteristics and results. *J Pediatr Surg* 2012;47:1874–9.
15. Lee CC, Lien R, Chiang MC, et al. Clinical impacts of delayed diagnosis of Hirschsprung's disease in newborn infants. *Pediatr Neonatol* 2012;53:133–7.
16. Ekenze SO, Ngaikedi C, Obasi AA. Problems and outcome of Hirschsprung's disease presenting after 1 year of age in a developing country. *World J Surg* 2011;35:22–6.
17. Miyano G, Takeda M, Koga H, et al. Hirschsprung's disease in the laparoscopic transanal pull-through era: implications of age at surgery and technical aspects. *Pediatr Surg Int* 2018;34:183–8.
18. Doodnath R, Puri P. A systematic review and meta-analysis of Hirschsprung's disease presenting after childhood. *Pediatr Surg Int* 2010;26:1107–10.
19. Jarvi K, Laitakari EM, Koivusalo A, et al. Bowel function and gastrointestinal quality of life among adults operated for Hirschsprung disease during childhood: a population-based study. *Ann Surg* 2010;252:977–81.
20. Hyman PE. Adolescents and young adults with Hirschsprung's disease. *Curr Gastroenterol Rep* 2006;8:425–9.
21. Meinds RJ, van der Steeg AFW, Sloots CEJ, et al. Long-term functional outcomes and quality of life in patients with Hirschsprung's disease. *Br J Surg* 2019;106:499–507.
22. Meinds RJ, Timmerman MEW, van Meegdenburg MM, et al. Reproducibility, feasibility and validity of the Groningen Defecation and Fecal Continence questionnaires. *Scand J Gastroenterol* 2018;53:790–6.
23. Mearin F, Lacy BE, Chang L, et al. Bowel disorders. *Gastroenterology* 2016;150:1393–1407.
24. Agachan F, Chen T, Pfeifer J, et al. A constipation scoring system to simplify evaluation and management of constipated patients. *Dis Colon Rectum* 1996;39:681–5.
25. Rao SS, Bharucha AE, Chiarioni G, et al. Anorectal disorders. *Gastroenterology* 2016;150:1430–42. e4.

26. Jorge JM, Wexner SD. Etiology and management of fecal incontinence. *Dis Colon Rectum* 1993;36:77–97.
27. Verkuijl SJ, Meinds RJ, van der Steeg AFW, et al. Functional outcomes after surgery for total colonic, long-segment, versus rectosigmoid segment Hirschsprung's disease. *J Pediatr Gastroenterol Nutr* 2021;74:348–54.
28. Seo S, Miyake H, Hock A, et al. Duhamel and transanal endorectal pull-throughs for Hirschsprung' disease: a systematic review and meta-analysis. *Eur J Pediatr Surg* 2018;28:81–8.
29. Hackam DJ, Reblock KK, Redlinger RE, et al. Diagnosis and outcome of Hirschsprung's disease: does age really matter? *Pediatr Surg Int* 2004;20:319–22.
30. Ouladsaiad M. How to manage a late diagnosed Hirschsprung's disease. *Afr J Paediatr Surg* 2016;13:82–7.
31. Ademuyiwa AO, Bode CO, Lawal OA, et al. Swenson's pull-through in older children and adults: peculiar peri-operative challenges of surgery. *Int J Surg* 2011;9:652–4.
32. Joinson C, Grzeda MT, von Gontard A, et al. Psychosocial risks for constipation and soiling in primary school children. *Eur Child Adolesc Psychiatry* 2019;28:203–10.
33. Olaru C, Diaconescu S, Trandafir L, et al. Chronic functional constipation and encopresis in children in relationship with the psychosocial environment. *Gastroenterol Res Pract* 2016;2016:7828576.
34. Gleich SJ, Shi Y, Flick R, et al. Hypotension and adverse neurodevelopmental outcomes among children with multiple exposures to general anesthesia: sub-analysis of the mayo anesthesia safety in kids (MASK) study. *Paediatr Anaesth* 2020;31:282–9.
35. Ing C, Jackson WM, Zaccariello MJ, et al. Prospectively assessed neurodevelopmental outcomes in studies of anaesthetic neurotoxicity in children: a systematic review and meta-analysis. *Br J Anaesth* 2020;126:433–44.
36. McCann ME, de Graaff JC, Dorris L, et al. Neurodevelopmental outcome at 5 years of age after general anaesthesia or awake-regional anaesthesia in infancy (GAS): an international, multicentre, randomised, controlled equivalence trial. *Lancet* 2019;393:664–77.
37. Davidson AJ, Disma N, de Graaff JC, et al. Neurodevelopmental outcome at 2 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): an international multicentre, randomised controlled trial. *Lancet* 2016;387:239–50.
38. Davidson AJ, Sun LS. Clinical evidence for any effect of anesthesia on the developing brain. *Anesthesiology* 2018;128:840–53.
39. Warner DO, Zaccariello MJ, Katusic SK, et al. Neuropsychological and behavioral outcomes after exposure of young children to procedures requiring general anesthesia: the mayo anesthesia safety in kids (MASK) study. *Anesthesiology* 2018;129:89–105.
40. Valderas JM, Kotzeva A, Espallargues M, et al. The impact of measuring patient-reported outcomes in clinical practice: a systematic review of the literature. *Qual Life Res* 2008;17:179–93.
41. Gilbert A, Ziegler L, Martland M, et al. Systematic review of radiation therapy toxicity reporting in randomized controlled trials of rectal cancer: a comparison of patient-reported outcomes and clinician toxicity reporting. *Int J Radiat Oncol Biol Phys* 2015;92:555–67.
42. Flores LT, Bennett AV, Law EB, et al. Patient-reported outcomes vs. clinician symptom reporting during chemoradiation for rectal cancer. *Gastrointest Cancer Res* 2012;5:119–24.
43. Palsson OS, Whitehead WE, van Tilburg MA, et al. Rome IV diagnostic questionnaires and tables for investigators and clinicians. *Gastroenterology* 2016;150:1481–1491.