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Anorectal malformation and Hirschsprung's Disease: comparison of long-term outcome in patients with and without temporary ostomy regarding continence and quality of life

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"What is it you plan to do
with your one wild and precious life?"

Mary Oliver

Zusammenfassung (Deutsch)

Weltweit werden Patienten mit anorektalen Malformationen (ARM) und Hirschsprung' scher Erkrankung (HD) nicht nach einer einheitlichen Leitlinie behandelt. Abhängig von multiplen Faktoren werden die Patienten zumeist mit einer einzeitigen Reparaturoperation oder aber mit einem temporären Stoma und einer zweizeitigen Korrekturoperation versorgt. Bisherige Forschungsergebnisse zu Langzeitergebnissen sind uneinheitlich, jedoch mehren sich in der Literatur die Hinweise auf eine Überlegenheit der Primärkorrektur.

Das Ziel dieser Studie war es, die Langzeitergebnisse für Funktionalität und Lebensqualität von Patienten nach Primärkorrektur und mehrzeitiger Operation zu vergleichen. Diese ist die erste Studie mit diesem speziellen Fokus.

Zu diesem Zweck wurden alle Akten von Patienten ausgewertet, die zwischen 2002 und 2017 wegen ARM oder HD an einem der zwei Studienkrankenhäuser operiert wurden und Daten zum perioperativen Verlauf gesammelt. Anschließend führten wir Telefoninterviews mit allen Patienten durch, die einer Teilnahme an der Studie zugestimmt hatten. Der hierfür genutzte Fragebogen basiert auf den funktionellen Scores von Wildhaber und Krickenbeck, der Abschnitt zur Lebensqualität auf den Scores von Bai et. al. und Barrena et. al. Die erhobenen Daten wurden mit statistischen Standardmethoden analysiert.

Unsere Daten zeigen eine Tendenz zu besseren funktionellen Ergebnissen in der Gruppe der Patienten nach Primärkorrektur in beinahe allen Subkategorien. Die Ergebnisse bezüglich der Lebensqualität zeigten keinen relevanten Unterschied zwischen den beiden Gruppen. Aufgrund der kleinen Zahl kompletter Datensätze konnten wir keine statistische Signifikanz der gezeigten Unterschiede belegen. Dennoch halten wir unsere Ergebnisse für klinisch relevant. Da unsere Studie die erste ihrer Art ist, ist die direkte Vergleichbarkeit zwar eingeschränkt, bisherige Studien mit Fokus auf Unterkategorien unserer Forschung kommen jedoch zu vergleichbaren Ergebnissen und sprechen sich teils sehr deutlich für den bevorzugten Einsatz der Primärkorrektur wo immer möglich aus.

In Zukunft werden größere Studien notwendig sein, um statistisch belastbare Daten in diesem komplexen Feld zu generieren und die bestmögliche Versorgung von Patienten mir ARM und HD zu gewährleisten.

Abstract (English)

Worldwide patients born with anorectal malformations (ARM) or Hirschsprung's Disease (HD) are not being treated according to standardized guidelines. Depending multiple factors, they usually either receive a primary repair or a primary ostomy with a secondary repair surgery. Research on the topic is inconsistent so far but evidence proofing superiority of primary repair is growing. Tools such as scores and standardized questionnaires have been developed to objectify functional outcome as well as the patients' quality of life, however, there has yet to be reached consensus on which scores to use to facilitate international comparability.

The aim of this study was to compare patients' long-term outcome after primary and multiple-staged repair regarding bowel function and quality of life. This is the first study with this specific focus.

For this purpose, we evaluated patient charts from two clinics in Germany of all patients who underwent surgery for ARM or HD between the years of 2002 and 2017 and collected data concerning perioperative circumstances. Subsequently we conducted a phone interview with all patients who had consented to participate in our study. The questionnaire used for the interview was based on Wildhaber Score and Krickenbeck Criteria evaluating functional outcome and on Scores by Bai et.al. and Barrena et. al. analyzing quality of life indicators.

The collected data was evaluated using statistical standard tests.

Our results showed a tendency towards better outcome regarding bowel function in the primary repair group in almost all subcategories. Outcomes for quality of life were almost entirely balanced between the primary and the multiple-stage repair. Due to the small number of complete data sets we could not proof statistical significance of the difference shown. However, we believe the difference to be clinically relevant. As our study is the first of its kind, direct comparison with earlier findings is lacking and must rely on indirect comparison with findings focusing on subtopics of our research. Our findings match several recent studies of the field that strongly advocate to prefer the primary repair whenever clinically possible.

Further larger studies will be needed in the future to create the statistical power to find solid data in the complex field to ensure the best care possible to ARM and HD patients.

Abbildungsverzeichnis

Abkürzungsverzeichnis

AChE	acetylcholinesterase
ARM	Anorectal malformation
CCHS	congenital central hypoventilation syndrome
CF	cystic fibrosis
CIPO	Chronic intestinal pseudo-obstruction syndrome
ENS	Enteric nervous system
e.g.	For example
Et. al.	Et alia – and others
HAEC	Hirschsprung's associated enterocolitis
HD	Hirschsprung's disease
HSCR	colorectal Hirschsprung's Disease
ICD 10	International classification of diseases
ICC	interstitial cells of Cajal
ICU	Intensive care unit
LAARP	laparoscopic assisted anorectal pull-through
LEPT	laparoscopically assisted endorectal pull-through
MCA	multiple congenital anomalies
MEN	multiple endocrine neoplasia
MRI	Magnet resonance tomography
NB	Neurogenic bladder
NC	Neural crest
PSARP	posterior sagittal anorectoplasty
PSARVUP	posterior sagittal ano-recto-vagino-urethroplasty
QOL	Quality of life
RET	Rearranged during transfection – molecular modification on Protein
SRB	Suction rectal biopsies
TCA	total colonic agangliosis
TERP(T)	Total endorectal pull-through
VBM	Voluntary bowel movement

Inhaltsverzeichnis

1. Einleitung

1.1. Anorectal malformations (ARM)

1.1.1 Definition

Anorectal malformations (ARM) comprise by definition a complex subdivided group of anatomical anomalies caused by developmental errors affecting the formation of the anal canal rectum and colon (hindgut). The extent of affected bowel varies inter-individually but is often accompanied by a fistula connecting the bowel with the perineal surface or the urogenital tract. [1] Additionally, ARMs frequently are associated with other malformations or syndromic anomalies. [2]

1.1.2 Incidence and etiology

While being considered a rare disease affecting roughly 0.2% of all births, ARMs make up for around 1.2% of all reported birth defects and thus represent an important element of pediatric surgery. [2] The incidence of ARMs is reported to lie between 1 in every 3000 to 5000 live births with male infants generally being affected more often than females with a ratio of 56:44. [1, 2] Exceptions to this sex distribution are however anal atresia which is more common in males, congenital anal fistula and ectopic anus which are more commonly found in females. [3]

The exact etiology of anorectal malformations remains unclear to this day. It is being suspected that a developmental defect of the dorsal cloaca rudiment before 6-7th week of gestation plays a crucial part in the occurrence of ARMs. [1, 2]

Different patterns of familial inheritance have been described suggesting genetic factors as part of the etiology with chromosomal defects showing in 8% of all ARM patients. These genetic alterations frequently cause congenital anomaly syndromes. [2] (For more detail see chapter “Accompanying conditions and syndromes”) As a clear risk factor for ARM consanguinity has been identified. [2]

There is data indicating a different pathogenesis for supra-levator and infra-levator ARMs, the former far more frequently associated with further anomalies. [2]

An association of ARM with alterations on chromosome 13 have been reported the precise process of genesis of ARMs however remains subject of ongoing research. [2]

1.1.3 Classification

In 2005 during the Krickenbeck conference international experts held a meeting to agree on a standardized classification of anorectal malformations. [4] The prevailing classification before the Krickenbeck conference agreed on the new criteria had been the subdivision of ARM into low, intermediate and high ARM according to the Wingspread classification from 1984. [5] The new Krickenbeck classification is based on a classification suggested by Pena in 1995 systemizing the malformations by existence and location of fistulas. [6] The location of the fistula correlates with the extent to which the bowel must be mobilized during a pull-through and is thus directly relevant for choosing the adequate surgical procedure. [2, 6]

In the past studies on ARM had been hard to compare due to inhomogeneity of classifications, follow-up scores and variety of surgical procedures. Therefore, the Krickenbeck experts decided on a standard classification of the different forms of malformations. Additionally, they compiled a standard for the most commonly used operations and agreed on a new scoring system to standardize (long-term) outcome measurement in ARM patients which we also used for our study. [4]

The international standard for ARM diagnosis according to the Krickenbeck classification is divided into one group comprising the most common malformations (“Major clinical groups”) and “rare and regional variants” in a second group (Table 1).

“Major clinical groups” comprise perineal (cutaneous) fistula, rectourethral fistula (prostatic and bulbar), recto-vesical fistula, vestibular fistula, cloaca, malformations with no fistula and anal stenosis.

“Rare and regional variants” include pouch colon, rectal atresia or stenosis, rectovaginal fistula, H fistula and other malformations not named in specific among the others. [4]

International classification (Krickenbeck) for diagnostic procedures	
Major clinical groups	Perineal (cutaneous) fistula
	Rectourethral fistula
	Bulbar
	Prostatic
	Rectovesical fistula
	Vestibular fistula
	Cloaca
	No fistula
	Anal stenosis
Rare/regional variants	Pouch Colon
	Rectal atresia/ stenosis
	Rectovaginal fistula
	H type fistula
	Others

Table 1 Diagnosis standard according to Holschneider et. al

Table 1 provides a quick overview over the different types of ARM. The anatomical features range from mild defects such as an anal membrane to the most complex uro-rectal malformations. [2] The incidence varies according to the type of malformation and is not homogeneously reported by different studies Table 2. On average it can be concluded that roughly 50% of ARMs are categorized as low ARMs with high and intermediate ARMs being less common. [2]

Authors	High	Intermediate	low
Mittal et al.	52%		48%
Cook	28%	13%	51%
Rich et al.	28%	54%	18%
Melbourne series	37%		62%
Stephens series	46%		54%
Chen	20%	47%	33%
Endo et al.	26%	11%	57%

Table 2 Frequency of occurrence of types of ARM modified according to Holschneider et Hutson Edts. 2006 [2]

The occurrence of different types of fistulas is depicted in Table 3. [2, 5] Among male ARM patients rectourethral fistulas (36%) and covered anus with fistula (25%) represent the most common malformations while among girls, rectovaginal fistula (19%), ano-vestibular fistula (18%), covered anus with fistula (18%) and anterior anus (17%) are almost equally common. [5] As mentioned above, the location of the fistula has direct implications for the selection of the adequate surgical correcting procedure. Fistulas have been reported to occur more with an incidence of 53% in patients with supra-levator lesions compared to only 37% in infra-levator malformations. [2] Fistulas are considered ectopic anal canals in ARM patients and are thought to be the anatomical result of a failed fusion of the uro-rectal septum to the cloacal membrane. [2] In general fistulas are more frequently present in female than in male patients with ARMs which suggests a gender-specific difference in the embryological pathogenesis. [2] Among patients without fistulas the fetal death rate is reported to be higher than in those who do have a fistula making the presence or absence of fistulas a factor determining a patient's outcome. [2]

Type of anomaly	Incidence (%) male	Incidence (%) female
Recto-urethral fistula	36	-
Recto-cloacal fistula	-	5
Recto-vesical fistula	6	5
Recto-vaginal fistula		19
Complete anorectal agenesis (no fistula)	8	4
Anterior anus	4	17
Ano-vestibular fistula	-	18
Covered anus with fistula	25	18
Covered anal stenosis	10	4

Table 3 Incidence of ARM subtypes modified according to Stephens et al 1988 [5]

1.1.4 Accompanying conditions and syndromes

ARMs occur as isolated malformations in about 36% of all ARM cases. In the remaining 64% one or multiple other non-anal malformations occur in addition.

Most commonly associated malformations comprise renal malformations (40%), malformations of the urinary tract (28%) such as e.g. hypospadias, vertebral malformations (25%), cardiovascular malformations (24%), malformations of the extremities (18%) and esophageal atresia (17%). Syndromes commonly associated with ARMs are the VACTERL-association, trisomy 21 in 2-8% of all cases and Currarino Syndrome. [1, 2, 7] Chromosomal aberrations are detected in 8% and familial history may be positive for ARMs. [8]

The proportion of ARM patients with additional malformation strongly depends on a thorough diagnostic investigation which is not always at hand in countries with challenges considering medical resources. Therefore the official numbers of ARM patients with associated anomalies may vary highly among different countries. [2]

1.1.4.1 Isolated ARM

Isolated ARM patients show supra-levator lesions in about 10% of the cases while the prevalence of supra-levator lesions is considerably higher within the group of patients that show additional malformations or syndromes. This fact suggests that syn-

dromic and multiple anomalies are more frequently associated with high lesions. [2] Interestingly also low vaginal lesions have a similarly high incidence of associated malformations as high ARMs. [2]

1.1.4.2 Syndromes /Chromosomal aberrations

With an incidence of 2.2% - 5.1% of all ARM cases Down syndrome is the most frequently associated syndrome. [9, 10] It has been shown that among girls with ARM and other associated malformations but without a fistula the prevalence of Down syndrome is significantly higher than among male patients without a fistula. [9]

ARMs also are part of the rare Currarino Triad and in this context ARMs appear together with sacral aplasia or hypoplasia (hemi-sacrum) and sacrococcygeal teratoma or meningocele. The type of ARM in these cases usually is anorectal stenosis with rectoperineal fistula. [11] The syndrome is known to be caused by mutations in the MNX1 gene.

Among others trisomy 8 mosaicism and the fragile X syndrome are syndromes that have been described to be associated with ARMs. [2]

Combinations of malformations that frequently occur in ARM patients are OEIS and VACTERL association. Both mnemonics for the anomalies they describe OEIS syndrome comprises omphalocele, exstrophy of cloaca, imperforate anus and spinal defects. [12] The VACTERL association describes vertebral anomalies, anal atresia, cardiac defects (most frequently ventricular septal defect), tracheoesophageal fistulas with esophageal atresia, renal anomalies and malformations of the limbs (most frequently pre-axial anomalies such as radial dysplasia). [2] VACTERL association is known to be at least partly caused by genetic alterations while the syndrome mostly occurs sporadically with a chance of reoccurrence of about 1%. [2] Animal studies could link the VACTERL syndrome to the sonic hedgehog pathway (shh) the exact pathomechanism of its etiology, however, remains unclear. About 15% of all ARM patients' associated malformations can be categorized as VACTERL related. [2]

The occurrence of two or more congenital anomalies with no recognizable pattern are described as multiple congenital anomalies (MCA). MCA patients show a notable intersection with VACTERL patients considering the type of anomalies presented. [2]

Over half of all MCA patients present two or more anomalies that can be characterized as VACTERL associations which suggests a common pathogenesis. [2]

Frequent single associated malformations are urogenital malformations occurring in 20-54% of cases, most commonly in the form of unilateral renal agenesis or hydronephrosis. Cardiac malformations occur in about 9% of ARM patients and most commonly present as septal defects (both atrial and ventricular), truncus arteriosus, transposition of the great vessels aortic coarctation or infundibular stenosis. Gastrointestinal anomalies are mostly detected in form of malrotation, HD, duplications of parts of the intestine or duodenal obstructions. [2] The interesting association of ARM and HD has been investigated in a large study that concludes a 2.5% association of ARM in 1,200 HD patients. [2] In ARM patients not only spinal malformations but also anomalies of the enteric innervation can occur. A dysfunctional innervation of the bowel segment affected by the ARM could be shown in up to 81%. [2]

Patients with associated other anomalies or syndromes present with a lower weight at birth or even die before birth. Additionally, sacral defects present the most significant factor negatively influencing post-operative bowel control. [2]

The frequent occurrence of spinal defects in combination with ARM suggests a common developmental pathway. The malformation of this group most commonly associated with ARM is a tethered chord. [2]

In the face of this complex variety of associated malformations the pediatric surgeons attending the Krickenbeck conference in 2005 decided to record primarily those conditions known to have the strongest impact on the outcome and occur most frequently. Therefore, the Krickenbeck list of “complicating conditions frequently associated with ARM” comprises tethered chord and sacral anomalies. [4]

1.1.5 Diagnostic investigation

Patients with suspected ARM should receive a workup following a stepwise diagnostic approach with the aim of an accurate identification of the type and level of the malformation. Less invasive diagnostic procedures should be employed before specifying the diagnosis with more extensive measures.

History-taking and physical examination should form the basis of diagnostic investigations which are often complemented by radiological imaging.

Ruling out differential diagnoses is a natural part of the workup. Acute diagnostic procedures should be performed within the first 24 hours of life to determine the type and location of the anomaly on hand also taking into consideration the anal sphincteric muscles and their innervation. Additionally the first diagnostic phase is meant to identify associated malformations that might pose an immediate threat to the patient's life and thus call for acute intervention. [1, 2]

Clinical presentation

The vast majority of ARMs is detected in the neonatal period during neonatal review immediately after birth. The most obvious clinical feature is the absence or anteriorization of the anal opening that can be identified in the physical examination. Attempts to identify ARMs in prenatal ultrasonography have been made but to this day sensitivity and specificity of the diagnosis are low. [2]

With time the lack of passage causes a colonic ileus with varying extent of correspondent symptoms. [1] If undetected immediately after birth the patients typically present with an extremely extended abdomen and bowel obstruction. The full-blown clinical picture additionally comprises progression into sepsis in the course of the first few days of life depending on the type and extent of the ARM. Patients with merely a mild alteration to the anal opening's position may be overlooked in the neonatal period and go undetected for years. In these cases patients often present with a long history of constipation or urinary tract infections [2]. In patients with rare ARM such as rectal atresia with an imperforate anal membrane or anorectal stenosis the anal inspection may be without abnormal findings. These patients however may present with ribbon stools or constipation. [2]

Physical examination

Perineal inspection is essential to evaluate the anomaly on a visual basis. Presence, absence and positioning of anal, vaginal and urethral opening can give crucial hints as to which kind of ARM a surgeon is dealing with. Presence or absence of a fistula, shape and size of the anal pit and development of the gluteal fold provide further details on the type of ARM and extent of malformation.

In boys, special attention should be given to the scrotum and the midline raphe on the search for a fistulous opening. genital anomalies like atypical hypospadias may hint at recto-bulbar urethral fistula. In some cases, pressure on the meatus may release meconium proving the presence of a fistula connecting bowel and urogenital tract. It should be kept in mind that meconium needs 1-2 days to reach the fistula, which means that a small fistula may be overseen if not searched for after this period.

In girls the careful examination of the visible structures will usually provide even more information concerning the inner anatomy of the anomaly. The number and location of orifices is likely to disclose which ARM the surgeon is dealing with. For example, cloacal anomalies will present with a single opening that is smaller than expected in a normal female. If three openings in the vulva with a normal vaginal and urethral opening the third can be expected to be an abnormal anal opening or a fistula. The direction of a fistula when probed will hint at the type of fistula on hand: the track will be oriented posteriorly and backwards in rectovestibular fistula while cranially in rectovaginal fistula [1]. If a fistula is present it may be detected by identifying its opening. Alternatively, a blue color seen behind a membrane may give away the course of the fistula.

In cases of a covered anus, meconium may be seen behind the anal membrane [2].Typical signs in patients with a fistula include stool contamination of the patient's urine [2]. If the contamination is macroscopic it may be seen in the physical exam or during diaper inspection, microscopic traces will be found in the urinalysis.

Without meconium in the urine the patients might have an ARM without communicating features i.e. either no fistula or a fistula congested by meconium.

In both sexes a present but anteriorly displaced anus is the finding in an anterior perineal anus. A normal outer appearance of the anus can still hide a variety of ARM such as an imperforate anal membrane, anorectal stenosis, rectal atresia or covered anal stenosis.

An orifice anterior to the anal dimple can be the sign of either a cutaneous fistula or an anterior perineal anus.

If the perineum shows no opening at all a determination on a type of ARM cannot reliably made without further diagnostic investigation.

Urinalysis

Urinalysis can detect meconium in the urogenital tract as proof of a fistula e.g. in rectourethral fistulas. [1] To detect even small amounts of meconium a microscopy of the urine is indicated. [2]

Sonography

Perineal sonography can be employed to detect the rectal blind sac behind the covered anus. Additionally, sonography is used to rule out accompanying malformations e.g. of the kidneys or the spinal canal. [1]

X-ray

If neither physical examination nor sonography can reveal the anatomy of the malformation an abdominal X-ray in prone position with elevated pelvis can help identify the rectal blind sac's location. The rectum should be given 24 hours to entirely fill with before attempting imaging. [1]

Miction urethro-cystography

Depending on the primary findings diagnostic should be completed with a voiding uretero-cystography, cloacography or cysto-genitoscopy respectively to clarify the anatomical situation. [1] Many institutions nowadays prefer an MRI which needs sedation but provides the best anatomical images of the malformation and accompanying disorders.

Chromosomal workup and ruling out of other malformations

For etiological investigation chromosomal testing for the chromosomal aberrations most commonly associated with ARMs should be performed. Additionally, other possibly life-threatening malformations commonly associated with ARMs and should be ruled out using adequate diagnostic procedures. Sonography or MRI can be employed to rule out malformations of the abdomen or spinal column and spinal canal such as tethered chord or coccygeal or sacral anomalies. [1, 2] Additionally a presacral mass should be ruled out as it can be present as part of the Currarino syndrome. [2] Urodynamic ex-

ams can visualize the anatomic situation and possibly coexisting malformations of the urogenital tract. A cardiac ultrasound should be employed to rule out cardiac anomalies as they appear in VACTERL syndrome. [1]

Contrast enema

In case of a preexisting colostomy further visualization of the rectal blind sac can be achieved by performing an antegrade contrast enema of the distal ostomy. The contrast medium should be applied via a blocked urinary catheter in the aboral ostomy. In patients eligible for a one-stage repair a retrograde contrast enema can be considered in patients with a dislocated but existing anal opening. [1]

1.1.6 Therapy and techniques

1.1.6.1 Evolution of repair surgery for anorectal malformations

Proof of attempts to surgically repair ARM date back as far as the second century AD when the first “dilations” were reported from Rome. [2] In the eighteenth century the permanent colostomy was introduced as the new standard procedure for ARMs and in 1835 the first basic “proctoplasty” was performed. [2] After antibiotics became more available a previously suggested abdominoperineal approach became more popular in the middle of the 20th century. [2] 1959 Rehbein revived combination of abdominoperineal approach and endorectal pull-through. He was followed by Stephens who focused his surgical repair on the puborectalis muscle to achieve continence. The rate of incontinence remained high in the abdominoperineal approach and Stephens’ approach was modified by Kiesewetter abdomino-sacro-perineal who also sought to save the external sphincter muscle. The approaches of Kiesewetter and Rehbein later were combined including both, puborectalis sling and Rehbein’s endorectal idea. In 1970 experts created a classification for ARM that was published by Stephens and Smith after Stephens had already published the first modern book on the topic in 1963. [2]

The current era of ARM repair, however, was opened up by Pena and de Vries introducing their PSARP repair in 1982. The technique spread quickly and was widely and internationally accepted by many pediatric surgeons. [2] However again, the routine was to create a colostomy and perform the repair in several stages. [13] In 1990 Moore successfully performed the PSARP as primary repair and advocated for a wider use of

the single-stage repair as it proved to be superior in many ways among others considering continence outcome. [13]

1.1.6.2 Overview surgical techniques

During the Krickenbeck conference a classification of ARMs as well as a follow-up score were proposed that aim to make studies of ARM more comparable. To achieve this, it was additionally decided on a standardized list of the surgical approaches most frequently employed in ARM repair (Table 4).

International grouping of surgical procedures in ARM for follow-up evaluation (Krickenbeck)
Perineal operation
Anterior sagittal approach
Sacro-perineal procedure
PSARP
Abdomino-sacro-perineal pull-through
Abdominoperineal pull-through
Laparoscopic-assisted pull-through

Table 4 International grouping of operation techniques for ARM modified according to Holschneider et al. 2005

1.1.6.2.1 Perineal operation

Traditional approach of choice for perineal (cutaneous) fistulas as well as ano-vestibular fistulas. Limited perineal incision with limited access.

Not suitable for cases of intermediate or high ARMs. [14]

1.1.6.2.2 Anterior sagittal approach

Alternative procedure for the repair of perineal cutaneous fistulas and ano-vestibular fistulas. Anterior perineal incision to preserve the internal anal sphincter (also achieved by PSARP). [15]

1.1.6.2.3 Sacro-perineal procedure

Traditional approach with sacro-perineal incision used for repair of low ARMs without fistula. [16]

1.1.6.2.4 Posterior sagittal anorectoplasty

Posterior sagittal anorectoplasty (PSARP) currently is the gold standard of surgical repair of the majority of all ARMs. The soft tissue surrounding the anal sphincter is divided by a posterior sagittal midline incision. The extent of the incision should be adapted to the individual ARM and its dimension. [2] Rectum, urethra and according to the type of ARM remaining involved structures are then visualized and divided where they share a common wall (e.g. urethra and rectum in male patients with rectourethral fistula). The rectum is mobilized and brought down to the perineum forming the neoanus [17]. The PSARP technique is used for the majority of ARM: applicable for 90% of all ARMs in male patients (10% need additional abdominal approach in addition), all ARMs in females except 30% of cloacal ARMs which require an additional abdominal approach [15]. In patients with rectovestibular fistulas the incision can be performed sparingly and often the tissue must only partly be divided [15].

1.1.6.2.5 Abdomino-sacro-perineal pull-through

Like sacro-perineal operation but with an additional abdominal incision to enable the surgeon to mobilize a high rectum and “pull it through” to the perineal neoanus site. [16].

1.1.6.2.6 Abdominoperineal pull-through

Traditional approach for intermediate and high ARMs with perineal and abdominal incision. First described by Rhoads in 1948. [18]

1.1.6.2.7 Laparoscopic-assisted pull-through

Downsized version of an abdominal approach complementing a minimal perineal incision. The additional laparoscopic approach enables a good visualization of a high rectum and its safe pull-through. [15, 16, 19] Also a PSARP repair can be complemented by a laparoscopic visualization if needed (e.g. in cases of a bladder neck fistula). [16]

1.1.6.2.8 Colostomy

Aside from the different surgical techniques there is the additional possibility of a staged repair with a primary diverting colostomy and the subsequent repair surgery with a simultaneous colostomy closure or a third operation for this purpose. Advantages and challenges of this approach are discussed in detail in the chapter “One stage vs. three stage approach with temporary ostomy”. If considered necessary after careful consideration the colostomy in ARM patients should always meet several special criteria to prevent complications and set best possible conditions for the later pull-through. The aim

should always be a descending colostomy in the lower left quadrant with separated stomas. Under any circumstances a dividing colostomy should be preferred over a loop colostomy. This way only a small part of the colon is bypassed and in patients with a recto-urinary fistula the urine can exit through the fistula and ascending UTIs as well as distal stool impaction are avoided. The separated stomas also avoid a fecal contamination of the distal stoma and thus of a distal fistula connecting bowel and urinary tract. With this technique sparing the sigmoid loop distal of the colostomy it is hoped to secure enough length to pull the rectum down to the perineum in the future repair surgery. By performing the colostomy in a fixed part of the colon prolapses can be avoided. [15, 20, 21]

1.1.6.3 Choice of surgical approach

Accompanying malformations have to always be taken into consideration individually. A severe malformation that poses an immediate threat to the patient's life will naturally have priority over the desire to perform a primary repair rather than create a colostomy. Nowadays the PSARP technique is used for the majority of all ARMs. In general, 90% of all ARMs in males can be successfully repaired in a posterior sagittal approach with no abdominal incision. In boys with a perineal fistula, it is advised to perform a primary PSARP without a colostomy. The preparation of the anterior rectal wall poses the most challenging part of the operation since rectum and urethra lie in close spatial relation. The repair should be completed within the first 48 hours of life unless the size of the fistula allows for a sufficient evacuation of the stool in which case an elective operation is possible.

Recto-urethral fistulas are the most common ARM in male patients. The fistulas can end in the bulbar or prostatic segment of the urethra and are subdivided as low and high rectourethral fistulas. The repair procedure usually is a PSARP with its focus on the dissection of the common wall between urethra and rectum cranially to the fistulous connection. Laparoscopic surgery is being employed mostly for the high fistulas since the long common wall of rectum and urethra regularly leads to iatrogenic urethral lesions when laparoscopy is performed in low fistulas. [1] The higher variant (recto-prostatic) regularly goes in hand with malformations of the sacrum and surrounding soft tissue such as insufficient gluteal muscle development which is normally without pathological findings in patients with low urethral (bulbar) fistulas. [1] More extensive malformations of pelvic sacral bones and gluteal soft tissue can regularly be found in pa-

tients with a recto-vesical fistula where a primary repair with a perineal approach is often not possible. In these cases – as in high recto-urethral fistulas – laparoscopic procedures are regularly and successfully employed (LAARP - laparoscopic assisted anorectal pull-through). [1]

In male ARM without a fistula and display of air in the rectal pouch caudally to the sacrum on the x-ray study a primary repair can likewise be performed. If the rectal pouch is located cranially to the sacrum or other malformations are more pressing the creation of a colostomy is considered the safest way. The definite repair (mostly PSARP) will then follow 4-8 weeks later.

In girls and in boys a perineal fistula can be corrected in a one-stage repair without colostomy. In this ARM rectum and vagina are developed separate but adherent. Complete separation is usually feasible with a minor incision. The most common ARM in girls is the recto-vestibular fistula. It is eligible for primary repair but shows the highest complication rate which is why some surgeons regularly choose to decompress the bowel with a colostomy. If a sufficient decompression can be achieved through the (dilated) fistula a colostomy can be avoided in selected cases. To enable a sufficient mobilization of the rectum for a later anastomosis during PSARP the dissection of the common wall between rectum and vagina is crucial and must be performed meticulously. A vaginal septum may be present in patients with rectovestibular fistula. [1]

If a female patient presents with only one perineal opening a cloacal malformation is present and a primary colostomy is advised. Cloacal malformations are regularly associated with hydrometrocolpos that can present already in prenatal sonography. Because of the considerable connection of rectum and urogenital tract in cloaca patients a preoperative antibiotic prophylaxis should be started. [22] Generally cloacal malformations are the most severe ARM and show a high incidence of associated malformations. Cloacal malformations are usually complex and involve both systems the bowel and the urogenital tract to a considerable extent. Associated malformations of the urinary tract affect 60-80% of all cloaca patients. [22] Malformations of the inner genitalia are present in half of all ARM patients with cloacal malformation. [22]

The repair surgery is a combination of a repair of the urogenital tract and a PSARP procedure. During the PSARVUP (posterior sagittal ano-recto-vagino-urethroplasty) rectal and vaginal wall are separated from each other and the anterior wall is dissected

from the urethra. [22] The challenging procedure should be performed in specialized centers by experienced surgeons and within the first year of life. [22]

Less than 10% of female ARM patients will have an ARM without a fistula in which depending on the individual distance of rectal pouch and perineum a primary repair or colostomy can be considered. [1]

In females and males alike, an ARM without a fistula (rectal stenosis and rectal atresia without fistula) is rare and is usually associated with well-developed surrounding tissue. An additional association with trisomy 21 is not uncommon and should be ruled out. The distance between rectal pouch and perineum is typically short and can be repaired with a primary PSARP procedure. [1]

Postoperatively the urethral catheter should remain in place for up to 7 days and an antibiotic prophylactic coverage should be ensured to prevent urinary tract infections in girls and in patients with a preoperative connection between bowel and urinary tract. [1]

1.1.6.4 Postoperative management

The recommended follow up time varies, a minimum of 12 to 24 months is however considered the minimum. Starting on the 14th postoperative day a regular anal dilation is the standard method to keep the neoanus open and the sphincters dilated to adequately pass stool. The frequency of dilation will decrease over time while the Hegar size will be increased up to 12/13 after 6 months. [1] Newer studies question the necessity of dilatation for longer than 10 months and larger than Hegar 15 [23].

If created the colostomy should be closed after the anal wound has healed and allows a stool passage considering its width. A close observance of signs of obstipation is crucial after the closure of the colostomy. If obstipation is suspected dietary adjustments should be started to avoid severe constipation and a consequential dilation of the rectum. [1]

1.1.7 Complications

Intraoperative complications are not uncommon and, in some cases make a secondary operation necessary. The rate of complications and the need for reoperations is not limited to patients with complex ARMs but interestingly occurs rather frequently in patients with less complex malformations. [2]

1.1.8 Perioperative complications

The structures at the highest risk of iatrogenic trauma are the urethra and in boys the prostate gland, seminal vesicles and the vasa deferentes. [24]

Many of these injuries can be avoided by performing a routine distal colostogram prior to the repair surgery. Thus, knowing the location of the fistula can help to prevent urethral injuries while knowledge of the rectums position makes the surgical search for a high rectum redundant that regularly endangers the vasa deferentes which lie very close to the rectum. [24] If a laparoscopic approach is chosen the risk for unintentional iatrogenic trauma to the pelvic structures increases especially if the performing surgeon is inexperienced in the laparoscopic operative perspective. [2] A clean dissection is crucial to ensure a strict separation of bowel and urogenital tract and prevent postoperatively ongoing pollution of the urinary tract with meconium or stool and the consequential ascending urinary tract infections. [2]

In addition, intraoperative inadvertent nerve trauma can lead to neurogenic urinary voiding disorder. [1, 2] An incidence of up to 55% of neurogenic bladder (NB) has been described yet it is scarcely being investigated to which extent the NB is a problem inherently associated with the ARM or a secondary problem caused by the repair surgery. Experts suppose that an atonic NB is an iatrogenic complication while a hyper reflexive NB most likely originates in a motor neuron defectiveness. [24]

Postoperative fistulas between rectum and urethra (recto-urinary fistula) or rectum and vagina (rectovaginal fistula) occur in different variants and can be the result of an insufficient repair (persistent fistula) or the result of trauma to the urethra (acquired fistula). Reoccurrence of a congenital fistula (reoccurring fistula) is mostly explained by anastomotic dehiscence or injury. [1, 2, 24]

With the introduction of the total urogenital mobilization technique the occurrence of rectovaginal fistulas during the repair of rectovestibular fistulas decreased significantly [2, 25]. The complication of transient femoral nerve palsy due to too much pressure on the nerve during operation can be avoided by adequate positioning. [2]

One of the most severe complication of ARMs in females is the insufficient repair of a cloacal malformation due to an underestimation of its extent. If only the rectal portion of the malformation is repaired a persistent urogenital sinus remains. [2]

Another rather common complication is traumatic injury to rectum, vagina or both during the dissection of the common wall in vestibular fistulas. Acquired vaginal atresia can be a result of an excessive dissection to achieve vaginal mobilization in cloaca patients. [2] Likewise acquired atresia of rectum or urethra are usually the result of exceeding tension or insufficiency of the local blood supply. The formation of anal strictures is additionally supported by an inadequate fulfilment of a patient's dilation protocol. [2]

Irrespective of the patients' sex an incorrect positioning of the neo-anus in relation to the sphincteric muscles will necessarily lead to an impaired function considering the patient's continence. [1]

Early postoperative complications comprise wound dehiscence and possible retraction of the neoanus. Creating the neoanus under traction due to insufficient mobilization of the rectum is the most common reason for this complication. Also, an insufficient perfusion of the bowel following trauma to the supplying vessels can be a cause. [26]

Rectal prolapse after PSARP repair is seen in 3% of cases and mostly in patients with high ARMs and underdeveloped pelvic muscular support. Massive or reoccurring prolapses can interfere with anal sensation and compromise stool continence. [2, 27]

As in any surgical wound infection can develop post-operatively but is rather uncommon and usually limited after PSARP repair. [2]

A posterior urethral diverticulum can occur if during the abdomino-perineal repair of a recto-urethral fistula rectum and urethra remain unseparated over a too long distance. It can lead to reoccurring UTI (urinary tract infections) or

urinary incontinence. Since malignant transformation of the diverticulum has been described a surgical excision is advised in such cases. [24]

1.2. Hirschsprung's Disease and Dysganglionosis

1.2.1 Definition

After the disease was first described by Dutch anatomist Frederik Ruysch in 1691, it was named after the Danish pediatrician Harald Hirschsprung who was first in describing the clinical presentation in 1888. [28]

Hirschsprung's disease (HD) is a congenital malformation of the enteral nervous system. Insufficient migration of enteral neurons of submucosal plexus (Meißner) and myenteric plexus (Auerbach) during the first 12 weeks of fetal development causes a disfunction of the distal intestinal tract most commonly affecting colon and rectum.

Clinically the disorder manifests as an agangliotic segment of distal colon and rectum incapable of relaxation impairing stool passage (functional stenosis) and inducing a compensatory extension of the proximal colon (megacolon).

1.2.2 Incidence and etiology

In central Europe an incidence of HD of about 1 per 5000 life births is recorded.

The disease is more frequently found in males, with an incidence up to four times higher than in females (sex ratio 4:1). [29, 30]

Interestingly, the male to female ratio is significantly higher for short segment HD (4.2-4.4) than for long-segment HD (1.2–1.9). [31]

Nowadays HD is widely recognized as a multifactorial genetic malformation.

In most cases its occurrence is sporadic while familial inheritance amounts to up to 20% of HD cases. [32, 33] According to Amiel et al. the underlying inheritance pattern can be described as "complex non-Mendelian inheritance with low, sex-dependent penetrance, variable expression according to the length of the agangliotic segment and suggestive of the involvement of one or more gene(s) with low penetrance". [31]

As a consequence, the risk of reoccurrence differs according to sex of the newborn as well as to length of the agangliotic segment but averages out at roughly 4%.

The highest probability of reoccurrence of 33% is observed in male infants with a mother born with a long-segment HD. [34]

On a molecular level RET protooncogene on chromosome 10 (10q11.2) is described to hold the main gene even though colorectal Hirschsprung's disease (HSCR) is - according to recent theories - thought to be a multigenetic disease. [34]

10q11.2 encodes for a membrane-bound receptor tyrosine kinase that plays a crucial part in embryonic neuronal migration and differentiation.

In familial HD cases germ line mutations of 10q11.2 have been reported with an incidence of about 50%, 15-20% in sporadic cases. Mostly heterozygote nonsense or mis-

sense mutations have been documented. [31, 35] Other genes in which even single mutations can result in HD phenotype are EDNRB, EDN3 and ECE1 genes. [31, 36]

1.2.3 Pathophysiology

The physiological peristalsis of the intestine is based on its muscular wall innerved by the enteric nervous system (ENS). The muscular tube of the intestine consists of a longitudinal outer layer and a circular inner layer of smooth muscle cells. Additionally, a thin muscular layer named the lamina muscularis mucosae supports the mucosa layer that forms the intestines inner surface. The ENS comprises the myenteric plexus (Auerbach Plexus) between longitudinal and circular muscular layers and the submucosal plexus (Meissner Plexus) on the mucosal side of the circular muscle layer.

The ENS performs mostly autonomously with interstitial cells of Cajal (ICC) acting as pacemakers. The ICC are spread out between and inside the muscular layers of the intestinal wall. The ENS is further influenced by the autonomous nervous system represented by the vagus nerve on the parasympathetic side and by sympathetic neurons the coeliac ganglion. In HD patients during embryonic development the cell migration of the neural crest (NC) is impaired in the area later forming the intestine. HD is therefore regarded as a neurocristopathy [31]. Since the neurons migrate in craniocaudal direction the intestine later lacks innervation in varying length of the intestine caudocranially affecting both plexus, submucosal and myentericus [34].

The disorder leads to a hypoplasia or entire absence of ganglion cells of the myenteric plexus (Auerbach plexus). This in turn leads to a compensatory increased innervation by cholinergic interneurons budding further in the futile attempt to receive feedback from the missing neurons. The overly active cholinergic neurons play a major role in pathological diagnosis from colon biopsies as described in the respective paragraph. As a result of this lack of ENS neurons the physiological peristalsis is impaired. The agangliotic segment is unable to relax and thus appears constricted while the healthy proximal colon distends as a reservoir for the stool unable to pass the obstruction. An achalasia of the internal anal sphincter further enhancing the obstructive complex of symptoms is an additional typical element of the disease. [37]

1.2.4 Classification of Hirschsprung's Disease

The length of the affected colonic segment can differ depending on the extend of the disease. It typically extends from the anus towards proximal segments of the intestine and is most frequently limited to the rectosigmoid as in 80-85% of all patients. In these cases, the disease is categorized as "short-segment aganglionosis". As a special type among the short-segment aganglionosis the ultra-short-segment aganglionosis is characterized by a malformation limited to the anal ring or extending 3 - 4 cm into the rectum. [38]

In contrast to the short-segment HD in the "long-segment aganglionosis" half of or the entire colon is affected as in roughly 15-20% of all HD patients (half of colon 10-15% of all patients; entire colon ca. 5% of all patients). Aganglionosis extending over the entire colon is also known as Zülzer-Wilson-Syndrome or total colonic agangliosis (TCA).

A further proximal extension is possible and in very rare cases can comprise the entire gastrointestinal tract. This extreme form affects only about 1% of all HD patients and is thus far less common than the distally limited forms. [34]

Disregarding of the extent of HD the agangliotic segment usually is proximally preceded by a hypo-ganglionic zone of varying length. This hypoganglionic zone does not correlate with the length of agangliotic segment meaning there will be patients with short agangliosis but a long hypoganglionic zone and others with a long agangliotic segment but a short hypoganglionic zone. [16] This variation must be kept in mind especially when taking biopsies preoperatively or intraoperatively. [16] Furthermore, the hypoganglionic zone has in some cases proven to be expanding and that apoptosis of ganglion cells can lead to a further proximal extension of the zone even after the repair surgery. [39]

This way hypoganglionosis – undetected in surgery or extended after the repair – can lead to long-term postoperative complaints. [16]

Hypoganglionosis as an independent disease occurs in about 5% and is defined by a number of ganglion cells reduced by 10 and a density of nerve fibers 5 times lower than usual. Amount of neurons in the myenteric plexus is reduced by 50%, distance between ganglions is increased and the size of ganglion cells themselves is reduced. [16]

1.2.5 Clinical presentation

Nowadays 90% of HD patients are diagnosed in the newborn period due to early symptoms and distinctive clinical presentation. About 10% of these patients are premature infants. Failure to pass meconium within 24 hours after birth is a typical manifestation. Since 92% of healthy newborns will pass meconium within the first 24 hours failure to do so should lead to screening for HD using suction biopsies. This way a delay of HD diagnosis can be prevented successfully. [40, 41]

Other symptoms include severe obstipation, abdominal distension, enhanced peristaltic sounds (borborygmi), emesis and enterocolitis. A main sign for enterocolitis may be fever accompanying these episodes of varying intestinal symptoms. [37] HD also has to be suspected in full-term newborns with necrotizing enterocolitis. [42] An overview over the most common symptoms is depicted in Table 5.

Patients who show onset of symptoms after the newborn period often present after the first introduction of solid food after an initial period of exclusive breast feeding.

Symptoms then mainly comprise obstipation caused by the tightened agangliotic bowel segment which can escalate to (sub-)ileus or toxic megacolon with corresponding symptoms as emesis and systemic affection. Additionally, HD patients frequently show overflow incontinence as clinical manifestation of the filled proximal rectum pressing on the obstructing constricted distal colon. In these cases, the rectal ampulla is empty and tight in rectal exam in a patient with obstipation. However, the patient or parents report thin stools in the otherwise obstipated child. Massive defecation triggered by rectal exam can occur in these patients while they report an inability to pass stool without assistance such as irrigation or rectal stimulation. [37]

Unspecific yet important to keep an eye on during follow-up visits is a general failure to thrive that can also be the leading symptom.[34]

Main clinical presentation	% of patients	Author
Intestinal obstruction	55	Sieber WK, 1978
Early mild constipation with secondary abrupt obstruction	24	Sieber WK, 1978
Chronic severe constipation	3	Sieber WK, 1978
Enterocolitis/ Toxic megacolon	18 25 25 25 10	Sieber WK, 1978 Werbeloff L, 1974 Nixon H, 1982 Deucher F, 1977 Grand RJ, 1975
Clinical early signs		
Prematurity	2.6 3.5 10	Sieber WK, 1978 Ehrenpreis T, 1971 Swenson O, 1973
Delayed passage of meconium	94 90	Swenson O, 1973 Dasgupta R and Langer JC, 2004
Distension of abdomen	55 87	Sieber WK, 1978 Swenson O, 1973
Diarrhea	14 22	Langer B, 1959 Lillie JG, 1971

Table 5 Clinical presentation of HSCR in the first 6 months of life [43]

1.2.6 Differential diagnostics

Differential diagnoses to be ruled out comprise meconium ileus from cystic fibrosis (CF) as well as other forms of intestinal and anorectal malformation, such as e.g. congenital microcolon. Congenital bands and malrotation can also be the underlying cause of obstipation and intestinal symptoms. [37]

In untypical cases other causes of megacolon with and without ganglion cell abnormality should be considered. Patients with anorectal malformations for example can

present with a secondary i.e. symptomatic megacolon: An absent or stenotic anal orifice will lead to stool conglomerate in the colorectum presenting as megacolon. Obstructive symptoms can be caused by embryonic or otherwise congenital tumors or by the rare EHLERS-DANLOS-Syndrome in which a lack of collagenous fibers in the intestinal wall can lead to symptomatic megacolon. Chronic inflammatory diseases such as Crohn or ulcerative colitis can result in toxic megacolon and should be ruled out in the workup. [36] In newborns intestinal disfunction due to infection or voluntary or involuntary intoxication of the mother during pregnancy should be considered as a possible cause. Chronic intestinal pseudo-obstruction syndrome (CIPO) is another rare differential diagnosis. [44]

If biopsies are obtained these will show unimpaired ganglionic cell patterns and an additional expert evaluation of imaging diagnostics will be helpful identifying the next step to take in diagnostics in many cases. [36]

Furthermore, Hirschsprung's disease can in rare cases appear in combination with multiple endocrine neoplasia (MEN) type 2 (former MEN 2a) or MEN 3 (former MEN 2b) syndrome, another disorder caused by alterations in RET-oncogene. MEN 2 often debuts with medullar thyroid carcinoma in early infancy which is why genetic testing in HD patients can be used to help identify MEN 2 patients quickly and enable an early preventive possibly life-saving intervention. [34]

Especially in older children however the more basic alternative causes such as functional, alimentary and psychosomatic constipation must not be disregarded. They occur with a much higher frequency than most of the rare conditions named above and play a major role in everyday clinical considerations. In these patients the rectal ampulla is filled with stool and the sphincter tone is found to be normal as opposed to HD patients.

1.2.7 HD accompanying syndromes and malformations

HD presents as an isolated malformation in roughly 70% of all cases. Of the remaining patients 18% show accompanying malformations without being allocable to a certain syndrome while in 12 % of the remaining patients, chromosomal aberrations are verified in the diagnostic process. [31]

Accompanying syndromes are more often found in familial cases (31%) of HD than in patients with sporadic mutations (21%). This makes an inheritance of Mendelian pattern very likely [31]. The most commonly associated syndrome is trisomy 21 (Down's

Syndrome) accounting for 90% of all syndromes in HD patients and 2-10% of all HD cases. [31] In trisomy 21 patients HSCR has been shown to occur 100 times more frequently than in the average population [45]. It has been shown that gastrointestinal malformations, cleft palate, polydactyly, cardiac septal defects and craniofacial malformations coincide with HD more frequently than explicable by pure chance. [31] Genetical correlations are being discussed in current studies but have not definitely been identified yet [31]. Additional commonly associated syndromes and anomalies comprise other neurocristopathies i.e. anomalies based on a structural anomaly in the neural crest (NC) during embryonic development. These are e.g. neuroblastoma, Waardenburg Syndrome, multiple endocrine neoplasia type 2 (MEN 2A and MEN 2B) and congenital central hypoventilation syndrome (CCHS). The coincidence of HD and CCHS is also known as Haddad Syndrome present in about 20% of all CCHS patients [31].

A far less sharply defined “syndrome” is the so called VACTERL complex. Less of a syndrome it really depicts a descriptive attempt to integrate the multiple malformations that fall in that complex. The acronym describes: Vertebral defects, Anorectal malformation, Cardiac anomalies, Tracheophageal fistula, renal anomalies and Limb defects.

A variety of other anomalies and syndromes have been reported in HD patients including a wide spectrum of malformations such as sensorineural problems, malformations of the skin, central nervous system and malformations of genitalia (2-3%), kidneys (4,4%) and the heart (5% of all HD patients without simultaneous trisomy 21). [31]

Because HD is that commonly attended by associated malformations and syndromes it is crucial to widen the diagnostic accordingly. That includes an expert evaluation on dysmorphia of the facial treats as well as an x-ray to rule out osseous anomalies. Cardiac and urogenital workups should routinely include ultrasound examination. If besides HD any anomaly is found a genetic workup should be initiated. [31]

1.2.8 Diagnostic investigation

1.2.8.1 General

As a standard, suspected HD patients should receive a diagnostic workup following a stepwise diagnostic approach. Less invasive diagnostic procedures should be employed before specifying the diagnosis with more extensive measures.

Careful history-taking and thorough physical examination should form the basis of further investigations and are often complemented by radiological imaging. Valid evidence to proof an HD diagnosis can only be provided by histological findings pathognomonic for HD. Ruling out differential diagnoses that can present with a similar clinical picture should naturally be part of the workup.

1.2.8.2 Imaging diagnostics

1.2.8.2.1 sonography

Using sonography for a first noninvasive, painless and radiation free tool a distention of the proximal colon can be seen as a hyperechoic mass without acoustic shadow. The transition zone into the constricted agangliotic segment appears cone- or funnel-shaped. A challenging factor of sonography – as everywhere in the pediatric field – is the patient's cooperation that may be difficult to obtain.

1.2.8.2.2 contrast enema x-ray

An x-ray of the abdomen with contrast enema is a standard diagnostic procedure in the workup for suspected HD. The collaboration required from the patient can be kept to a minimum and it offers the additional possibility of adding a contrast agent obtaining further information. Findings in contrast enema x-ray will show the cone- or funnel-shaped transition zone between the mostly dilated proximal healthy segment of the bowel and the distal agangliotic constricted segment. A crucial piece of information, surgeons hope to obtain from such enema studies is the exact location of the transition zone.

Just like in sonography however the transition zone can be hard to identify in very young infants or newborns who do not present with a filled colon. The same goes for patients who previously underwent irrigation, stool evacuation or colostomy and older patients with a very short agangliotic segment. [37, 46] Specificity of this diagnostic exam thus lies between 76 and 92%. [34] Many studies have however shown that up to 10 % of newborns do not show a transition zone in enema x-ray. [47] Even in cases

where a transition zone is identified its exact location may not be depicted accurately in the enema study as it was shown that up to 12% of cases when operated had a pathologic transition zone different from the location seen on the x-ray. [37] [48, 49]

To increase accuracy De la Torre suggested discontinuing irrigation for up to 3 days before performing the contrast enema x-ray in a lateral projection. [37]

1.2.8.3 Anorectal manometry

Anorectal manometry is a diagnostic procedure to measure anal resting pressure as well as intentional relaxation or constriction of the internal anal sphincter. Physiologically an expansion of the rectum caused by accumulation of feces will induce a relaxation of the internal sphincter thus allowing for defecation. In HD patients the typical findings are characterized by an often increased sphincteric resting pressure (achalasia) and a missing relaxation of the internal anal sphincter as a sign of missing rectoanal inhibitory reflex. [36]

Additionally, a lack of propulsive waves in the constricted agangliotic colon as the manifestation of the lack of ganglion cells in the colonic wall can be recorded. [36]

While frequently performed in the 1980s due to many limitations the test is no longer among the standard workup for HD in most hospitals in Germany or the US. [50]

An immature nervous innervation of the anorectum may lead to false positive results of the exam according to Holschneider [34, 51]. The occurrence of false positive results in general is up to 62% while false negative results are less common but far from rare with 24%. Thus, a single negative test result (i.e. a normal sphincter relaxation) cannot disproof the diagnosis and should be followed by biopsies to confirm the diagnosis [34, 37]. Lastly, manometric sphincter studies are especially difficult to perform in young infants and newborns [52].

1.2.8.4 Molecular genetic diagnostic

Because HD is frequently associated with other neurocristopathies and chromosomal alterations a genetic workup in HD patients should comprise exploration for genetical causes with HD being the “tip of the iceberg”. Genetic workup should be employed to detect the underlying genetical cause at an early point of time and to deduce optimal diagnosis and therapy for the patient and, if applicable, for the patient’s family (family planning with genetic risk factors etc.). As mentioned above, Hirschsprung’s disease is a multigenically encoded disease with RET-oncogene on chromosome 10 (10q11.2)

being the most influential single gene in its pathogenesis. Interstitial deletion in RET oncogene (10q11.2) was identified after being found in long-segment and TCA patients.[31]

Since up to 50% of long-segment HD patients carry germ line mutations of RET-oncogene genetical analysis is especially advised in these cases to rule out or confirm a genetic cause. Thus, possible accompanying malformations and syndromes can be detected early and patient care can be adjusted correspondingly. [34] A screening of RET alterations associated with MEN 2 is advised in all HD patients to enable an early initiation of prophylactic therapy (early manifestation of thyroid carcinoma).[34]

If the patient shows typical signs of one of the many syndromes or malformations commonly associated with HD a genetic workup should be initiated to detect a possible underlying genetic cause - the most common genetic syndrome to rule out being trisomy 21 which occurs in 2-10% of all HD patients [31]. Alterations of a variety of gene loci has been reported in HD patients, the following comprising only an incomplete sample that should be considered for genetic workup. EDNRB (13q22.1-32.1; identified in a number of short-segment HD patients), ZFHX1B gene (former SIP1 gene; 2q22-23; identified in patients with a multiple congenital anomaly-mental retardation (MCA-MR) syndrome with HD, EDN3 or ECE1. [31, 36]

1.2.8.5 Histological diagnostics

1.2.8.5.1 levelling biopsies of the colorectum

The gold standard to solidly proof the diagnosis of HD tissue samples remains in obtaining tissue from the suspected agangliotic bowel segment and having the samples evaluated by histopathology experts [34]. To not only verify diagnosis but preoperatively determine the extent of the aganglionosis, taking levelling biopsies is a standard procedure. Due to the varying extent of the hypoganglionic transition zone proximal to the agangliosis the extent of the removal can be hard to determine.

Biopsies can be obtained in a preoperative rectoscopy or via diagnostic laparoscopy prior to or during the repair surgery. Albanese, Yamataka and Somme e.g. support a laparoscopic approach to obtain serial biopsies and confirm the location of the transition zone before performing the primary dissection of a correcting procedure. [46, 49, 53] [54] Somme et al reported no increase in operative time, length of hospitalization or “analgesic requirements” secondary to obtaining laparoscopic biopsies. [49]

Other surgeons take a first biopsy sample prior to the main procedure to proof aganglionosis in general. The leveling biopsies are then obtained during the repair surgery to identify the transition zone and determine the extent of the pull-through procedure.

This approach however holds the risk of identifying a high HD or TCA only after having already made the irreversible perianal dissection and having given away the opportunity to adapt the surgical approach to an unexpected TCA if necessary. [46, 49]

Surgeons who, in the case of an unexpected long-segment HD, would prefer Duhamel Procedure rather than Soave or Swenson, could then be forced into an unpreferred procedure.[37, 55]

In consideration of the fact that around 80% of HD are limited to the colorectum however the approach may be considered justifiable as a standard for the majority of HD cases. [54, 56, 57]

Biopsies can either be obtained as aspiration biopsy or full-thickness biopsy.

1.2.8.5.1.1 Suction rectal biopsies (SRBs)

A main advantage of suction biopsies is their rather easy accessibility. Suction biopsies can be attained during preoperative rectoscopy or even as a bedside procedure in critically ill newborns. [40] The procedure can be performed without anesthesia and complications more severe than self-limiting rectal bleeding are rarely reported. [40, 58] For the reason of convenience and patient safety suction biopsies are the standard diagnostic procedure when HD is suspected. [59]

Some surgeons however doubt that a final HD diagnosis can safely be made by a mere submucosal biopsy when HD also affects the deeper myenteric plexus. Studies have shown that the myenteric plexus extends invariably further than the submucosal plexus. It can therefore safely be deducted that if ganglion cells are proven present in the submucosa, ganglion cells will also be found in the myenteric layer of the same level [60]. Some authors of studies on this topic therefore recommend suction biopsy only as a screening instrument when HD diagnosis should be ruled out.[40] HD diagnosis can be considered safely disproven if the suction biopsy shows normal innervation patterns in the attained tissue sample. [40] If the innervation shows to be insufficient however, it might be hard to safely differentiate between real HD and a damaged tissue sample. Deficient sample quality leading to inconclusive results is a different matter of

discussion about SRB. A considerable number of biopsies obtained by this method is claimed to be unfeasible for definite diagnosis. Considering the definition of HD for adequate evaluation the tissue sample must comprise enough submucosal tissue to reliably evaluate the presence or absence of ganglion cells, only then HD can be verified or disproven.

The problem however lies not within the technique of SRB itself but within the execution of both surgical biopsy-taking and pediatric pathological evaluation.

A recent study could show that if both steps are performed meticulously SRBs have a sensitivity and specificity of both 100% for HD diagnosis in patients younger than 6 months including preterm infants. [59] The discussion if SRB alone are sufficient to prove an HD diagnosis is still a topic of ongoing research. [59, 61, 62]

1.2.8.5.1.2 Full-thickness biopsies

To verify a suspected HD diagnosis many surgeons (39% according to Allen et al) still prefer to obtain full thickness biopsies in addition [40, 59]. As the name states these samples comprise all layers of the intestinal wall and thus provide highly reliable information on the presence of absence of ganglion cells in both the submucosal and myenteric layer. Acquisition of full-thickness biopsies however requires general anesthesia and hold significant risks for the patient including anesthesia complications. Complication rate has been reported to be rather high with 6,6%; the complications however being of minor severity. [62] Additionally full-thickness biopsies preceding an operation according to de la Torre can complicate the repair surgery itself and possibly endanger the patient [57].

It has not finally been clarified if full-thickness biopsies provide additional validity to an extend that justifies the additional costs on the part of the health care system and the additional risk for the patient. Historically grown, full-thickness biopsies are still regarded as a standard in HD diagnosis by many surgeons however increasingly challenged by SRBs. [61]

1.2.8.5.2 Enzyme histochemical and immunohistochemical evaluation

In practice the typical histological findings correspond to the underlying malformation in HD. Most specific for HD is therefore an absence of intramural ganglion cells (myenteric and submucosal plexus) usually visualized in a lactate dehydrogenase reaction (LDH) [34, 39, 63]. In additional cholinesterase staining an enhanced activity of

acetylcholinesterase (AChE) can typically be observed as the biochemical equivalent of a submucosal hyperplasia of cholinergic neurons. [34]

More recently calretinin has become a significant additional histochemical marker used especially when the suction biopsies at hand were inadequately taken. [34] A lack of calretinin immunoreactive mucosal innervation is typical for HD and visualizes the absence of ganglionic cells in the examined segment of the bowel. [39]

When attaining the bioptic sample the area directly neighboring the pectinate line should be avoided since physiologically a paucity of ganglion cells is found in this location. Imprecise information on the tissue samples' original location in the colorectum can therefore lead to false positive test results. [37, 64]

Even with modern diagnostic procedures HD diagnosis remains difficult. If the absence of intramural ganglion cells in the colorectum cannot be proven sufficiently 4 cm and more above the anocutaneous border a repair surgery must be postponed until the diagnosis is confirmed by solid diagnostic evidence. [52]

1.2.9 Preoperative management and conservative therapy strategies

Preoperatively as soon as HD diagnosis is confirmed a program of enemas is initiated. They help to evacuate stool, prevent a distension of the colon and clean the bowel for the upcoming surgery. Additionally, a colonic irrigation regimen helps to treat and prevent enterocolitis. [65] Holschneider recommends enemas should be used for at least 2 days prior to the repair procedure. [39] Especially in older children who present with a highly dilated colon it can however take much longer to achieve a satisfactory decompression of the colon [37]. In addition to enemas, sphincter dilations are used to counter and prevent sphincter achalasia which is associated with postoperative ileus [39]. Depending on the patient's overall condition intravenous fluid and antibiotics as well as a nasogastric tube should be applied to counter shock symptoms. Colonic decompression as mentioned above plays a crucial role in these infants especially [37]. Since HD is commonly associated with other deformities (amongst others cardiac problems) these must be dealt with before the HD repair if they show to be more pressuring. [37]

1.2.10 Operative techniques for HD repair

1.2.10.1 Surgical procedures - a quick overview

All of the following techniques follow the main objective to remove the malfunctioning part of the bowel and minimizing damage to the surrounding tissue especially the sphincter muscle while doing so. The "evolution" of surgical approaches is described in further detail in the paragraph following this overview containing mere short descriptions of the surgical techniques.

1.2.10.1.1 Swenson's Procedure

Abdomino-perineal rectosigmoidectomy in pull-through technique with end-to-end anastomosis. (Swenson, 1948) [66]

1.2.10.1.2 Rehbein's Procedure (Deep anterior Resection)

Open surgical rectosigmoidectomy via abdominal approach with low colorectal anastomosis. (State-Rehbein 1952/1958) As Rehbein was a German pediatric Surgeon his technique was widely adapted in central Europe and well known internationally.

1.2.10.1.3 (open) Duhamel Pull-Through

Retro-rectal transanal pull-through operation. Modification of Swenson procedure in which the retro-rectal dissection is made without resection of rectum. The created rectal reservoir has an anterior aganglionic wall and a ganglionic posterior wall. Side to side retro-rectal anastomosis. (Duhamel, 1956) Later laparoscopic modifications have been described for the Duhamel and Swenson operations which produced excellent short-term results. [37]

1.2.10.1.4 Soave Pull-Through

Transanal endorectal pull-through procedure named Soave pull-through.

Open surgical endorectal dissection and pull-through rectosigmoidectomy. [67]

First endorectal approach. Later also Soave procedure was modified with a laparoscopic approach instead of an open abdominal approach.

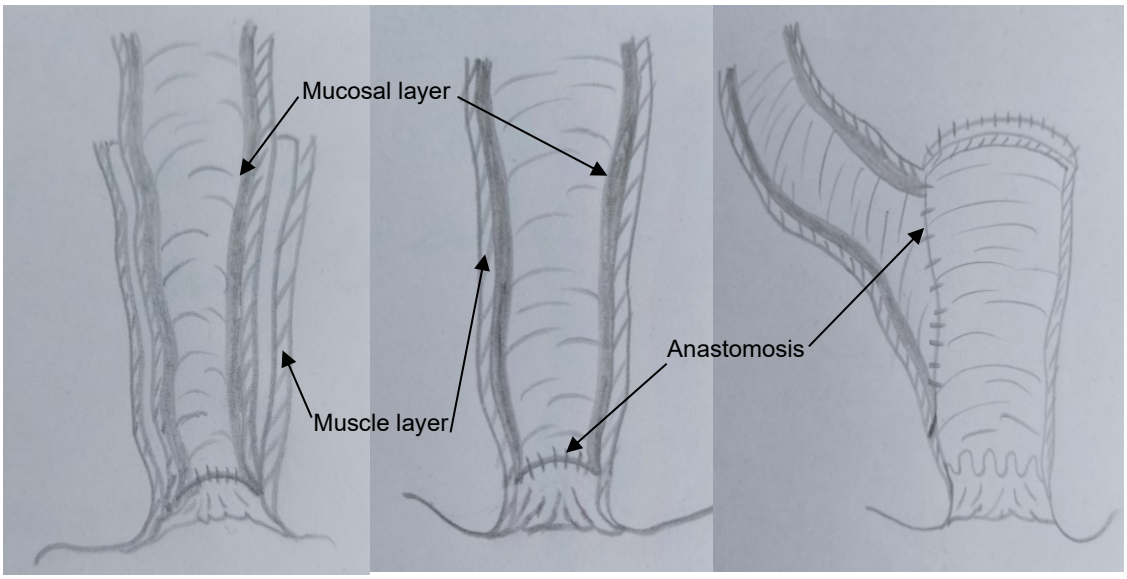

Fig. 1 **Anatomy after Swenson, Soave and Duhamel surgery (Left to right)**

1.2.10.1.5 Georgeson

Laparoscopic assisted abdominal and endorectal pull through with transanal mucosectomy. First laparoscopic modification. [68]

1.2.10.1.6 Laparoscopic Duhamel

Modified Duhamel procedure using a laparoscopic approach instead of an open surgical abdominal incision. Considering the outcome only slight differences were reported compared to the open Duhamel Procedure. Studies showed a slightly higher rate of enterocolitis, less adhesions but a far better cosmetic outcome. [69]

1.2.10.1.7 Total endorectal pull-through (TEPT) De La Torre / endorectal Soave

Endorectal transanal rectosigmoidectomy in pull-through technique. First purely endorectal procedure. Mucosectomy with remaining muscle cuff that is split posteriorly to cover pulled through colon. Anastomosis is performed transanally in end-to-end technique. (De la Torre, 1998)

1.2.10.1.8 Partial sphincter myotomy according to Lynn

Procedure of choice for ultrashort HD or idiopathic megacolon without aganglionosis as it occurs in Ehlers-Danlos syndrome.

The aim is to relieve the hyper-contracting internal anal sphincter muscle. [36]

1.2.10.2 Evolution of surgical HD repair

Evolution of surgical HD-repair
Permanent colostomy
Colostomy and abdominal surgery
Colostomy and abdominal surgery plus endorectal per-anal approach
Colostomy and laparoscopic surgery plus endorectal per-anal approach
Laparoscopic endorectal pull-through [19] [70]
Laparoscopic Swenson pull-through [71]
Colostomy surgery solely per-anal endorectal [57] de la Torre
Endorectal pull-through surgery without colostomy

Table 6 Evolution of surgical HD repair

Since Hirschsprung's disease is an anatomical congenital malformation, the only causal therapy at hand is surgical removal of the agangliotic intestinal segment while minimizing collateral damage to adjacent nerves and muscles and organs of the lesser pelvis. Structures at risk include - depending on extent of aganglionosis - the patients' bladder, urethra, ureters, vascular arcades of the intestine and vas deferens in male patients. Special attention is given to the anal sphincter and preserving its integrity to increase the chance of long-term continence [72]. The following paragraph is meant to give a more detailed overview over the evolution of operation techniques most frequently used. Table 6 gives an overview over the development of surgical HD repair over time.

Historically a long time to diagnosis regularly lead to possibly life-threatening emergency situations in patients with Hirschsprung's disease. Therefore, a quick and safe relief of the bowel was the main prospect of surgeons in the field supporting the convention of creating a diverting colostomy soon after diagnosis as the definite treatment approach.[49]

However, within the last 40 years the treatment of HD has evolved steadily.

The first to successfully operate a 6 year old HD patient were Swenson and Bill in 1948. [66] Their technique became widely used after its publication.

Rehbein introduced his open surgical rectosigmoidectomy with a low colorectal anastomosis in 1958. The low anastomosis enabled the surgeons an easy access for postoperative follow up checks.

Swenson's procedure was then modified by Duhamel in 1956 inventing the retro-rectal transanal pull-through operation. In this procedure the retro-rectal dissection is made without resection of the rectum thus forming a rectal reservoir. Soave subsequently introduced the first endorectal pull-through procedure in 1964 breaking ground for further modifications to come. [67]

All of these four traditional approaches have shown to be equal considering functional long-term outcome. Their common trait is the open surgical transabdominal approach. [34] Duhamel and Soave's procedure in theory had the advantage of sparing the neurovascular plexus innervating the rectum. Long-term follow up however could show no significant difference in sexual function or continence between Swenson, Duhamel or Soave procedures. [49]

Probably because of the historical development the traditional approach has been to perform Swenson, Duhamel or Soave procedure as a sequence of 2 to 3 operations. Relieving possibly dangerous situations of the patient and initiating treatment with a diverting colostomy usually was the first procedure. This way decompression of the proximal mostly dilated bowel could be ensured. In a second stage leveling biopsies had to be attained to identify the transition zone between agangliotic and adequately innervated intestine. Many surgeons however combined this step with the creation of the colostomy during one session. The remaining operation was the main correcting procedure i.e. the removal of the agangliotic segment and anorectal anastomosis which was traditionally performed at 12 months of age. [66] After the removal of the agangliotic constricted colon the proximal healthy bowel segment was mobilized and anastomosed to the anus. As an established approach many surgeons secured the anastomosis with a proximal loop ostomy which was then closed later in a third operation when the anastomosis had safely healed. [49] [73]

As a further evolutionary step Georgeson et al introduced the laparoscopic assisted single stage pull-through for HD in 1995 further improving HD therapy by using minimally invasive techniques and setting a new gold standard in HD therapy. [73] [19] The

new method proved to cause less pain, less formation of adhesions due to the minimally invasive laparoscopic approach, shorter in-patient time and a better cosmetic result. [19]

Since Georgeson the trend has continuously been towards less invasive approaches and one-staged repairs where possible. Corresponding laparoscopic modifications have also been applied to Swenson and Duhamel procedures by other authors.

The transanal endorectal pull-through emerged in the late 1990s as the most recent step in the evolution of the surgical correction of Hirschsprung's disease. The transanal endorectal resection in pull-through technique has been referred to as TERPT after it was first described by de la Torre et al. in 1998 [57]. De la Torre clearly sets indication of the TEPT as surgical procedure for HD limited to sigmoid and rectum which accounts for roughly 80-85 % of HD cases making it the procedure of choice for the majority of HD cases.[34, 57]

While in cases of a proximal aganglionosis or TCA a complementary laparoscopy can be necessary Wildhaber et al. reported favorable outcome with TERPT even in TCA patients.[74]

When compared to the open approach complication rates of TERPT were found to be similar. The advantages of the transanal approach comprise the advantages already achieved by laparoscopic approach such as prevention of postoperative ileus, less postoperative pain and shorter hospitalization.[72]

Pain levels are especially low due to the absence of abdominal incisions and the absence of somatic pain fibers in the area of the anal dissection. [53] Also length of hospitalization, costs and need of anesthesia for the patients is significantly lower in the transanal approach compared to the open operation. [75] The purely transanal approach does not require any abdominal dissection and thus holds new additional advantages such as extended protection of the abdominal and pelvic organs and structures from unintentional injury caused by laparoscopy [57, 72, 75] and abdominal contamination. [76] Local blood supply and innervation of the colon remain untouched and thus according to de La Torre less impairment of continence is to be expected. [57] Also blood loss is minimized, the operating time is shortened [76] and the occurrence of postoperative abdominal adhesions and consecutive complications is expected to approach zero as there are no dissections to the abdomen in this approach. [57, 72, 75] Furthermore, the cosmetic result is superior as to be expected in a procedure with no abdominal incisions

and consecutively no visible scars. [57, 76] Lastly – especially in an international context – the transanal approach can be performed even in centers without laparoscopic equipment and by surgeons inexperienced in laparoscopy thus granting more equality in medical care for HD patients. [49, 75] [37, 77]

For all of the reasons listed above the transanal approach without laparoscopy has been increasingly used by surgeons worldwide since its publication by de la Torre in 1998. A further modification made over time is the gradual shortening of the length of mucosectomy to minimize the constriction caused by the remaining muscle cuff. [49]

There are however significant theoretical advantages to a laparoscopic visualization. In cases of a higher transition zone a laparoscopic approach enables the surgeon to easily obtain high biopsies to verify ganglion cells proximal to affected bowel even in aganglionosis extending to the right colon or TCA before dissection. [53, 73] Also, laparoscopy makes it possible to mobilize the splenic flexure while a purely transanal approach might lead the surgeon to a "dead-end" situation if the transition zone unexpectedly is found to be more proximal than can be repaired via the anal incision. [75] Furthermore, laparoscopy ensures a visualization of the pulled through bowel to ensure the absence of twisting or injury. [75] Despite of these theoretical arguments however, data so far has not shown any benefit of routine employment of laparoscopy. [75]

1.2.11 Complications

1.2.11.1 Complications in the pre-operative period

The most severe complication of HD is enterocolitis also referred to as Hirschsprung's associated enterocolitis (HAEC). Since it occurs pre- and post-operatively it is described in further detail in the chapter on post-operative complications.

As another complication HD patients rarely present with perforations secondary to the intestinal distension. [39] In these patients, early diagnosis is mandatory to prevent emergency situations.

Postoperative complications

Early complications are not less common in laparoscopic procedures though the cosmetic outcome is significantly better in this group. [19, 34] Depending on the procedure chosen for removal of the agangliotic segment the type of complications will differ

accordingly. A major factor is whether or not an abdominal open or laparoscopic approach was performed in contrast to a TERPT where the surgeon abstains from any abdominal manipulation. Overall complications have however been shown to be evenly common irrespective of the operation performed. [78]

Therefore, we could safely assume for our research that including patients who underwent various types of operation would not confound with the validity of this study's findings. More than on the operation technique complications and long-term outcome depend on the initial extend of the agangliotic segment with longer segments holding a higher risk for severe complications and an overall poorer outcome considering both functional outcome and experienced quality of life. [34]

Long-term data about outcomes after the laparoscopic or transanal approaches have not yet been evaluated through a reliable number of studies, but since none of these operations are fundamentally different from traditional open pull-throughs, the long-term outcome is expected to be similar.

[34, 49]

1.2.11.1.1 Early complications

A rather common early postoperative complication after primary HD repair surgery with an incidence of 1.7-19.2% is wound infection. The rate of wound infections seem to be positively influenced by preoperative bowel preparation and shorter operative duration. [39]

Probably the most severe complication after a repair is Hirschsprung's associated enterocolitis (HAEC) which can occur both before and after the repair surgery.

It presents with diarrhea, abdominal distension and fever.

Several studies have investigated the incidence of HAEC and report highly inhomogeneous numbers between 18% and 58%. [39, 74] Longer agangliotic segments and male sex were found to coincide with increased incidence of HAEC (two to three times more frequently). [74] Also differences between the repair procedures have been reported. [39] HAEC has also been reported to occur more often in infants who have been diagnosed with HD after the newborn period which is one more factor emphasizing the importance of an early diagnosis. [39] Other risk factors for HAEC comprise history of

HD and trisomy 21. HAEC is known for its severe impact on morbidity and mortality in HD patients being the most common cause of death in HD patients. [39, 74, 79, 80]

HAEC can develop quickly as a feared pre- and postoperative complication [39] and was long reported to have a high mortality rate of up to 30% [81]. Fortunately, this number decreased drastically over the years and lies around 1% nowadays. [39, 74] Despite numerous studies the exact mechanisms of HAEC are still unknown, although a number of theories regarding its pathogenesis exist. [39] Preventive measures that have proven successful are early diagnosis, prompt upstart of colonic washouts for colonic decompression and early repair surgery. [39] Fluid resuscitation, administration of antibiotics and bowel rest should be initiated If the patient's general condition deteriorates. [39] In emergency cases of peritonitis etc. resection and diverting colostomy might be indicated [39]. A much rarer early complication is severe bleeding after the repair procedure which in most cases can be avoided by paying close attention to a meticulous operation technique. [39] The same caution is needed to prevent dehiscence which occurs in about 3% of HD repair patients. Complications concerning the newly established anastomosis comprise anastomotic leak, pelvic and cuff abscess. Anastomotic leak being the most severe of anastomotic complications, occurs more likely when the anastomosis is sewn under tension, when blood supplying vessels have been compromised and bowel becomes ischemic or when the use of steroids interferes with wound-healing. Down's syndrome is suspected to be more frequently associated with anastomotic leak. [39] Incidence is reported to range between 1% and 10% of the cases. [39] Leaks can result in anastomotic stricture as a long-term complication. [39] Pelvic and cuff abscess are less common and occur in 5% - 7% but can lead to sepsis. Patients with suspected abscess should be promptly evaluated with CT scan and treated accordingly to the findings [39]. Retraction of pull-through segment usually occurs in the early postoperative period with an incidence of about 10% according to Holschneider. Some cases may be corrected transanally while others may require a protective colostomy before a revision surgery. [39]

Lastly stoma complications such as skin problems, prolapse or retraction, stenosis or hernia can occur in patients with an ostomy.

1.2.11.1.2 Late / long-term complications

When evaluating complications secondary to surgical intervention it is often hard to differentiate between complications caused by the operation and the unfortunate but natural course of the disease. One should bear in mind that certain conditions might appear to be an iatrogenic complication that might however have occurred to the same or more severe extent without the operation.

Constipation is probably the most common long-term complaint expressed by post-repair HD patients. While little variation depending on the repair procedure is described among Swenson, Duhamel and Soave, Rehbein's procedure seems to cause constipation more likely. In general its incidence has been described to range around 7.9% of all cases. [39] Symptoms may strongly resemble those of the patient's initial presentation the main symptom being inability to pass stool without assistance or manipulation. [37]

Constipation has been reported to subside with time and Rescorla and coworkers stated that in the first five years after repair surgery 88% of all patients complained over constipation issues. After 15 post-operative years the same study found satisfactory data in all of their patients. [82] Other studies support the fact that after an average of 5 years incidence of constipation decreases significantly. [39] As with incidence of enterocolitis also constipation is reported to occur more frequently in patients with HD and trisomy 21. [39]

Causes of constipation are versatile the most common being incomplete resection, sphincter achalasia, strictures after surgery or "functional constipation".

As treatment options sphincter dilations, sphincter-myotomy and further resection of a possibly remaining agangliotic segment must be considered cautiously. [39]

The most common reason for incomplete resection is intraoperative identification of the transition zone based on Frozen section biopsy. Sampling and interpretation errors regularly occur in these samples [39]. Enemas can be applied to control both constipation and soiling after HD repair [39].

Continence is – together with constipation – the major long-term topic in post-repair HD patients. Evaluation of continence has proven to be difficult due to variable factors. First and foremost an objective report of a patient's stooling pattern is hard to obtain.

Continence issues occur within a wide range from occasional soiling to severe incontinence and objective details on a patient's stooling pattern are hard to retrace.

One possible cause of continence problems is retained aganglionosis which should be ruled out by adequate diagnostics such as repeat barium enema or repeat biopsy.

Another reason for a patient's incontinence may be an iatrogenic trauma to the nerves providing sensation of the most distal anorectum. This can be avoided by placing the initial incision in TERPT high enough above the dentate line [37].

The best treatment for incontinence or soiling in most cases is time: A satisfactory degree of continence is reached by the majority of patients and soiling has shown to subside with time. In a study where 12% of the under 5-year-old patients were reported to have continence problems, among the 10 to 15-year old the incidence was down to 6% and no patient over 15 years of age reported incontinence problems.[82]

Other studies have since supported the trend of improving continence after reaching adolescence, reporting an average incidence of 7.1% after evaluation of nine thousand patients. [83, 84] Supportive treatment options such as dietary adjustments should be attempted before a surgical solution is considered [39].

Over time several expert groups have been established, including psychologists and physiotherapists cooperating and focusing on bowel management in patients with defective bowel function. Bowel obstruction as a possible acutely dangerous complication can originate from different sources. Adhesive bowel obstruction occurs secondary to alterations of the intraperitoneal tissue and organs after a (surgical) trauma. Incidence has been reported between 7.5% and 18%. With an increasing number of surgeons using purely endorectal and laparoscopic approaches a further decrease of its incidence is to be expected. Internal hernia is another cause of bowel obstruction with an incidence of less than 2% [39].

Anastomotic strictures occur rather rarely and usually present as obstipation. Causes are a too narrow muscular cuff, insufficient blood supply, insufficient dilations or secondary to a leak. Treatment ranges between dilations and an open surgical revision depending on the severity of the case. [39] Whether or not prophylactic daily anal dilations prevent anastomotic stenosis is controversial, some surgeons start dilation two weeks after surgery, some instruct the parents on performing dilations for up to 6 months postoperatively. [37]

A very common problem that affects at least 50% of HD patients after repair is perianal excoriation. Liquid and frequent stooling can weaken the perineal skin for weeks to

months after the repair before subsiding. To support healing barrier products and medication to regulate stool consistency should be administered. [37] While not life threatening the lesions can be a lengthy source of stress for both, patient and parents.

Pelvic nerve damage can result in voiding and sexual disfunction. Enuresis occurs in around 9.5% post-repair HD patients but is expected to decrease as the TERPT is increasingly used as correcting procedure. [39]

Overall readmission rate of post-repair HD patients has been reported to be around 70% [85]

Lastly mortality is reported to be roughly 2% with enterocolitis being the most common cause of death. Due to the frequently associated other malformations patients may die of e.g. cardiac difficulties. [39, 85]

1.3. One stage vs. three stage approach with temporary ostomy

1.3.1 Current situation

1.3.1.1 Hirschsprung's disease patients

Considering HD patients Swenson published a first study performing a primary repair on HD patients within the first 4 months of life already in 1975 [86]. However, this pioneer study showed a higher mortality rate in the primary repair group convincing many surgeons the primary repair was an unsafe approach and thus lead to the consolidation of the traditional multi-stage approach as the standard procedure in HD even if Swenson's increased mortality rate later showed to be mainly anesthesia related [49]. Five years later in 1980 So et al became the first to report successful primary pull-through using Soave's endorectal technique in HD patients. [65] Carcassonne presented two studies as early as 1982 and 1989 which concluded one stage repair (Swenson, Duhamel and Soave) was safe even for infants less than 3 months of age. [52, 87] Cilley then confirmed Carcasonne's findings that primary PT was safe even in neonates in 1994 as did Wilcox et al in 1997. [88, 89]

Georgeson published on transanal mucosectomy and primary laparoscopic pull-through in 1995 [57] and Van der Zee et al [90] safely performed Duhamel procedure in one stage in 1996, in the same year Langer et al [91] published on safety of primary Soave. Hackam et al [92] performed single-stage repair using the endorectal pull-

through technique and Pierro et al [56] proved that the three-staged procedure was not safer than a single-stage approach both in 1997.

Single stage approaches had thus been described for Swenson, Duhamel and Soave and with Georgeson [19] as a further advancement the evolution towards minimal invasive surgery began.

As the trend towards one-stage operations and the development towards laparoscopic and transanal approaches happened parallelly numerous studies were published comparing one of the numerous options to another.

Earlier studies mainly take into consideration the postoperative complications as well as the short-term outcome while more recent studies increasingly focus on long-term outcome in HD patients. Complexity and rarity of the disease, inhomogeneity of the study groups, multitude of operations and varying extend of malformations showed to make significant study designs difficult and to limit comparability to former studies.

Over time, it was however recognized that a primary pull-through could be performed safely in the first few days or weeks of life, as soon as the diagnosis of Hirschsprung's disease has been made and already in the late 1990's the trend was toward early repair and primary repair over a staged approach [68].

Thus, after several studies proofed all of the established procedures to be feasible as a one stage repair over time routine colostomy was increasingly abandoned. [53]

1.3.1.2 ARM patients

While surgeons were very cautious in implementing primary repair procedures in HD patients the development was faster for the repair of ARMs. [93]

Since the introduction of PSARP by Pena and de Vries in the 1980's the operative care for ARM patients improved significantly as measured by the clinical outcome. Satisfactory continence was achieved in over 70% of patients. [21] Traditionally the PSARP repair was performed as a three-stage procedure with a primary colostomy in the neonatal period, the main repair surgery at an age of about 6 months and the colostomy closure several months later. [94]

As early as 1999 Pena wrote ‘‘we should all move in the direction of repairing anorectal anomalies earlier and in a single operation’’[95]. However, in 2006 he still stated that the majority of ARM patients still received a primary colostomy before a definite

repair and Adeniran repeated Pena's plead for a new standard for primary repair in 2005. [20, 94]

The intention of creating a primary colostomy is decompression on the one hand and protection of the future operation site on the other hand. [21, 94] In fact one unaltered advantage of the colostomy is a decrease in rates of infection. [21] Although one reason to create a colostomy is often the prevention of wound dehiscence in fact this complication does also occur under colostomy protection and is not preventable in all cases. [96] An additional argument is a better preoperative radiologic display of the individual anatomic situation. Some surgeons also argue that in the newborn the anal sphincteric muscle is too weak and thus the misplacement of the neoanus too high if the site cannot clearly be identified [21]. All these pose reasons for opposition to the newer idea of a primary repair. In summary surgeons arguing in favor of a staged repair with a primary colostomy mostly state three main arguments: safety of operation in newborn period, more time for pre-operative diagnostic investigation of the anatomic situation and practical feasibility in newborns [21]. All these concerns could however be proven to be unnecessary in the last decades. Several studies could show that a one-stage primary PSARP repair of ARM is possible even in intermediate and high malformations. [21, 94]

In terms of safety it has been shown that neonate mortality for PSARP is very low. [21, 97] Considering the preoperative time available to collect as much information as possible concerning the individual patient's ARM it is true that a colostomy buys time for further diagnostic procedures and renders a distal colostogram possible in the first place. Physical examination however, including examination of the normal or altered outer gluteal and sacral appearance is crucial and will provide much information considering the typical findings hinting at certain subgroups of ARMs. The presence of a cutaneous fistula e.g. makes a low ARM most likely and a catheter can help to quickly verify or falsify a rectourethral fistula. X-ray diagnostics to determine the osseous extent of the malformation can take place irrespective of the presence or absence of a colostomy. Prone lateral x-ray to locate the rectal pouch can likewise be taken. Even more detailed depiction of the malformation and its' extent can be achieved by MRI and real time MRI. When taken together all the diagnostic investigative procedures feasible without a colostomy can provide sufficient information to gain a clear overview of the malformation and anatomic situation of the individual patient and plan the operative

repair in the majority of the cases. [21] Additionally, in those cases, where the rectum cannot be found from the posterior sagittal incision an abdominal approach can immediately be initiated without further delay and without the need for a colostomy even in high ARMs. [21]

Considering the feasibility in the newborn bearing in mind the unusual small size of all pelvic structures Liu et al. could show a satisfactory outcome in 2004. [21] In the same study primary PSARP patients showed a higher incidence of infections and wound dehiscence and anal stricture in the short-term outcome while other studies reported no difference in early complications. [21, 98] It is reported however that most cases of wound dehiscence can be avoided with a regimen of preoperative irrigation, no oral food for 5 days together with antibiotics and loperamide administration. [96] If the general risk is kept in mind and all precautions are taken primary PSARP safe and superior to the traditional three staged PSARP procedure in many ways. [21]

In conclusion a primary repair in the newborn has been shown to be safe and feasible in the majority of all ARMs including high malformations. Leading experts in the field [13, 94, 95] strive to establish the primary PSARP repair as the new standard for all ARM patients. Primary PSARP relieves the fecal impaction, removes a contaminating connection between bowel and urogenital tract where present and provides an early definite anatomy allowing for neurological training of the ano-cerebral reflex which can improve bowel control in the long-term outcome. [13, 94, 99]

1.3.1.3 Single-stage Advantages

Initial reports did not focus on the comparison between the single-stage repair and staged approaches. More recent studies however demonstrated a number of advantages of the single-stage repair. [49]

While the one-stage approach has proven to hold many advantages over the three-stage repair the most obvious is the reduction of total number of surgical procedures. While - as the name implies - the one-stage repair is entirely performed during one operation the three-stage approach requires two to three surgical sessions: one for the creation of the stoma, another one for the actual repair and in some cases a third session for ostomy closure, if not combined with the second session. [68] [19] [56] [73]

Fewer operations conclusively lead to a reduction of general surgical complications such as intestinal obstruction, adhesion formation, incisional hernia, wound infection,

bleeding, sepsis or death. [20, 21] Additionally enterocolitis does not pose a routine indication for colostomy since it can adequately be treated with strict colonic irrigations in most cases [65]. Fewer operations naturally mean less use of anesthesia and thus a reduction of anesthesia related short-term and long-term complications. [68] [19] [56] [73] This point is especially important for patients with associated malformations that considerably increase the anesthesia risk. [99]

In addition, a reduction of surgical procedures holds a significant economic advantage due to a subsequently reduced number of hospitalizations and total in-patient time, saving health resources and reducing costs. [85, 88] [92] [19] [56] [100] The frequency of readmission after repair surgery has been shown to be significantly higher in HD patients operated in a staged approach than in patients after one-stage repair. [85]

In an international context it should be considered that in areas of the world where transportation to the hospital is problematic and strenuous for the patients and their families, the single-stage repair allows for adequate treatment without the necessity of readmission. [94, 99]

On a functional level immediately affecting the patient the delay of rectal feces passage is thought to be disadvantageous for later defecation control in both groups HD and ARM patients. [88] An early formation and use of neurons needed for adequate bowel control, has suspected to be disturbed by the artificial ostomy even if temporarily as it interferes with the “neuron training”. [13, 88, 93-95] Thus, an early reestablishment of anorectal reflex and immediate colon continuity are desirable factors improving long-term outcome. [19] [56] Functional outcome after primary PT repair for HD have been shown to be similar to multi-stage repair outcomes in early and medium term follow up. Even if long-term results are yet scarce, expert do not expect them to be much different than those of the staged procedure since the surgical technique has not been significantly altered. [49, 92]

Considering functional long-term outcome in ARM patients, the primary PSARP repair proved to be equally good as the staged approach in high and intermediate ARMs. In the long-term outcome patients who underwent primary repair showed no difference in continence, sphincteric pressure, incidence of soiling and constipation compared to patients who underwent a staged repair surgery. [21]

On a whole different level, the psychological burden that comes with the creation of a colostomy for both, patient and in newborns mainly for the patient's parents is not to be underestimated. In newborn patients parental bonding may be hindered. The stress and trauma that can come with the experience is successfully avoided by the one-stage repair of either ARM or HD. [19] [88] In their study Somme et al psychiatrists pledge for a colostomy closure as soon as possible and a reduction of hospitalization time. [52]

Considering life quality and social standing in an international context the family's social situation can drastically deteriorate due to the stigma of having a colostomy which can be considered a burden avoidable by single-stage repair. [49, 94]

While the single-stage approach has shown a similar rate of complications as the three-staged procedure comparative studies (with groups of patients with and without colostomy) could show that the increased complication rate in the colostomy group was indeed mainly caused by problems directly related to the stoma itself rather than to general surgical complications. [91, 100]. In terms of complications in general it has been reported that definite surgery in the neonatal period is not associated with a difference of incidence of postoperative enterocolitis or internal sphincter dysfunction. [100]

Thus lastly and most understandably any kind of complication caused directly or indirectly by the stoma itself can be prevented by avoiding the creation of an ostomy in the first place. [68] [56, 73] [88] [49] Complications commonly caused by colostomy comprise dislocation, prolapse – possibly causing necrosis of colon cut off from its blood supply - or retraction – allowing for stool passage in a loop colostomy. In ARM patients with a fistula this would consecutively hold the risk of fecal contamination of the urinary tract or distal fecal impaction and megacolon in the fistula itself. UTIs were found in 29% of ARM patients in a study investigating colostomy complications. [101] In patients with a fistula wide enough to decompress the colon through the fistula however, the argument of decompression should be considered before performing a colostomy. [99] Other stoma complications are stenosis of stoma, infection, parastomal hernia and necessity of stoma revision. [20, 39, 91, 102]

Such mechanical stoma related complications were found in up to 74% of ARM patients in a study by Nour and colleagues. [103]

A severe problem that has been identified is a significantly higher mortality rate of infants with primary colostomy in countries with limited medical resources. One study

found that less than half of the participating colostomy patients survived until the definite repair could be performed. [104]

Another fact to consider is the possibility of the ostomy interfering with the actual repair operation due to lack in mobilization and vulnerability of the colon close to the ostomy site depending on individual management in each case. [20] If parts of the colon are lost due to ischemia in a prolapsed stoma the repair might be unsatisfactory in terms of long-term results as more length of colon increase the patients chances of continence after the repair. [20]

By paying meticulous attention to a proper technique - such as choosing the right ostomy site in a fixed portion of the colon, using diverting colostomy instead of loop colostomy etc. - many colostomy complications can be prevented to the greatest possible extend. [20] Avoiding colostomy in the repair of HD or ARM whenever possible will however naturally remain the most effective approach in prevention of stoma complications.

1.3.1.4 Considerations and requirements for single stage success

"Primary corrective operation without decompression requires that two conditions be met: absolute security in the diagnosis […]; and efficiency of medical treatment." [52] This quote from Carcasonne's study in 1982, is still valid to this day. Security of diagnosis, the first point mentioned, for HD patients is generally based on biopsies.

For the repair surgery to be successful biopsies must reliably identify the exact localization of the transition zone. Imprecise biopsy reading is inacceptable in both ways as it would lead to either continuous obstructive symptoms due to a remaining aganglionic segment or – probably worse because irreversible - needless resection of healthy bowel. Leveling biopsies are usually obtained intraoperatively and interpreted by the pathologist in the form of frozen sections. Interpretation of this type of biopsies is however especially challenging and therefore requires a skilled pathologist with sufficient experience in pediatric pathology and with frozen sections in particular. Contrast enema can give a hint as to where the transition zone is located it should however not lead to a false impression of security, as a considerable number of patients has a pathological transition zone more proximal than the one seen on contrast enema (8%) and up to 20%

of newborn patients do not show a transition zone on contrast enema at all. [49] If only suction biopsies were taken to confirm the diagnosis, a good imaging study can hint at the length of affected bowel. In this case the exact localization is left to the intraoperative macroscopic finding paired with the frozen biopsy result. If, however, an unexpected long-segment HD or TCA is discovered after the perineal dissection has already been made the surgeon will be forced into doing a Swenson or Soave repair since the possibility of doing a Duhamel will have been given away by the early dissection. Experienced pathology support for frozen section is therefore crucial for a reliable diagnosis and localization of the transition zone that ensures a safe single stage repair with a removal of only the affected part of the bowel. The equivalent to a good biopsy in HD diagnosis is the accurate identification of the individual anatomy in ARM patients. Generally the diagnosis of the exact type of ARM and identification of the fistula does not necessarily depend on the presence of a colostomy and the distal cologram as sole diagnostic procedure. All the diagnostic equipment needed such as x-ray or MRI and laboratory for urinalysis can usually be expected to be present at hospitals performing PSARP repairs for ARMs. In the rare case, however, where a clear preoperative diagnosis cannot be made and an intraoperative switch to an abdominal approach is not possible if needed, a colostomy can be considered as a safer option.

“The efficiency of medical treatment” as mentioned as the second point by Carcassonne in our opinion depends on mainly two factors: Timing of the repair and the patient’s age and weight at time of the corrective procedure in connection with local availability of pediatric ICU care as well as the experience of the surgical team.

A common approach among many surgeons for HD patients is to wait for the newborn (and diagnosed) child to grow and gain weight before the repair surgery is undertaken. [94] During this time the child will usually receive regular rectal irrigations. Reasons for this might be the hope for better visualization in a bigger child and a decompressed distal colon by the time of the operation [37]. Studies have however shown that many HD patients develop enterocolitis during this waiting period. [37] Additionally a long-time treatment with enema implicates changes to the intestines mucosa and can render a de la Torre repair more difficult.

In ARM patients undergoing the traditional staged repair the waiting period with a colostomy can lead to a significant distension of the bowel and a thickening of the bowel wall. [13] In patients with a fistula connecting bowel and urinary tract the urinary

tract will additionally be constantly contaminated with feces throughout the entire colostomy waiting period [13]. Many studies during the last decades have demonstrated that a primary repair can safely be performed even in newborns – for both HD and ARM patients. [13, 21, 49, 52, 73, 87, 95, 100] For HD patients Pierro and Wilcox in 1997 independently showed that age at the repair operation does not coincide with a higher frequency of postoperative complications and that complications do occur irrespective of age at operation. [56, 88] Also low weight (less than 4 kg) has been shown to be inconsequential for frequency of complications. [92]

On the contrary, an increasing number of advantages to an early operation have been identified over the years. An early definitive repair within the first 3 months shortens the waiting period and reduces the number of washouts thus reducing the risk of chronic proctitis which could complicate an endorectal dissection. [105] Additionally an earlier repair does simply give the patient less time to develop enterocolitis and thus decreases HAECs preoperative incidence [68]. For ARM patients, similar findings have been reported since Moore performed the PSARP as a one-stage repair at birth. [13, 95] In 2004 Liu et al. showed feasibility and safety also in intermediate and high ARMs. In their study also, functional outcome proved equal to that of the staged approach. [21]

Additionally, if the challenge of the small anatomy is overcome with loupes, operating on a younger patient holds several advantages concerning surgical techniques. Firstly, a newborn's pelvis is anatomically more shallow and easier accessible for mobilization of the rectum. [37, 88] Also the colon's fixation to the retroperitoneum is looser which enables a tension-free mobilization with a low rate of ischemia [106] and blood loss can be kept to a minimum. [107] Anastomosis however has been described to be more challenging in newborns. [56] A supposed functional long term-advantage is the fact that the child's anatomy is brought to its' "final state" immediately after birth so that neural connections for physiology of sphincter control and defecation are established and "trained" as early as possible. This might be one factor for earlier repairs seeming to be advantageous for long term continence. [78, 88]

As for the "availability of pediatric ICU care" a great advancement on several levels over the last decades has improved the overall HD treatment significantly.

For HD patients first of all, awareness and a deeper understanding of their disease has increasingly led to an earlier diagnosis thus preventing patients from going undiag-

nosed long enough to develop life-threatening complications. Thus, in our experience, over time less HD patients initially present as emergency cases.

Additionally, ICU care itself evolved greatly during the last decades enabling for a successful outcome even for severely sick children. During the repair operation patients profit additionally from steady improvements in the anesthetic field which originally posed an endangering factor and lead to doubt in the one-stage repair in early stages [66, 92].

In summary an operative center providing one-stage repairs should be able to provide dependable ICU care including nursing care on a high level as well as a team of surgeons experienced in the particular surgical repair technique performed [49] [37]

For HD repairs the center should additionally have a skilled pediatric pathologist at hand to reliably secure diagnosis pre- and above all intraoperatively through frozen biopsies. [37, 49]

1.3.1.5 Remaining colostomy indications

Despite the decreasing popularity of routine diverting colostomy due to the numerous advantages of a single-stage repair, specific indications for colostomy still remain valid for selected patients with HD or ARMs.

First of all, a patient in unstable life-threatening condition who is not eligible for a major surgery such as an HD or ARM repair qualifies for an emergency diverting colostomy to stabilize the patient. [52] Such a situation can be caused by a variety of the following problems, which in themselves are colostomy indications. According to the current literature the remaining colostomy indications in ARM patients are becoming less and less. The official German clinical guideline for ARMs e.g., recommend a temporary colostomy in males and females with a high malformation depicted as air in the rectal pouch cranial to the sacrum in the initial x-ray study and in case of associated malformations and malformations of the sacrum. Additionally, for female patients with cloacal malformations an initial colostomy is advised. In case of a vestibular fistula the guideline left it to the surgeon to decide if a colostomy should be created. [1]

Recent studies however suggest that the choice of the right surgical approach has to be made to individually suit the patients' needs and that a colostomy can be avoided in the vast majority of cases [108].

High ARM

A high malformation as the equivalent to long-segment HD in ARM patients should not regularly lead to a colostomy since the anatomy can be expected to be sufficiently depicted in an adequate x-ray study preoperatively. If however the repair turns out to be more difficult than expected and for some reason a switch to a laparoscopically assisted or open approach is not possible a colostomy can be a temporary solution that should however be considered carefully. [20]

Long-segment HD and TCA

Unsuspectedly finding TCA or long-segment HD in intraoperative frozen section biopsies is a relative indication for ileostomy. If the biopsies are trusted and a close to total colectomy is performed there is no going back if later biopsies demask a pathologist's error in the frozen section reading. Additionally, colectomy is often postponed until stool consistency becomes less fluid which an ileostomy permits to await. [49]

Cloaca patient

One remaining relative indication for a colostomy is the female cloaca patient that was not identified prenatally. Cloacas are considered the most challenging ARMs to repair for a pediatric surgeon and should – at least in cases where the common channel is more than 3 cm – be operated in specialized centers. If a patient like this presents after birth and cannot be transferred to a suitable center immediately a colostomy is indicated. [15]

Associated syndromes and delay in development

One of the syndromes most commonly encountered when dealing with HD and ARM patients is trisomy 21. These patients have been reported to have an overall poorer outcome considering soiling and a higher likelihood for enterocolitis. If enterocolitis is present in the initial evaluation of a patient, a colostomy is often considered the safer option. An additional issue to consider is hindered management of possible complications after an HD repair due to developmental delay that affects the majority of patients

with trisomy 21. Such comprise incontinence constipation or excoriation which may be easier to manage with a permanent colostomy. [49]

In HD as well as ARM patients other associated anomalies such as cardiac malformations with more pressuring threat to health and life should lead to an initial colostomy until the patient is stabilized and ready for the HD repair.

Anastomosis protection and intraoperative difficulties

There are several reasons why surgeons would want to protect a newly created anastomosis in both ARM and HD patients with a proximal colostomy. The most common reasons comprise tension on the anastomosis or insecurity concerning the intestine's blood supply. Unforeseen great volumes of intraoperative blood loss can lead to destabilization of the patient which might make a colostomy the fastest way out of the OR and into ICU. [49]

Severe enterocolitis in HD

The most common emergency indication for a colostomy in HD patients is probably the critical HD patient with severe enterocolitis that does not respond to intravenous fluids, antibiotics and decompression. If sepsis cannot be controlled despite aggressive conservative measures a colostomy can no longer be avoided. [37, 49] If a patient's condition improves under supportive measures, however, the primary endorectal PT can be performed as soon as the patient is stabilized. [37]

Perforation

HD patients may rarely present with bowel (cecal) perforation which will be apparent as free air on an abdominal x-ray. Since the perforation releases the distended colon megacolon will most probably not be visible in these patients. In such cases of atypical bowel perforation that cannot clearly be explained by focal perforation biopsies should be obtained. In some cases enterocolitis is the first hint at coexisting HD. According to the patient's general condition a cecostomy or immediate repair with proximal loop ileostomy should be considered. [49]

Fecal impaction and (toxic) megacolon

If an HD patient is not diagnosed in the newborn period, the time it takes until diagnosis is confirmed gives the agangliotic colon time to massively dilate. In some cases, the extreme dilation may hinder a proper repair PT surgery. Even if enema decompression should be attempted, some of these patients will need a colostomy or ileostomy to adequately tackle their condition. [49, 68, 91] In others conservative measures such as irrigation might take weeks or months to reduce the dilated colon to an operable size. [37]

ARM patients generally face a similar problem if the rectal pouch enlarges with fecal impactation. However, due to their anatomically more obvious malformation they are usually identified earlier than HD patients and thus their risk for complications due to negligence is lower in comparison. However, girls with perineal or even vestibular fistulas are sometimes diagnosed after several weeks of life because initially they pass stool without problem.

Organizational

As mentioned in the chapter on “Considerations and requirements for single stage success” HD diagnosis must be rock-solid before initiating the repair surgery.

Questionable pathology due to lacking access to an experienced pediatric pathologist thus states another colostomy indication.

If the transition zone cannot clearly be identified unsatisfactory outcome is too likely to proceed with repair surgery. A false positive (undetected absence of ganglion cells) reading of the sample will lead to insufficient bowel removal leaving an agangliotic segment in place which will result in additional surgery for removal of the remaining segment. A false negative reading (overseen presence of ganglion cells) will entail unnecessary removal of healthy bowel. [49, 52, 91] In such cases some centers perform a proximal ostomy in the right transverse colon to secure the repair surgery even for cases of a high transition zone proximal to the ostomy. [37] In ARM patients the organizational indication applies for patients with malformations that are too complex to be repaired in the institution they were diagnosed in (e.g. cloacal ARMs).

1.4. Functional long-term outcome

"Long-term follow-up is an important component of patient care." [82]

Evaluation of long-term outcomes in HD and ARM patients is a complex matter.

There are no prospective controlled studies on the matter and long-term follow-up studies are inhomogeneous. The relative rarity of both conditions combined with the needed long-term follow-up to obtain credible data makes comparability of studies and provision of practical instructions challenging. Additionally, a lacking agreement of assessment tools such as a standardized score contributes to the inhomogeneity. [109]

This chapter intends to provide an overview about the findings on functional long-term outcome in HD and ARM patients after repair surgery so far.

Due to the fact that the evolution of HD and ARM correcting procedures and surgical techniques has been ongoing for decades long-term outcomes for the newer techniques could not been reported until recent years. [109, 110]

What can be concluded from the reports published so far is that post-repair HD and ARM patients share a lot of common long-term problems. Both groups are prone to developing incontinence and constipation as the main symptoms. [2, 21, 111] These long-term problems have often been reported to be more severe in ARM patients than in HD patients. A recent study however detected a greater negative impact of long-term complications on the lives of HD patients. [109, 112] Even though in both groups, bowel dysfunction to a certain extent is quite common the majority reaches social continence between adolescence and adulthood. [109]

In the HD group enterocolitis is an additional feared complication. Obstructive symptoms of varying extent are reported to occur in up to 75% of all patients. [37, 39, 45, 113, 114] Roughly 10% of HD patients require a permanent colostomy. [45] Many early studies on long-term complications in ARM patients suggested a good outcome in the majority of the cases with very limited complications. Nowadays this has been doubted and disproven in many studies as the "good" outcome was supposedly due to underreporting of complications and a heterogenous definition of "good" outcome. A good outcome in most studies thus does not mean that the result is equal to the healthy control group. [115-117]

The long-term prognosis depends on several factors such as the initial type of ARM or the extent of the HD respectively, the quality of the surgical repair the preoperative

preparation and associated malformations. The latter comprise especially anomalies of the sacrum which have a significant influence on the prognosis in ARM patients. [118] The frequency of the occurrence of these long-term complications in HD patients, is irrespective of the surgical procedure chosen for the repair according to de la Torre in 2010 and supported by similar studies [37, 119, 120].

In ARM patients the long-term prognosis additionally depends on the type of malformation the patient presents with. Patients with perineal fistulas, rectovestibular fistulas and patients with no fistula usually have a good prognosis considering continence but tend to have problems with constipation. Prognosis in terms of continence is variable in patients with rectourethral fistulas but still satisfactory in most cases with 70%. Constipation is more common in these cases. In recto-vesical fistulas continence can regularly not be achieved due to insufficiently developed pelvic muscles. In cloaca patients about 60% reach sufficient continence, most with a life-long need for enema regimen [22]. Interestingly there seems to be a balance between incontinence and constipation – those patients with an excellent prognosis in terms of continence tend to have higher incidences of constipation and vice versa [1]. In general the long-term outcome of HD and ARM patients has been improving continuously over the last decades with the improvements made in the surgical procedures and the follow up care [2, 121].

Continence

Post-repair HD patients generally tend to have a higher incidence of soiling and urgency as well as more frequent need for laxatives, loperamide or enemas compared to age and sex-matched healthy controls. [112] The same is valid for ARM patients, however, after PSARP repair especially constipation is a common problem. [2, 114]

Continence is defined as the ability to voluntarily initiate a bowel movement without soiling. Incontinence is thus defined as soiling once daily ore more frequently. Overflow soiling secondary to constipation is mentioned in detail in the paragraph on constipation.

Naturally continence usually is achieved around the age of three years which is why well established scores state to be applicable from that age upwards. [2]

Incontinence is a rather common long-term issue in post-repair HD patients after losing (part of) their colorectum and is considered an iatrogenic problem. [110] In ARM

patients the muscles and structures responsible for continence may be injured during the repair but the malformation itself additionally contributes to incontinence being a common problem. [2] Obtaining definite numbers on its occurrence has however proven to be difficult. Most studies on HD report incontinence rates of 3-8%, some however state an incidence of up to 50%. [39, 122] In other studies the incidence of soiling is reported to be as high as 40-65%, adding to the inhomogeneous data of other studies. In ARM patients an incidence for fecal incontinence between 16.7% and 76.7% has been described in a review in 2016. [123] The highly variable numbers once again depict the non-uniform situation considering follow- up studies.

One possible reason to explain this variability are limitations such as proxy bias (questioning the parents about the actual patient) or shame to report a socially uncomfortable issue such as soiling or incontinence which lead experts to believe the unreported number to be much higher than published in some studies. [84, 110, 120, 124]

Incontinence is considered the long-term complication with the greatest negative impact on quality of life. [125, 126]

While a common problem during the first postoperative months and possibly years, incontinence and soiling in many studies has been reported to subside with time. A common consequence of persistent soiling or incontinence is perineal excoriation which has been reported to occur in as many as 50% of all HD patients for a varying length of time after an HD repair procedure and being considered “normal” for the first weeks post-operatively [127]. Usually excoriation or ulceration subside as the number of daily bowel movements and the fecal volume decrease enabling the patient to better control bowel movements. [127].

Many studies have shown that incontinence and soiling are most frequent among younger children while numbers are lower in patients evaluated after adolescence. Adults who have undergone repair for HD in their childhood usually do not show soiling and report full continence in most cases. [74, 82, 83, 86, 127, 128] As one example in a study by Rescorla et al among the patients younger than 5 years 12% presented incontinence or soiling of some degree, while between the age of 10 and 15 years it was only 6% and no patient complained about incontinence after reaching 15 years of age. [82] Also soiling has been reported to be less frequent with increased age. [84] These

trends have however been reported on inconsistently as contrarious findings have been reported from other studies. [78, 80, 129, 130]

To point out one problem of "long-term" outcome studies one may name a study by Langer et al that stated an 80% rate of bowel function "normal for age" among their 141 patients in a 20-month follow-up. However due to the short follow-up period only 13 of 141 had been potty-trained and could be evaluated accordingly. [53]

One third of the adult patients however state occasional soiling, mostly in connection with diarrhea but according to established scores can be considered continent [30, 127]. 68% of adult patients in a study by Heikkinen et al stated to have some degree of incontinence under physical stress or when having severe diarrhea while otherwise continent [128].

While the frequency of bowel movements per week in post-repair HD patients is no different from healthy controls a study from 2007 reported looser stool consistency in patients with a history of long-segment HD. [84]

In general, for a long time it was supposed that HD patients had a positive prognosis considering continence problems. As studies increasingly include adult patients however evidence has emerged that bowel function is significantly impaired throughout HD patients' lives which is mostly manifests in symptoms of constipation and fecal incontinence of some degree. [112]

Additionally, the equivocality problem of "good" outcomes after HD or ARM repair remains that a patient rated as "good" by an established score, does in most cases not have the unimpaired functional continence situation as an entirely healthy control individual of the same age group. [111]

On outcome in patients with Down's Syndrome studies report ambiguously.

While Quinn et al found an impairment of bowel control exceeding that of patients with isolated HD, Stensrud et al found no correlation between Down's Syndrome and increased incidence of soiling. [110, 131]

To achieve continence, many factors have to coaction in a complex way which makes the reasons for soiling and incontinence versatile. As incontinence in HD is considered an iatrogenic complication [110] many surgeons suspect unintended trauma during the repair procedure as a cause. It was suspected that sphincter stretching during TERPT supported the occurrence of incontinence. Stensrud et al, however, found in

2010 that there was no significant difference in long-term soiling in HD patients operated with TERPT and laparoscopically assisted endorectal pull-through (LEPT). [110] Manometric findings have also been shown to be comparable after transanal and abdominal approaches for HD repair. [30, 53, 110, 132] Additionally, manometry has shown no difference when comparing patients with soiling to those without incontinence symptoms of any kind. [84]

In ARM patients the presence or absence of accompanying malformations of the sacrum is considered the most powerful factor in the patients' prognosis for fecal continence [2].

Another possible reason for incontinence in HD patients is a sensational deficit caused by a mucosal incision during TERPT not maintaining a safe distance to the dentate line. [37] The treatment of incontinence in post-HD repair patients should first and foremost consist of conservative management including dietary measures and medicated modification of liquid stools before considering irreversible surgical measures. [39]

Care for ARM patients displaying some degree of incontinence should first of all consist of a good investigation whether the symptoms are a matter of real incontinence or an overflow incontinence or soiling based on constipation. The two can usually be differentiated using rectal palpation and electro-manometry. [1]

Conservative therapy comprises bowel management regimen of retrograde enema and reaches social continence rather than definite functional continence. Another option is the appendicostomy enabling the patients to perform the antegrade enema themselves more comfortably. [1]

For ARM patients, studies have shown that therapeutic intervention – frequently practiced in the past - in form of a reoperation is only successful in very selected cases. Only if the patient originally had a good prognosis and the sigmoid is undamaged, the sacrum is normally developed and the sphincter is intact a completely dislocated rectum should be reoperated [2]. Patients with complex and high ARMs or with associated further anomalies experts advise to refrain from reoperation. It has been shown that these patients do not benefit from reoperation but on the contrary their situation may worsen after another surgical intervention [2]. With increasing popularity of PSARP repair replacing the abdominal pull-through procedures with endorectal dissection of the sigmoid the incidence of fecal incontinence has decreased markedly. [2] This is in line

with Rintala's study from 2002 that found more fecal incontinence after traditional repair methods such as the perineal, sacro-perineal, abdominoperineal and sacroabdominoperineal approaches. [114]

Enterocolitis

Another feared complication in HD patients is enterocolitis. As with continence obtaining concrete numbers on incidence of enterocolitis is difficult despite the quite frequent occurrence of the condition. Problems of definition and differentiation seem to play a major role.

Incidences between 0-42% have been reported in HD patients after one-stage repair depending on the study. [30, 39] A significantly higher incidence was reported after Swenson's pull-through. [39] Incidence for TERPT has been described to be 6% by Langer et al and 35% by Minford et al. [53, 133]

Enterocolitis is known to hold a high share of overall mortality in HD patients. Several studies analyzed 50% of their deaths to be enterocolitis related. [80, 82, 86] Antibiotics and wash-outs are the well-established therapeutic approach [39].

Constipation

Constipation is the most common functional problem after PSARP ARM repair surgery. [6] So far the reason for the high incidence is unknown but it has been identified unrelated to an organic stenosis. [114] Rintala found an incidence of constipation among ARM patients of 30-60% while a more recent review states an even higher incidence of 22.2-86.7%. [114, 123] The highest incidence was shown among those patients who had a urethral (bulbar fistula 55.5%, prostatic fistula 41.4%) or vestibular fistula (61.4%). The lowest incidence was reported among those with a high ARM (18.2% in bladder neck fistula, 25% in vaginal fistula). Patients with perineal fistula showed severe constipation in 28.6% of all cases. [6]

If constipation is neglected and remains untreated it can lead to overflow pseudoincontinence. [2] It occurs in patients with chronic constipation when bacteria dissolve the retained stool, and the visible symptom is soiling and seeming incontinence. Interestingly it almost exclusively occurs in patients with benign malformations without as-

sociated anomalies and a good prognosis after immaculate surgical repair. Also, patients with the worst prognosis considering continence least frequently suffer from constipation [2]. Chronic constipation has been reported to occur more frequently in patients with a high degree of sacral mobilization of the rectal pouch during the repair surgery [4]. The therapy of constipation should comprise medication, dietary adjustments and physiotherapy to strengthen the muscles of the pelvic floor. As for patients with incontinence similar bowel management programs for patients suffering from constipation can be employed [1]. The main reasons for obstructive symptoms in HD patients comprise mechanical obstruction, recurrent or acquired aganglionosis, proximal motility disorder, internal sphincter achalasia, functional megacolon. [30]

Mechanical obstruction

Mechanical obstruction can be caused by several different anatomical divergences. Amongst others the development of an anastomotic stricture, formation of adhesions secondary to a (mostly) open repair procedure, unintended bowel twisting during repair surgery. [53]

Another common cause is a rolling down and narrowing of the muscular cuff after ERPT, causing mechanical obstruction. [53] This can be avoided in most cases by leaving a shorter cuff. [37, 55]

Recurrent or acquired aganglionosis

A residual agangliotic segment may be found after insufficient removal. This may be due to a too high anastomosis using agangliotic bowel that later causes constriction. Another reason may be histological error in reading of frozen sections on which intraoperative identification of the transition zone is based.

In some cases it has been described that ganglion cells are lost over time. [134]

In such cases a repeat pull-through procedure is the therapeutic approach.

Motility disorder in the proximal bowel

Despite of its regular ganglion cells the normally innervated bowel in HD patients is known to present motility disorders that can cause obstructive symptoms of varying

degree. If the anomaly is focal a repeat pull-through with removal is the therapy of choice. [37] There are studies which likewise suggest an impaired motility in ARM patients as one contributing factor in constipation. [4, 114]

Internal sphincter achalasia

Typical for all HD patients is the absence of a recto-anal inhibitory reflex which leaves them unable to relax their internal sphincter. Many patients overcome this problem with time and develop normal function but in others it may result in obstructive symptoms.

Since an improvement with time has been reported corrective surgical measures such as myectomy should be considered carefully.[37]

In the majority of all ARM patients the preservation of a functioning internal sphincter can be achieved with PSARP even in high and intermediate ARMs. This way postoperatively the internal sphincter can keep up the anal resting pressure and contribute to the patient's continence. [121, 135]

Functional megacolon

Lastly functional problems such as stool-holding habits that can result in severe stool accumulation and megacolon. Therapy usually consists of dietary and behavioral modification as well as the use of laxatives. [37] In ARM patients it has additionally been shown that patients with a history of megarectum present with a significantly higher degree of constipation than those who did not develop megarectum. [20]

Overflow soiling

Overflow soiling may appear as soiling as a symptom of incontinence.

As the name implies however, overflow soiling is a paradox symptom of constipation. Held-back stool is decomposed by bacteria and thus liquified. The visible symptom is therefore soiling as if the patient had a too loose stool consistency despite the constipation that poses the actual problem.

This can occur due to sensational defects after repair surgery that leave the patient unable to sense an urge to defecate. [114]

Overflow soiling is in fact thought to be more frequent than soiling due to sphincter insufficiency and at the same time treatable more easily. [114] Additionally, overflow incontinence and functional soiling has been shown to improve with time in HD as well as ARM. [37, 114]

Postoperatively arising constipation that remains untreated can result in fecal impaction and consequently in overflow pseudo-incontinence. [2] The treatment of pseudo-incontinence should focus on relieving the constipation which will eventually lead to satisfactory continence in the vast majority of the cases. [2] The greatest risk for this group of patients lies in falsely treating them for actual fecal incontinence possibly further aggravating the fecal impaction situation. [2]

Recently obstructive symptoms have been reported to occur more frequently in patients with Down's Syndrome. Patients who have long-segment HD show in fact a lower incidence of constipation, instead they are more prone to developing distension, enterocolitis and vomiting [37]. Repair surgeries in Rehbein, Soave, Swenson and Duhamel technique have similar incidence of complications as Holschneider and Nixon showed [129, 130].

There has been reported to be no difference in continence and stooling patterns between TERPT and transabdominal (i.e. open) correcting procedures. The open repair however resulted in more cases of enterocolitis and more bowel movements per day. [30] Other studies comparing TERPT and open procedures found that TERPT patients were more likely to be completely continent in the follow-up while having a lower risk of early and late complications as well as HAEC. [106, 136] Comparing TEPT (total endorectal pull-through) and LEPT (laparoscopically assisted endorectal pull-through) constipation as well as soiling problems have been shown to be comparable in both groups. Early follow-ups showed a higher incidence of soiling among LEPT patients which had been resolved by the next control 4 years later. [110]

Even if early problems of constipation, incontinence or enterocolitis are rather common HD have a positive long-term prognosis regardless of the surgical procedure

chosen for their repair. [37] HD repair shows steadily improving long-term outcome especially in comparison to ARM patients. [112, 121]

Urinary and sexual problems

As recent studies increasingly focus on long-term outcomes the impact of HD and its repair on urinary and sexual functioning are being increasingly evaluated alongside fecal continence. When compared to a healthy control group, post-repair HD patients report no difference in urinary leakage according to Gustafson et al. Catto-Smith et al however report an enuresis incidence of 25% with long-segment HD patients being more likely to have day- and night-time enuresis. [84] Bladder emptying, and sexual functioning has been reported impaired in male patients as post-repair HD patients show a significantly higher incidence of problems with ejaculation than healthy controls. Erectile problems were not reported more frequently in any of the two groups. This is most likely caused by unintended damage to the spermatic duct or nervous innervation around the bladder neck during the dissection. [112] The group most frequently affected by urinary incontinence however are female ARM patients with a congenital cloaca defect. A long-term follow-up study that followed the patients for 11.3 years showed a urinary continence rate of 80% leaving 20% with urinary disfunction of varying extent. [22]

Lastly as mentioned above it is important to keep in mind that a “good” outcome does not compare to a patient born with a perfectly functional bowel and thus does not describe a normal bowel function. [114, 137]

“Every child should therefore be followed up on a regular basis until at least the age of 5 years, or longer if they are still having problems at that point”, as De la Torre wrote. [37]

Bowel function in later adult life in post-repair HD patients remains unknown until further long-term studies emerge that follow patients to an advanced age when bowel function might deteriorate [138].

1.5. QOL Outcome in studies today

The field of long-term outcome considering the patients' quality of life in everyday life is not easy to evaluate as it covers many factors that are hard to categorize. Inherently it comprises numerous aspects that are difficult to grasp such as physical as well as mental health, psychosocial adjustment, family and peer group support, socioeconomic status and educational achievement [139]. In addition, perception of QOL is highly individual and depending on social context as well.

Studies so far conducted on QOL-outcome in ARM and HD patients have focused on the three domains of physical, mental and social impact of the disease on patient's lives. Over the years several scores have been developed aiming to provide tools to gather more standardized and thus more reliable data. Unfortunately, there has yet to be found a consensus on which score to use internationally and until now studies have shown to be heterogenous in that matter and therefore hard to compare.

Some of the QOL questionnaires in use are the SF-36 (which was not designed for the special group of ARM and HD patients in particular), the GIQLI (Gastrointestinal Quality of Life Index) as well as QOL Scores suggested by Bai et al and Barrena et al ([127, 140]).

When regarding patients' long-term QOL-outcome it can never be assessed entirely separately from the functional long-term outcome as the two are inherently intertwined.

While several studies have shown that bad functional outcome does not necessarily correlate with an impaired QOL when compared to a healthy control group [117, 141] many have concluded that the impact the often impaired bowel function poses to the patients' QOL is a lifelong issue that needs structured long-term follow up [112].

Therefore, it is essential to not just evaluate the functional outcome and draw conclusions regarding the QOL but to evaluate the QOL separately and with a widely used score instrument. It is not surprising that many studies have found a significantly lower QOL in patients after repair of anorectal malformation or HD than healthy controls [140, 142].

Incontinence has been identified as the factor with most negative influence when quality of life is evaluated [125]. The inability to control one's bowel movements results in physical and psychological stress [143] and in many patients a non-satisfactory school performance has been shown as a result of continence problems [39].

Also, Social activities are reported to be limited due to soiling, incontinence or odor in about 15% of all post-repair HD patients in a long-term study on QOL conducted in 2007. [84] In the same study 11% of all patients reported to limit their physical activity to prevent soiling. Roughly 18% reported having been picked on in social context for odor or soiling [84]. Absence from school due to their bowel condition was more frequent in HD patients with long-segment disease before their repair and in those patients, who reported soiling incidences [84]. Hassink et al. showed a direct impact of fecal incontinence on patient's level of education as well as their social relationships including the ability to make new friends [141]. Children with additional challenges such as associated malformations of the heart, vertebrae, trachea or anorectal malformations as well as patients with limb abnormalities such as VACTERL association scored lower in terms of QOL than otherwise healthy patients in a study by Raman et. al. [117]. The same study however found no effect on QOL caused by the patient's age when interviewed, the type of anomaly as well as the type of surgical procedure. In Gustafson et. al. HD patients reported a significantly greater dissatisfaction with their bowel movement in general as well as the bowels negative impact on their everyday life when compared to healthy controls and Järvi at al as well as Granström et. al. found a lower result in the GIQLI questionnaire in HD patients (compared to healthy controls) [112] [138] [142].

With increasing age QOL has been reported to improve even if functional impairment remains unchanged [117] in some studies while others could show a negative effect of increasing age on QOL [29, 138]. Some Studies differentiated partly incongruent findings as to that HD patients showed an impairment concerning the disease specific QOL but scoring normal in non-specific QOL questionnaires [112, 142]. First findings considering resilience factors found by Dietesheim et. al. in 2017 showing that support from family and peers were associated with a higher level of QOL in adolescents with major impairment of defecation [144].

In the broad field of malformations of the intestine and the patient's long-term QOL after a surgical repair the literature comparing HD and ARM patients is yet hard to find. The studies which focused on the aspect often state a better QOL in HD patients compared to ARM patients often in correlation with a better functional outcome.

Gustafson et. al. however, suggested to reconsider this fact since they found only slight differences when comparing the two groups in terms of QOL as did Rintala et. al. in 2010 [109, 112].

1.6. View and aim of this study

The aim of this study was to compare patients' long-term outcome after primary and multiple-staged repair regarding bowel function and quality of life. This is the first study with this specific focus. Since research on long-term outcome in this area is yet scarce, we intended to explore the hypothesis and clinical observation that single-stage repair comes not only with less complications and short-term outcome but also with a more favorable long-term outcome concerning bowel function and quality of life. Our multi center cross-sectional study design was set up to provide solid data comparing long-term outcome between single-stage repair and three-staged repair to standardize and improve care for anorectal malformations (ARM) and Hirschsprung's Disease (HD) patients.

2. Patients and methods

2.1. Study design

In our multicentric, retrospective, observational study we collected data from patients operated for the diagnoses of anorectal malformation (abbreviated as ARM in the following) or Hirschsprung's Disease (abbreviated as HD) in the German medical centers of Mutterhaus der Borromäerinnen in Trier and University Hospital Duesseldorf (Universitätsklinik Düsseldorf) between the years of 2002 and 2018. Included were patients with formation of an ostomy and subsequent corrective procedure as well as those who received a single stage repair. Data was obtained by reviewing patient charts from the time period of the hospitalizations for the surgical procedure and conducting telephone interviews. Long-term outcome concerning functionality as well as quality of life were determined using the Krickenbeck criteria [4] and the Wildhaber Score [74] as well as the Criteria from Bai et al [140] and Barrena et. al.[127].

2.2. Patient population

Inclusion criteria

In our study we aimed to include all patients who received surgery for Hirschsprung's Disease (HD) or anorectal malformation (ARM) in the departments of pediatric surgery in our German study centers of University Hospital Duesseldorf (Universitätsklinikum Düsseldorf) and Mutterhaus der Borromäerinnen in Trier between the years of 2002 and 2018 (n=112). For HD patients only those patients were included whose diagnosis was confirmed with rectal biopsies. One participant with their main operation in 1992 (n=1) was additionally included due to complete record in archive.

Exclusion criteria

Those patients in whom Hirschsprung's disease was suspected but not confirmed were excluded from the study (n=4). Due to validity criteria of Krickenbeck score patients who at the time of the interview had not filled 3 years of age were likewise excluded (n=10). In cases where the main surgical repair took place in a hospital other than our study centers they were only included if date of main surgery, length of hospi-

talization and number of operations in general anesthesia could clearly be tracked by operation reports and doctors notes from the patient record (n=4). We excluded 2 patients with insufficient information from their patient's records (n=2) and 4 patients who had died from other causes than the intestinal malformation (n=4). 48 patients initially registered to take part in the study could not be included due to, incorrect or lack of contact information (n=48). After contact 8 denied consent (n=8) and 1 patient had to be excluded due to an incomplete consent form (n=1).

ICD 10 code	Description	included
Q42 Congenital absence, atresia and stenosis of intestine		
Q42.0	Congenital absence, atresia and stenosis of rectum with fistula	all
Q42.1	Congenital absence, atresia and stenosis of rectum without fistula	all
Q42.2	Congenital absence, atresia and stenosis of anus with fistula	
Q42.3	Congenital absence, atresia and stenosis of anus without fistula	all
Q42.8	Congenital absence, atresia and stenosis of other parts of large intestine	selected
Q42.9	Congenital absence, atresia and stenosis of large intestine, part unspecified	selected
Q43 Other congenital malformations of intestine		
Q43.1	Hirschsprung's Disease	all
Q43.2	Other congenital functional disorders of colon	selected
Q43.5	Ectopic anus	all
Q43.6	Congenital fistula of rectum and anus	all
Q43.7	Persistent cloaca	all
Q43.8	Other specified congenital malformations of intestine	selected
Q43.9	Congenital malformation of intestine, unspecified	selected
Q42 Congenital absence, atresia and stenosis of intestine		
Q42.0	Congenital absence, atresia and stenosis of rectum with fistula	all
Q42.1	Congenital absence, atresia and stenosis of rectum without fistula	all

Table 7 Patients included according to ICD 10

Recruitment

The digital patient archives of our study centers were searched for patients operated on between January 2002 and December 2018 with diagnoses as listed in Table 7. The patients found were screened according to the inclusion criteria.

In a next step the patients identified were contacted and informed about the study via mail. Information in easy language adequate for the patients age were provided where necessary. Consent was given by the patient or parent signing the consent form and stating their current phone number for the interview. In patients over 16 years of age return of the consent from signed by the patients themselves was obligatory while patients aged 3 years or older were given the opportunity to give consent voluntarily.

Those who did not respond until after the deadline or whose letters were returned due to a change of address in the meantime, were contacted once via phone call where numbers were still correct and invited to participate in the study. We tried to contact all patients nationally and internationally in the cases where they had moved abroad in the meantime. The recruiting process and the number of selected patients as well as reasons for not participating are shown in Fig. 2.

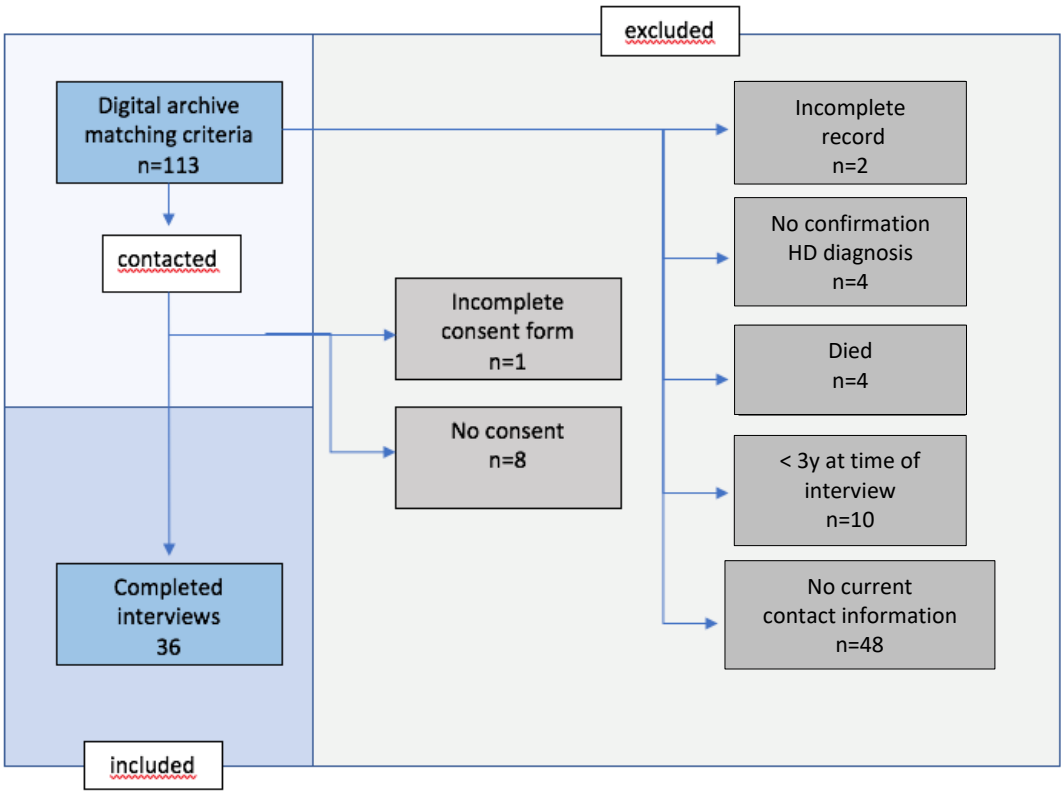

Fig. 2 **Recruiting process**

2.3. Data collection

2.3.1 Review of patient records

From the patient chart from the time of hospitalization at diagnosis and repair surgery the following data was collected:

Sex, birthdate, premature (≤ 36+6) or mature born (> 37weeks), age at definite repair surgery, number of surgical procedures, count of bougienage interventions and rectoscopies in general anesthesia, occurrence, time of presentation and type of complications, underlying disease (anorectal malformation or Hirschsprung's disease), length of segment in HD patients and type of anorectal malformation respectively, ICD10 code as stated in physicians report on the repair surgery, type of surgery performed, primary creation of ostomy or single-stage repair, length of time until ostomy reversal, associated diagnoses, count of hospitalizations due to the main diagnosis, overall duration of inpatient time (in days) and hospital and year of repair surgery. Patients with formation of an ostomy as a means to control complications after a primary repair were not part of the three-stage repair group. The first surgery being the creation of an ostomy, also in case of decompensation, made the patients part of the three-stage-repair group.

The type of anomaly was ranked by ICD10 and categorized as HD, ARM with or without fistula as stated in repair surgery's record. The position of fistula was likewise grouped as noted in the correcting procedures operation note. The length of the HD segment was retrieved from histological report where existing. In cases where length was taken from operation log if stated e.g. "10-15cm" the median was noted.

Dilatations performed by trained parents were not included in the count for bougienage and rectoscopy.

Hospitalizations clearly caused by associated diagnoses (VACTERL etc.) irrespective of the intestinal anomaly were excluded from the count. Hospitalizations for gastroenteritis on the pediatric ward were not counted while hospitalizations on the pediatric ward for enema treatments due to obstipation were considered relevant and added to the count. In patients with multiple malformations and "all-in-one" surgical procedures the hospitalization length was counted from first day of hospitalization until the first transfer from ICU to normal ward or to point of time where intestinal malformation was no longer the reason for hospitalization. Counted as surgical interventions were correcting procedure, ostomy revision or reversal as well as any other operation arising from com-

plications of the disease with the necessity for general anesthesia. Not included were cases of general anesthesia or sedation for imaging procedures such as MRI. Surgeries before the initial diagnosis were not counted (in one case anal abscess had to be treated surgically twice before adequate therapy was initiated). Complications were categorized by their time of occurrence into preoperative, perioperative and postoperative complications. Further the complications registered were ranked by severity from 1 (minor complication) to 3 (severe complication), 2 ranking as moderate complication. As “minor complications” or “grade 1” those complications were ranked that could be managed conservatively and did not require surgical intervention, did not pose a threat to life and did not cause a lasting disability. Ranked as “moderate” or “grade 2” were those complications that did require additional surgical intervention of minor extent but were neither life threatening nor causing a lasting disability. Considered as “severe” or “grade 3” were complications that posed acute danger to the patient’s life or that required an emergency or severe surgical intervention as well as those complications resulting in lasting disabilities or death. If more than one complication occurred, the severity of the most serious complication was registered. Since complications in the pre-operative period cannot be attributed to the surgical procedure as the causing factor those complications were not included to compare and determine the outcome of the single and multi-stage-repair group.

2.3.2 Interview

The Interviews were conducted via phone call consulting either the parents or the patients themselves where age enabled them to give adequate answers.

If not reached in a first call, at least three further calls were made before giving up on the patient’s inclusion in the study. The data earlier retrieved from the patient’s record was verified and confirmed by the parent or patient. Missing data from the patient record was added after obtaining the information from the parent or patient during the interview. Likewise, during the interview, the number of surgical procedures was verified and where necessary supplemented with procedures performed until the day of the interview as stated by the parent or patient. The main interview was conducted using the questionnaire as depicted in the appendix.

It was additionally asked if any surgeries, therapeutic procedures were performed outside of our study centers in the meantime or if any new complications had to be treated. Lastly it was inquired if any additional or special treatment measures were taken such as biofeedback training, physiotherapy or regular dilatations etc.

In patients with associated malformations, we asked the patient or parent to answer each question specifically regarding the limitations that could be attributed to the intestinal anomaly alone. (If for example a patient who showed mental retardation had problems leaving the house alone, we asked if the circumstances would be the same or different if the child had suffered from the intestinal anomaly only.) This was to measure the influence the intestinal anomaly had on QOL outcome as specifically as possible to avoid confounding through accompanying malformations or handicaps.

Since in patients who currently had an ostomy continence could not be evaluated adequately, they were excluded from questions concerning soiling and incontinence etc. while QOL questions were evaluated without restrictions.

2.4. Material

2.4.1 Scores

To evaluate long-term outcome in terms of function and quality of life preexisting scoring systems were employed.

2.4.1.1 Functional outcome - Krickenbeck Criteria and Wildhaber Score

As the evaluation of functional outcome is complex and involves many factors an international consensus of an evaluation tool has yet to be found. In our study we decided to use the Krickenbeck criteria with a secondary modification to simplify the outcome as good, fair and poor, as often done in other scores. We also made use of the numerical Score by Wildhaber et al [74]. The Krickenbeck criteria as depicted in Table 8 formed the basis of the functional portion of the questionnaire used in our interviews together with the items of the Wildhaber Score (Table 9).

International Krickenbeck classification for postoperative results according to Holschneider et. al.		
1. Voluntary bowel movements		Yes / No
	Feeling of urge	
	Capacity to verbalize	
	Hold the bowel movement	
2. Soiling		Yes / No
	Grade 1	Occasionally (1-2/week)
	Grade 2	Every day, no social problem
	Grade 3	Everyday, social problem
3. Constipation		Yes / No
	Grade 1	Manageable with dietary adjustments
	Grade 2	Need for laxatives
	Grade 3	Resistant to laxatives and diet

Table 8 **International Krickenbeck criteria according to Holschneider et. al.**

The Krickenbeck criteria Table 8 takes into consideration three main variables: voluntary bowel movement, soiling and constipation and is valid in children 3 years of age or older. It is supposed to help evaluate the outcome in patients currently not undergoing therapy. [4]

Voluntary bowel movement is defined as presence of a feeling of urge, the capacity to verbalize this urge and the ability to hold the bowel movement. Only if all of those three sub-variables are affirmed "voluntary bowel movement" is considered present.

Soiling and constipation are subdivided into grade 1, 2 and 3 depending on the frequency of occurrence. Occasional soiling once or twice per week is defined as grade 1, daily soiling without social problems resulting from it is considered grade 2 soiling and daily soiling as cause of social problems is defined as grade 3 soiling.

Constipation grade 1 are constipation symptoms that can be successfully managed with dietary adjustments while grade 2 constipation is defined as constipation only manageable with laxatives. Grade 3 constipation is defined as constipation not satisfactorily treatable with laxatives and or dietary adjustments. [4]

Subsequently patients were grouped into three groups defining their outcome as good, fair and poor taking into consideration all their answers.

A good outcome was attributed to patients with voluntary bowel movement (urge, announcement and ability to hold stool as defined above), no or occasional (once to twice per week) soiling and no constipation or constipation that is successfully treated with dietary measures. Patients were assigned to the fair outcome group if voluntary bowel movement was present, occasional (once to twice per week) soiling or daily soiling without social impact and constipation that was treatable with dietary measures or laxatives.

The remaining patients were scored with a poor outcome. All continuous stoma patients as well as those in need of frequent enemas were attributed a poor outcome as well as those patients with absence of voluntary bowel movement or presence of daily soiling with social implications.

Score criteria functional outcome from Wildhaber et. al. 2005			
Items	**Score 2**	**Score 1**	**Score 0**
Frequency of defecation	1-2/d	3-5/d	>5/d
Stool consistency	Normal	Loose	Liquid
Soiling	No	Stress/ diarrhea	Constant
Stool sensation	Normal	Uncertain	Absent
Discrimination between wel formed vs liquid	Normal	Deficient	Missing
Longterm use of medication (enemas, drugs…)	None	Occasionally	continuously
Diapers required	None	occasionally	Permanently
Range of Scores	**11-14**	**6-10**	**0-5**
Objective functional outcome	**Good**	**Fair**	**poor**

Table 9 Wildhaber Score (modified according to Barena et. al.)

The Wildhaber Score [74] was used to gain better comparability by using a numerical score in addition to the qualitative Krickenbeck Score.

As depicted in Table 9 this Score (modified after Barrena et al[127]) includes items related to functional outcome and necessity of supportive measures such as medication and diapers. Each answer scores a certain number of points which are then used to calculate the total score. The Wildhaber Score then defines three groups of “good”, “fair” and “poor” functional outcome according to the total number of points. Two patients

who were 3 years old were still wearing diapers. They were attributed 2 points in the Score regarding their need for diapers as age appropriate.

2.4.1.2 Quality of Life Scores – Barrena and Bai Criteria

The quality of life in patients after surgical repair of anorectal malformations or Hirschsprung's disease was evaluated by collecting data with a questionnaire containing items of two QOL scoring systems used in earlier studies. The areas evaluated include the diseases' impact on physical, mental and social functioning in everyday life.

Quality of life scoring criteria for children with fecal incontinence according to Bai et. al.		
Items	**Criteria**	**Points**
Soiling	Absent	4
	Accidental	3
	Frequent	2
Incontinence	Accidental	1
	Frequent	0
School absence	Never	2
	Accidental	1
	Frequent	0
Unhappy or anxious	Never	2
	Accidental	1
	Frequent	0
Food restrictions	No	2
	Somewhat	1
	Much	0
Peer rejection	Never	2
	Accidental	1
	Frequent	0
Good 9-12 points, fair 5-8 points, poor 0-4 points		

Table 10 Quality of life Score criteria from Bai et al [140]

Our QOL part of the questionnaire was based on items from the quality-of-life-score by Bai et al [140] as well as from Barrena et al [127]. The items of the scores are depicted in tables Table 10 and Table 11. Both Scores are numerical scores where points are given for each answer and a total Score is counted. Subsequently they both differentiate between patients with a "good", "fair" and a "poor" outcome. The ranges of points for each group are included in Table 10 and Table 11 respectively.

Quality of life Score criteria and points from Barrena et al 2008		
Items		**Score**
Dietary habit		
No feeding restrictions		3
Some feeding restrictions		2
Serious feeding restrictions		1
Schooling and work		
Normal daily activities		3
No regular activities		2
No activities		1
Leisure		
Regular sports, excursions etc.		3
Only occasionally and with precautions		2
No regular leisure activities		1
Impact of disease on personality		
No impact		3
Some impact		2
Serious impact (incapacitating disease)		1
Family life		
No influence on the family		3
The disease deteriorated family life		2
The disease devastated family life		1
Good 11-15, fair 6-10, poor 0-5 points		

Table 11 Quality of life Score criteria from Barrena et al [127]

2.5. Questionnaire

Our non-validated questionnaire used for the interviews contained a series of questions derived from the scores we intended to use for later data analysis.

It comprises questions providing information concerning bowel function, urinary function, limitations in physical activity, limitations in everyday life, effects on family life, social exclusion, sexuality (erectile dysfunction in males), impairment of schooling and career as well as feelings of inferiority in terms of likeability and attractivity, insecurity and unhappiness.

The respective questions and specific criteria can be reviewed in detail by studying the copy of the questionnaire in the appendix. The questions were adapted to the respective age of the patient and their expected daily activities (e.g. regular kindergarten/school/work attendance).

2.6. Statistical analysis and computer programs

Our hypothesis was that patients who underwent a one-stage repair of their anorectal malformation or Hirschsprung's disease without a temporary ostomy show better long-term results regarding functional outcome as well as quality of life. This hypothesis was evaluated using Fisher's exact test and T-test where appropriate, to compare the two groups in terms of their total scoring count in the Scores named above. The null hypothesis therefore was that there is no significant difference between those patients with a single-stage repair of their malformation and the group that received correction surgery in combination with a temporary ostomy regarding long-term outcome in terms of functionality and quality of life.

The studies primary target parameters were functionality and quality of life which were objectified as total score counts. Those then were processed with standard statistical methods and depicted as mean and range if not stated otherwise.

Groups were compared using Student's T-test with $p < 0.05$ defining significance of the findings. Since the Krickenbeck criteria do not offer a linear score the criteria were processed as all other categorical items with Fisher's two-tailed exact test ($p < 0.05$ defining significance).

Data retrieved from the patients' records was compiled in a table using Microsoft® Excel for Mac, Version 16.34 (© 2020 Microsoft, Redmond, Washington, USA). The

table was later filled in with the current information obtained during the interviews. The scoring into groups of "good", "fair" and "poor" outcome was then calculated based on this table using an Excel® formula. Additionally, Excel was used to perform the T-test where needed to compare numerical items. Further data analysis was performed using R (r-project.org, The R Project for Statistical Computing, © The R Foundation, R 3.6.1 GUI 1.70 El Capitan build (7684)) for Fisher's exact test. Due to the small number of complete Data sets Chi-Square-Test could not be employed.

The result of the statistical tests is the level of significance p (p-value). The smaller the resulting p-value the higher the probability that H0 (null hypothesis, no difference between the compared groups) can be rejected and H1 (which states that a difference between the compared groups does exist) can be accepted. The probability of falsely accepting H0 is given as level of significance α. As in our study mostly $\alpha<0.05$ is considered significant, which means that usually when showing a p-value of <0.05 the difference shown between two groups is considered to not be caused by coincidence.

2.7. Ethics and data security

Our study received ethical approval from the local research ethics committee of University Hospital Duesseldorf (approval Number 5601, dated 23rd February 2018) as well as the committee affiliated with Mutterhaus der Borromäerinnen Trier (approval number 2019-14621 dated 17th October 2019). Approval was also attained for the Hospital Munich Schwabing before limited resources forced us to exclude further centers from the study.

Pseudonyms generated with randomized number codes were used whenever the patient's data was processed. Since we had to be able to decode the pseudonyms to contact the patients for the interview an entirely anonymous data storage was not an option for this study. Patient's data, results from the interviews and all decoding files were stored separately at all times with access only to the study's leading physician.

3. Results

3.1. Patient collective

Of the total of 36 complete data sets 17 were provided by ARM patients (47%) and 19 by HD patients (53%). 22 out of the 36 (61%) were male patients, 14 (39%) were female. 21 patients interviewed were recruited from UKD (University Hospital Duesseldorf) (58,3%), 11 were recruited from MBT (Mutterhaus der Borromäerinnen Trier) (30,6%), 3 patients had their main surgery in different hospitals in Germany (8,3%) and one patient received repair surgery in a clinic in Japan (2,8%) (Fig. 3).

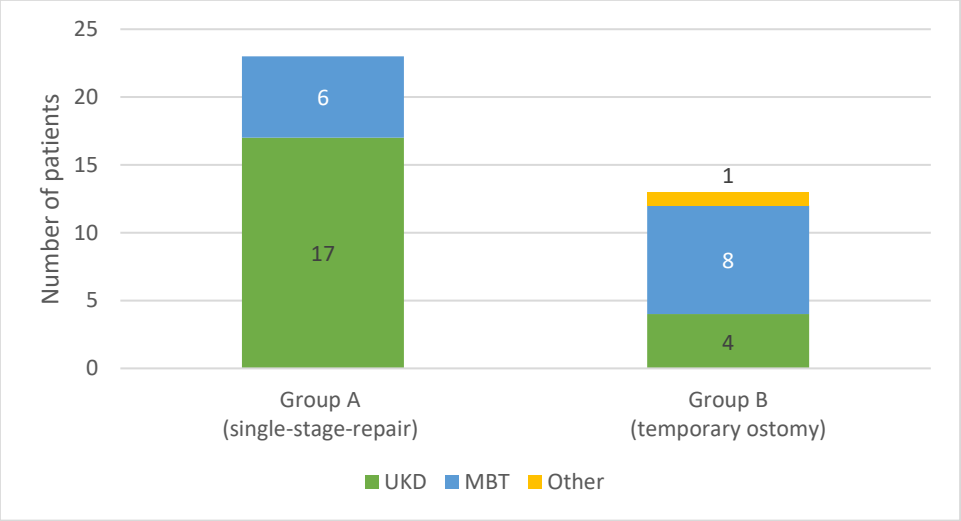

Fig. 3 **Patients numbers from each center operated in**

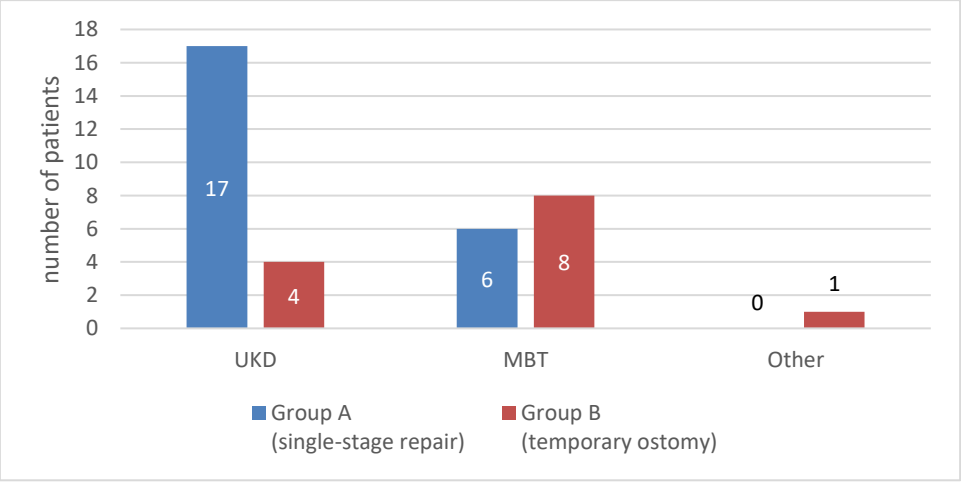

Fig. 4 **Single-stage and three-stage approach per clinic**

The majority of patients from University Hospital Duesseldorf (UKD) received a single-stage repair (80% Group A, 20% Group B) while in Mutterhaus der Borromäerinnen (MBT) the ratio between the two procedures was more balanced (43% Group A, 57% Group B) (Fig. 4).

11% (4) were born prematurely while 89% (32) were term infants.

Among the ARM patients 1 presented with anal stenosis without fistula, 10 had perineal cutaneous fistula, 5 had vestibular fistula, one presented with bulbourethral fistula,

And one patient had total colonic agenesis.

Among HD patients 17 had aganglionosis affecting 8-30 cm of the colon while one patient presented TCA.

All patients were divided into two groups: group A being the patients who received primary repair (single-stage repair) and group B being the patients undergoing planned colostomy before the main repair surgery (three-stage repair).

23 patients were included in group A, 13 patients were part of group B.

In group A with one-stage repair 48% (11) were ARM patients, 52% (12) HD were patients. 46% (6) of group B with primary ostomy and secondary repair were ARM patients, 54% (7) were HD patients (Fig. 5).

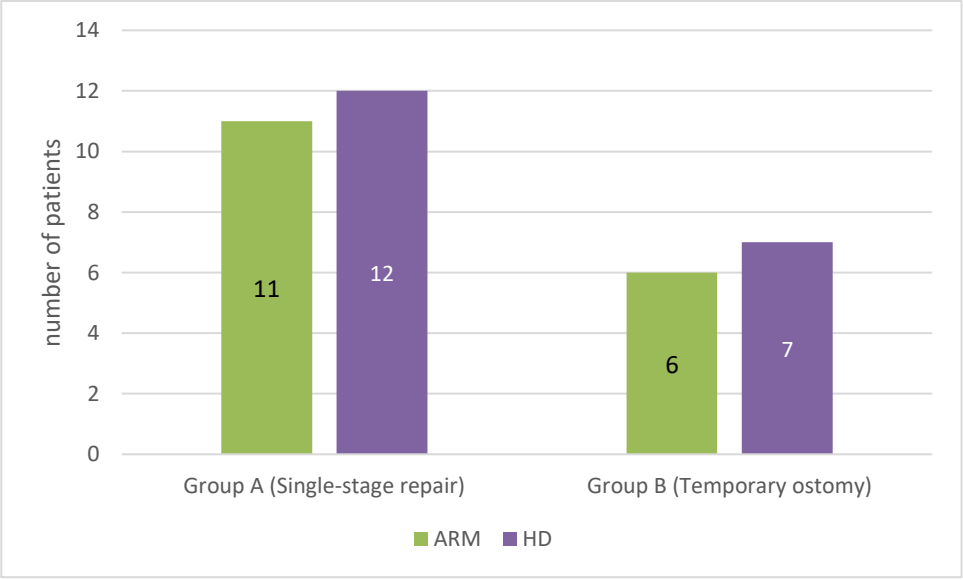

Fig. 5 **Distribution ARM and HD patients among Group A and B**

7 had Trisomy 21, VACTERL Syndrome was presented in 2 patients, 3 had cardiac malformations, 2 patients had urinary tract malformations, each one patient had tethered chord syndrome, malrotation of small intestine and urethral duplication, caudal regression syndrome, diabetes mellitus and one patient was deaf as well as mentally impaired.

15 patients had no comorbidity.

Associated syndromes were similarly distributed between Group A and Group B as well as between ARM and HD patients (Fig. 7) accounting for 57% (13 patients) in Group A group and 46% (6 patients) in Group B (Fig. 6).

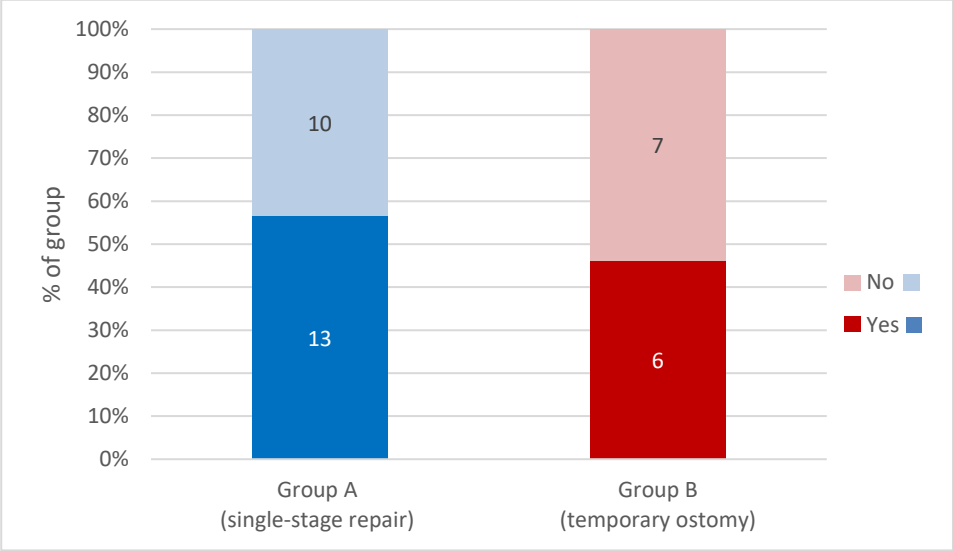

Fig. 6 Proportion of patients with other malformations in Group A and B

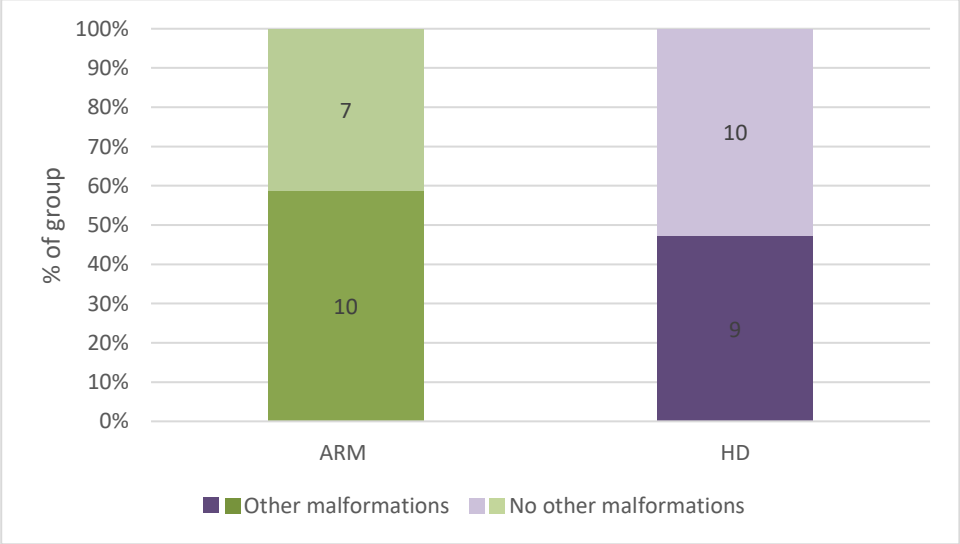

Fig. 7 Other malformations in HD and ARM group

Among the HD patients 9 received de la Torre repair surgery, 2 received Swenson repair, one received Duhamel repair, one had total proctocolectomy, partial resection of the colon (without further definition of the surgical technique) was registered twice as well as perianal excision with colorectal anastomosis. In 2 HD patients no record could be found concerning the definite surgical procedure.

Among ARM patients 14 had undergone PSARP procedures, one YV plastic and one abdominoperineal pull-through procedure was registered. In one ARM patient records of the exact procedure were missing.

The patients' age at the time of their repair surgery is shown below in Fig. 8. 7 patients were less than 7 days old, 2 were 8-14 days old, 4 patients were 15-21 days old, 2 were between 1 and 3 months old, 5 were 3-6 months old, 12 were 6-12 months old, 2 were between 1 and 2 years old and 2 were between 2 and 3 years old when their repair surgery was performed. The distribution of age at repair surgery between Group A and Group B is given in Fig. 8, showing a statistically non-significant tendency of older age at repair in Group B (p=0,31).

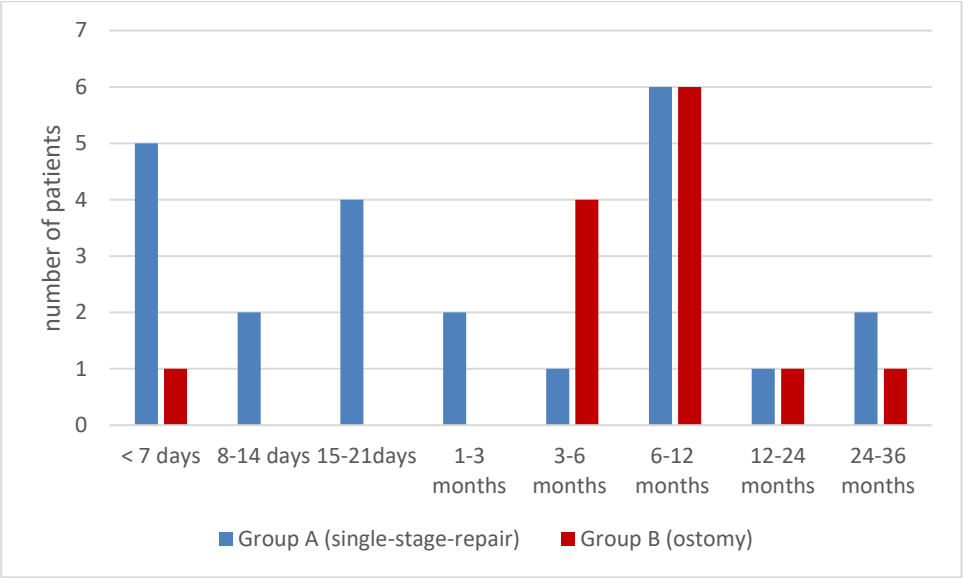

Fig. 8 Age at repair surgery

Mean follow up time was 8.1 years (range 1.8 to 24 years) after repair. 6.9 years (range 1.8 to 16.7 years) in group A (single-stage-repair) and slightly higher in Group B (ostomy) with 10.3 years (range 2,4 to 24 years) as shown in Fig. 9. Mean age at inter-

view was 8.8 years (range 3 to 27 years) being lower in the one stage-repair group A with a mean of 7.4 (range 3.3 to 17.4 years) and higher in the three-stage repair group with a mean of 11.3 years (range 3.5 to 27.7 years) (Fig. 9). The tendency towards older age in Group B could not be proven to be statistically significant (p=0.29).

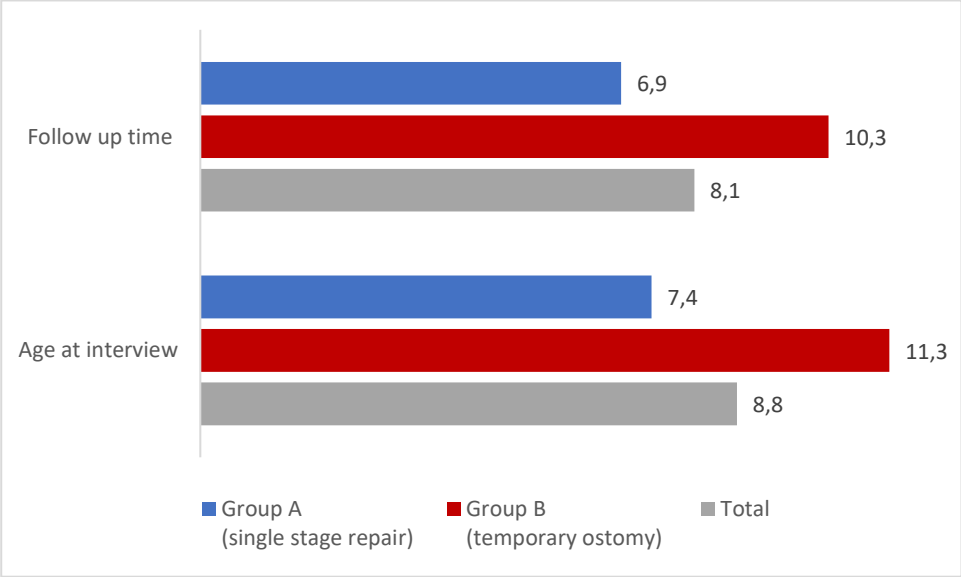

Fig. 9 **Comparison Follow up time and age at interview (years)**

Among those with a three-stage-repair the ostomy was left in place for a mean of 304 days (range 5 to 1223). Among those without primary ostomy one received an ostomy due to complications after the surgery.

3.2. Peri-operative findings

Mean of total days of hospitalization was 43.5 days (range 5 to 310 days) and a count of hospitalizations with a mean of 3.9 times (range 1 to 15 times).

Mean length of hospitalization in days was significantly (p=0.018) higher in group B (ostomy) with a mean of 84,8 days (range 25 to 310 days, SD 77,53) while it was 20 days (range 5 to 84 days, SD 16,62) in group A (single-stage-repair) (Fig. 10).

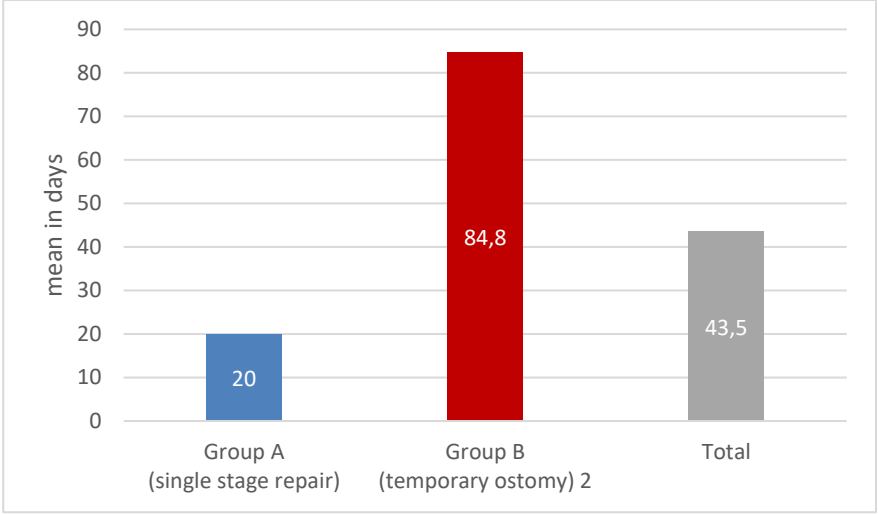

Fig. 10 Hospitalization length (days total) per group

Hospitalization count (the times a patient was hospitalized) in Group A (single-stage-repair) showed a mean of 2.0 times (range 1 to 7 times) and a statistically significantly higher (p=0.002) mean of 7.1 times (range 3 to 14 times) in group B (ostomy). Additionally, the number of surgical procedures showed a statistically significantly (p=0.008) higher mean in Group B (ostomy) with 5.4 (range 3 to 20 procedures) while in Group A (single-stage-repair) the mean was 1.3 (range 1 to 5 procedures) (Fig. 11). The mean of biopsies taken in the HD group was 1.67 (range 1 to 4, SD 0.77).

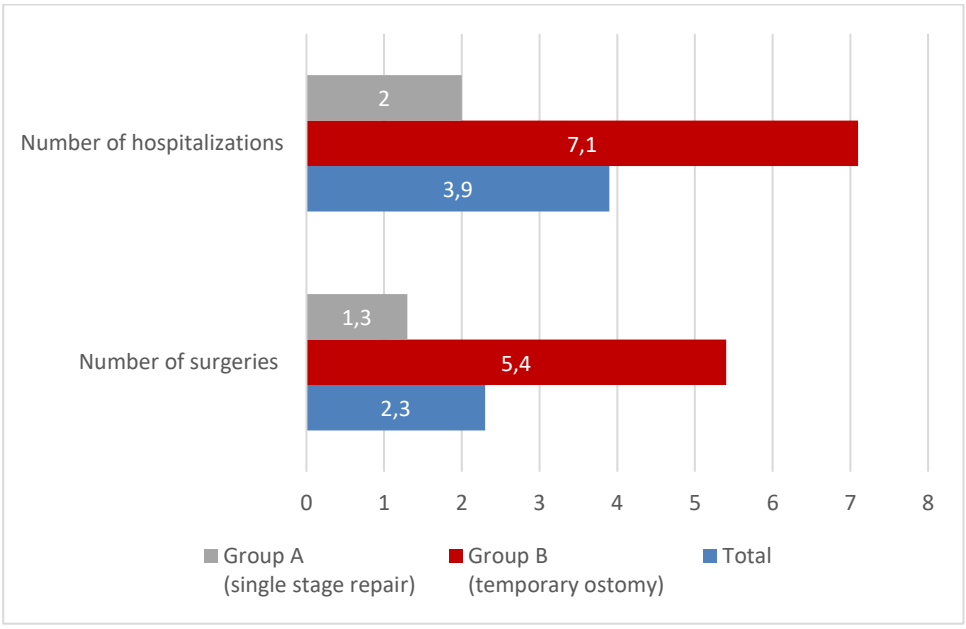

Fig. 11 Comparison of means Group A and B

Out of all patients 21 (58%) developed complications after surgery while 15 patients did not experience any complications (36%). The occurrence within Groups A and B by severity of the complication is shown in Fig. 12.

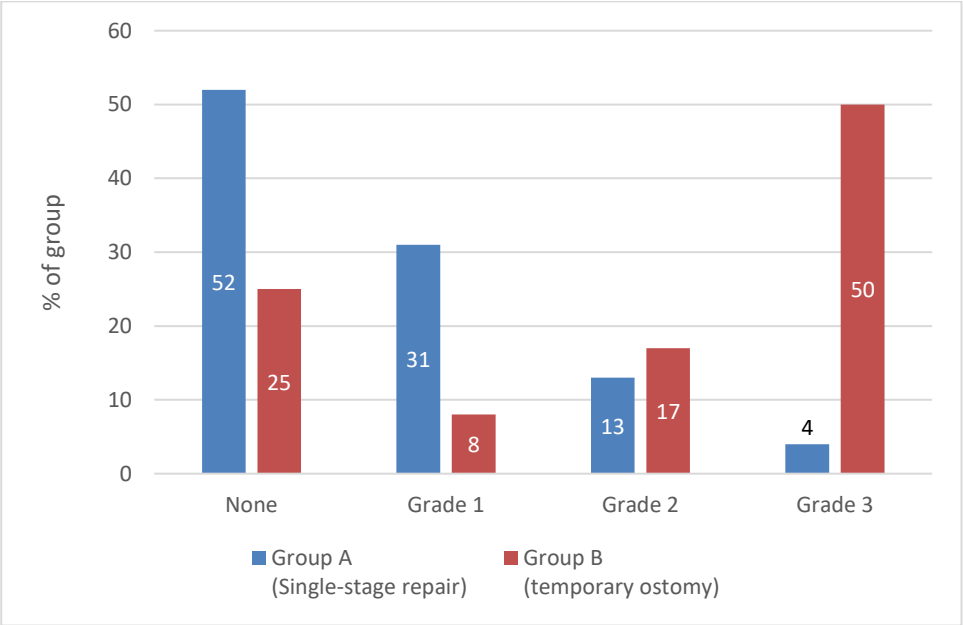

Fig. 12 Proportions of complications Grade 1-3 in Group A vs Group B

While 52% of patients in Group A did not experience any complications the number of patients without complications in Group B was as low as 23%. A significant difference could be shown when grouping "No complications, Grade 1 and Grade 2 complications" and comparing it to "Grade 3 complications" which occurred significantly (p=0.002) more frequently in Group B (46% of patients). When testing "no complications" vs. complications Grade 1-3 no statistical significance could be established (p=0.16). However, when testing "No" and "Grade 1" complications against "Grade 2" and "Grade 3" complications a significant difference could be shown with a p=0.003.

The types of complications that occurred are listed in detail in Table 12.

Times mentioned	Grade 1 – minor complications	
6	Perianal dermatitis (with or without fungus infection)	Group A 3 Group B 3
4	Prolonged wound healing	Group A 2 Group B 2
1	Exterior inflammation of ostomy	Group B
1	Anal prolapse (mild prolapse of mucosa)	Group A
1	Anal hemorrhage and retrograde bleeding from colostomy	Group B
1	Hematoma of intestinal wall after bougienage	Group B
	Grade 2 – moderate complications	
1	Absent sphincter tone (new post-operative)	Group B
3	Necessity of repeated bougienage in generalized anesthesia	Group A 2 Group B 1
1	Fecal impaction with surgical removal (6 months after surgery)	Group B
1	Wound dehiscence and secondary suture	Group B
2	Necessity of re-excision due to persisting narrow segment	Group B
1	Abdominal hernia at former colostomy site with surgical correction	Group B
1	Skin coverage of anus after healing with necessity of minor surgical procedure	Group B
	Grade 3 – severe complications	
1	insufficiency of anastomosis with re-anastomosis operation	Group B
1	tear of ileoanal anastomosis and secondary creation of protective ileostomy	Group A
2	stenosis of anastomosis with necessity of surgical intervention	Group B
1	perforation of small intestine and creation of protective ileostomy	Group B
1	adhesive ileus with extensive surgical procedure	Group B
1	postoperative respiratory exhaustion with CO2 retention and one-time generalized seizure during erythrocyte concentrate infusion	Group A
1	creation of temporary Hartmann situation	Group B
1	Volvulus and creation of ileostomy	Group B

Table 12 Complications presented ranked Grade 1-3

The complications named most commonly were perianal dermatitis (6), prolonged wound healing (4), stenosis of anastomosis and re-operation due to persisting narrow segment. (each 2). Of Group A one patient received a colostomy as a means to control complications. No relevant difference in complication rates could be found between ARM and HD patients (Fig. 13).

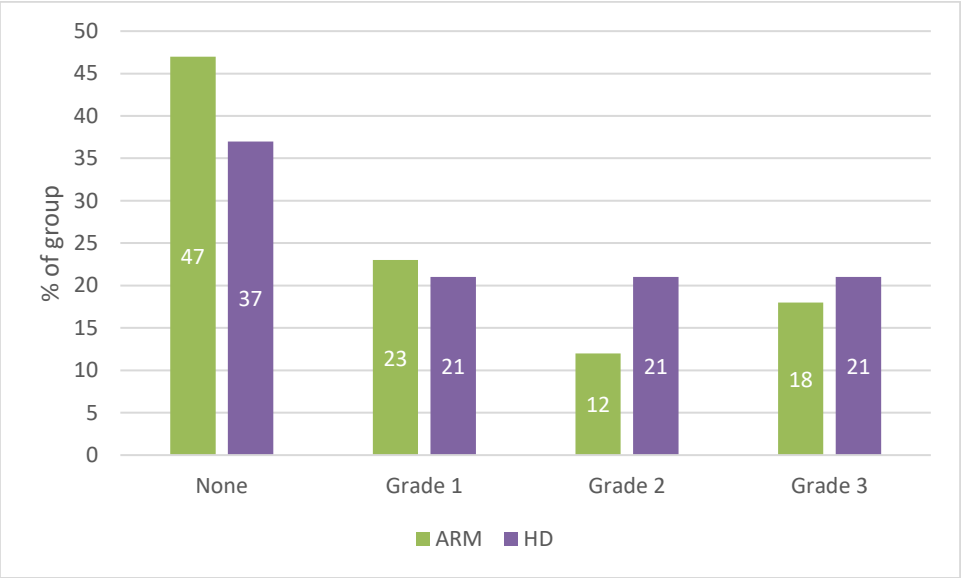

Fig. 13 Complication rates in ARM vs. HD patients

Among those patients with accompanying other malformations a higher percentage (74%) reported complications between grade 1 and grade 3 while in those patients without other malformations only 41% reported complications of any kind. (Fig. 14) However, the difference could not be proven statistically significant in Fisher's exact test (p=0.08).

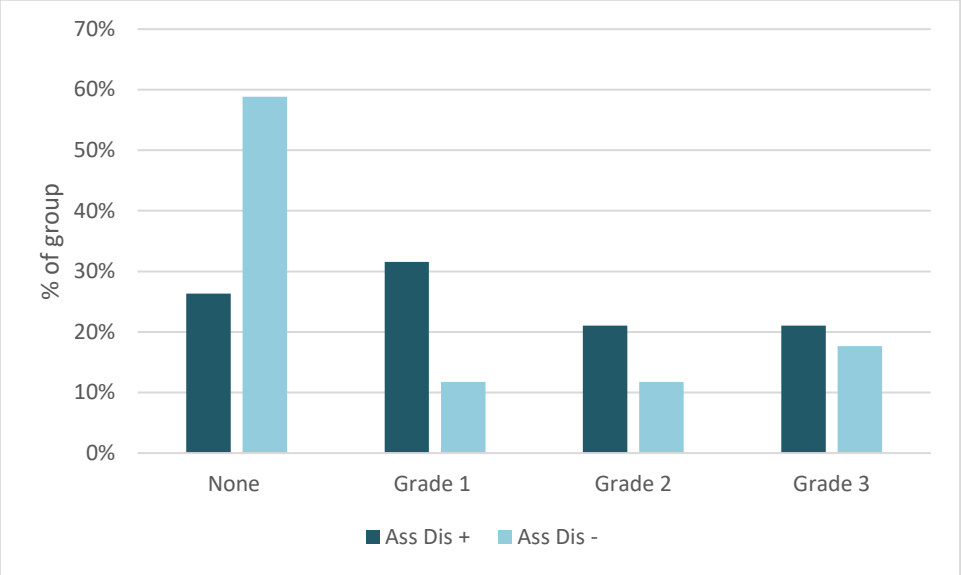

Fig. 14 Complications in patients with and without other malformations

Group B patients had a statistically significantly higher chance of needing an unplanned re-operation as a means to control complications (p=0.001). While in Group A only 4% received unplanned secondary surgery in Group B this affected 54% of the patients (Fig. 15). This significant difference could not be shown comparing the subgroups of ARM and HD patients (p=0.69).

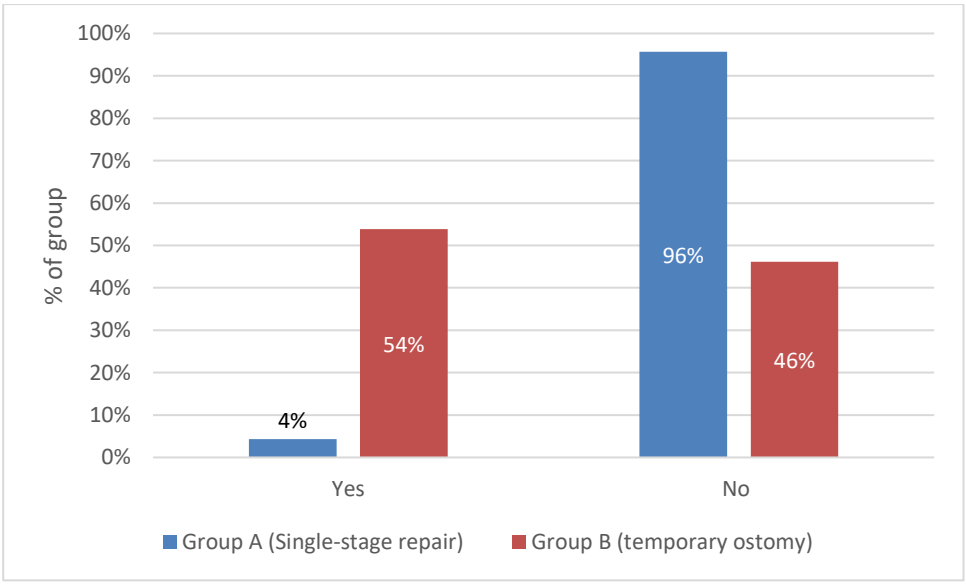

Fig. 15 Necessity of unplanned secondary surgery per Group

3.3. Long-term findings

In Group A one interview was conducted with the patients answering the questions themselves, in the remaining 22 interviews answers were collected from a parent. In Group B 2 patients answered themselves while 11 interviews were conducted with a parent.

3.3.1 Functional

At the time of the interview 5 patients from Group A (21%, age 3 to 9 years) and 3 patients from Group B (23%, age 3 to 9 years)) were unable to reliably use a toilet (not "potty trained"). One patient with HD in Group A was a long-term ostomy patient.

Age at reaching continence showed a mean of 4.2 years (range 2 to 10 years, SD 1.93) after subtracting 7 patients who never reached continence and 1 patient who still age appropriately wore diapers. In Group B 4 patients never reached continence and two patients between 3 and 4 years of age could not be evaluated conclusively. The remaining 7 patients showed a mean of 3.5 years of age when reaching continence (range 3 to 4, SD 0.53 years).

The single score criteria of functional outcome in our study are comprised in Table 13 and Table 14. We could show clinical differences between Group A and Group B regarding single criteria which however could not be shown to hold statistical significance as indicated by the p-value that (with one exception in the comparison between ARM and HD patients regarding stool frequency) was steadily >0.05.

Item	Category	Group A (n=23)	% of Group A	Group B (n=13)	% of Group B	p=	ARM (n=17)	% of ARM	HD (n=19)	% of HD	p=
Voluntary Bowel Movement	Yes	15	65%	6	46%	0.310	8	47%	11	58%	1
	No	8	35%	7	54%		5	29%	8	42%	
Soiling	No	5	22%	4	31%		2	12%	7	37%	
	Grade 1 - Occasionally	10	43%	3	23%	0.253	9	53%	4	21%	0.726
	Grade 2 - daily, no social problem	4	17%	1	8%		2	12%	3	16%	
	Grade 3 - Constant, social problem	0	0%	4	31%		3	18%	5	26%	
	Too young to tell	4	17%	1	8%		1	6%	0	0%	
Constipation	No	17	74%	6	46%	0.261	8	47%	15	79%	0.081
	Grade 1 - Manageable with diet	2	9%	4	31%		5	29%	1	5%	
	Grade 2 - requires laxatives	4	17%	2	15%		4	24%	2	11%	
	Grade 3 - Resistant to diet and laxatives	0	0%	1	8%		0	0%	1	5%	
Defecation strain	Never	14	61%	9	69%	0.726	10	59%	13	68%	0.730
	<50%	5	22%	4	31%		3	18%	6	32%	
	>50%	4	17%	0	0%		4	24%	0	0%	
Defecation pain	Never	19	83%	11	85%	1	13	76%	17	89%	0.391
	Occasionally	4	17%	2	15%		4	24%	2	11%	
	Regularly	0	0%	0	0%		0	0%	0	0%	
Stool consistency	Nomal / formed	10	43%	7	54%	0.730	9	53%	8	42%	0.738
	Loose	12	52%	5	38%		8	47%	9	47%	
	Liquid	1	4%	1	8%		0	0%	2	11%	
Discrimination fluid/ formed	Normal	11	48%	6	46%	1	7	41%	10	52%	0.525
	Unreliable	5	22%	1	8%		4	24%	2	11%	
	Missing	7	30%	6	46%		6	35%	7	37%	

Table 13 **Functional long-term outcome items (I)**
(Items above stated p-value testet vs. items below)

Item	Category	Group A (n=23)	% of Group A	Group B (n=13)	% of Group B	p=	ARM (n=17)	% of ARM	HD (n=19)	% of HD	P=
Stool frequency	<1/d	5	22%	2	15%		4	24%	3	16%	
	1-2/d	11	48%	7	54%	1	11	65%	7	37%	**0.031**
	2-5/d	6	26%	1	8%		2	12%	5	26%	
	>5/d	1	4%	3	23%		0	0%	4	21%	
Incontinence	Never	11	48%	6	46%		7	41%	10	53%	
	accidentally/when diarrhea	6	26%	1	8%	0.691	5	29%	2	11%	0.714
	Frequently/regardless of diarrhea	6	26%	4	31%		4	24%	6	32%	
	Altersbedingt	0	0%	2	15%		1	6%	1	5%	
Diaper	Never	16	70%	6	46%	0.436	11	65%	11	58%	0.712
	<5/week	0	0%	1	8%		1	6%	0	0%	
	>5/week	6	26%	4	31%		3	18%	7	37%	
	Altersbedingt unklar	1	4%	2	15%		2	12%	1	5%	
Panty Pads	Never	22	96%	10	77%	0.123	16	0%	18	0%	0.485
	Day only	0	0%	1	8%		1	0%	0	0%	
	Unclear (Diaper wearing child)	1	4%	2	15%		2	0%	1	0%	
Hold stool	Yes	15	65%	6	46%	0.471	10	59%	11	58%	1
	No	7	30%	5	38%		5	29%	7	37%	
	Unclear due to age	1	4%	2	15%		2	12%	1	5%	
Medication to control consis-tency	Never	18	78%	10	77%	1	13	76%	15	79%	1
	Occasionally	0	0%	2	15%		1	6%	1	5%	
	Regularly	5	22%	1	8%		3	18%	3	16%	
Incontinence Urine	Never	15	65%	9	69%	1	11	65%	13	69%	1
	Occasionally	4	17%	1	8%		4	23%	1	5%	
	Regularly	4	17%	3	23%		2	12%	5	26%	

Table 14 Functional long-term outcome items (II)

(Items above stated p-value vs. items below)

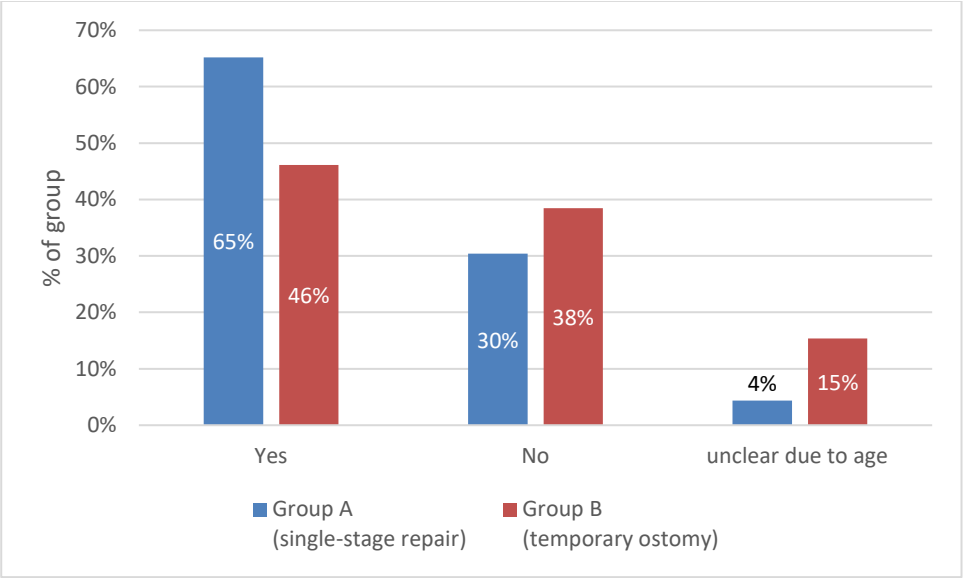

Fig. 16 **Ability to hold stool willingly comparison Group A and B**

Regarding the patients' continence, the ability to hold stool willingly was reported in 65% of patients in Group A while the same was the case for only 46% in Group B (Fig. 16). Also, no difference could be observed between the Groups of ARM and HD patients. Incontinence was reported in 52% of all patients in Group A, 26% each falling in the categories of accidental incontinence and regular incontinence (Fig. 17).

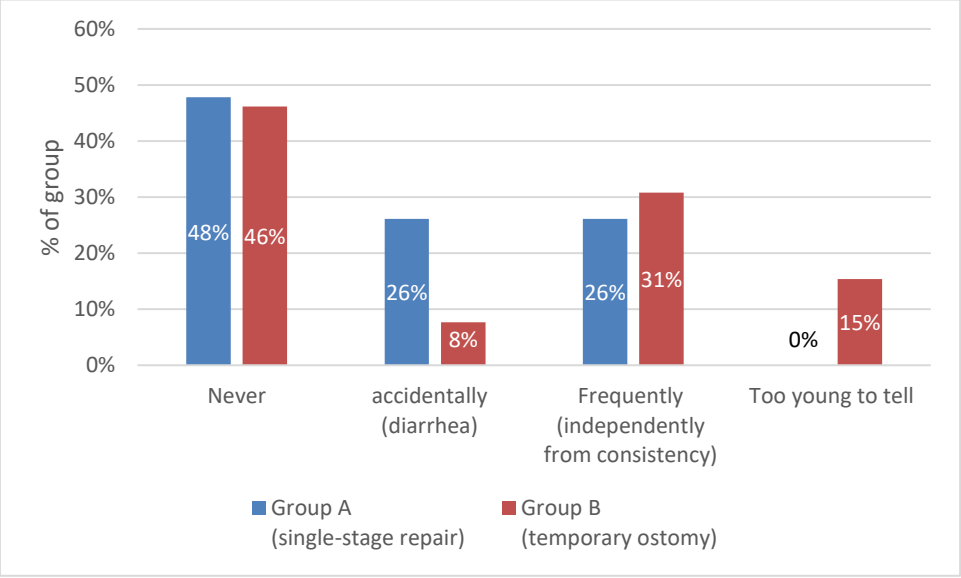

Fig. 17 **Reported incontinence in Groups A and B**

In Group B incontinence was reported for 39% of patients, 31% frequently and 8% accidentally. 15% in Group B were too young to finally tell. The percentage of patients who did not experience any kind of incontinence was similar in both groups being 48% in Group A and 46% in Group B. In the more detailed questions concerning incontinence in both groups the most frequent problem present was incontinence in episodes of diarrhea being present in 56% of patients in Group A and 54% in Group B. Incontinence due to physical activity and emotional outbursts was slightly more frequent in Group B as depicted in Fig. 18.

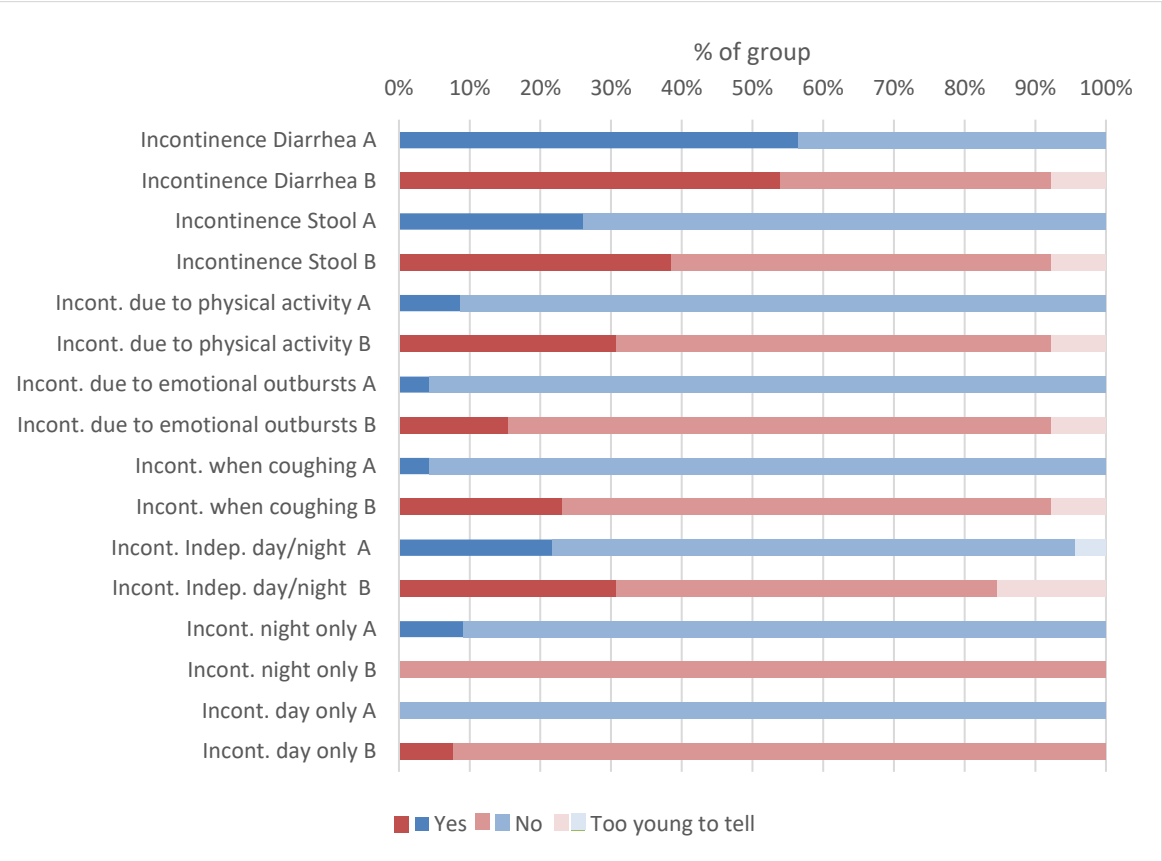

Fig. 18 **Situational incontinence in Groups A and B**

Soiling was absent in more patients of Group B (31% vs 22% in Group A) however, those who experienced soiling had a higher chance of a more severe presentation as in Group B 31% had regular soiling with social implications (Grade 3) while in Group A no patient had Grade 3 soiling and only 17% had regular soiling without social implications (Grade 2) (Fig. 19).

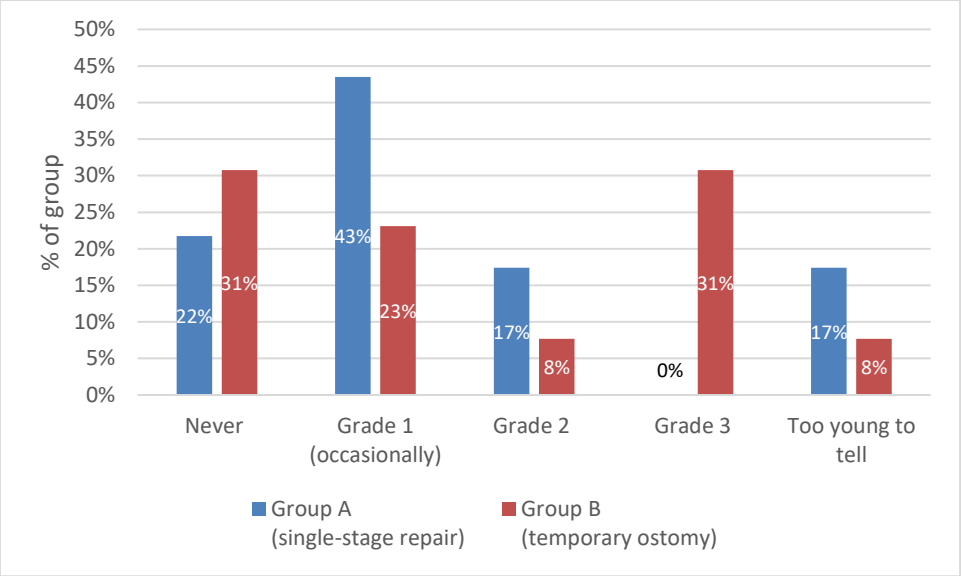

Fig. 19 Reported soiling in Groups A and B

Constipation was less frequent in Group A with 74% of patients stating no constipation while in Group B only 46% stated the same. Grade 1 constipation was most common in Group B (31%), Grade 2 constipation was recorded in 15% of this group and 8% showed constipation Grade 3. In Group A none of the patients showed Grade 3 constipation while 17% had the need for laxatives (Grade 2). Defecation strain was similarly present in both groups (Group A 39%; Group B 31%) as was defecation pain which was absent in more than 80% of both groups (Group A 83%; Group 85%) and if present only occurred occasionally in 17% (Group A) or 15% (Group B) of the patients.

Consistency of the stool was recorded to be slightly looser in Group A (formed 43%, loose 52%, liquid 4%) while Group B had a tendency to formed stool (formed 54%, loose 38%, liquid 8%). Discrimination between loose and formed stool was normal in 48% of patients in Group A and in 46% in Group B. Discrimination was unreliable in 22% of Groups A and 8% in Group B while it was missing in 30% of group A patients and in 46% of Group B patients. The difference was not proven to be statistically significant (p=1). As far as stool frequency is concerned although no statistical significance could be proven Group B was found to have a tendency towards more bowel movements per day (Fig. 20). While in both groups roughly half had 1-2 bowel movements per day (Group A 48%, Group B 54%) a frequency of more than 5 bowel movements per day was reported by 23% of Group B patients while only 4% of patients from Group A stated the same.

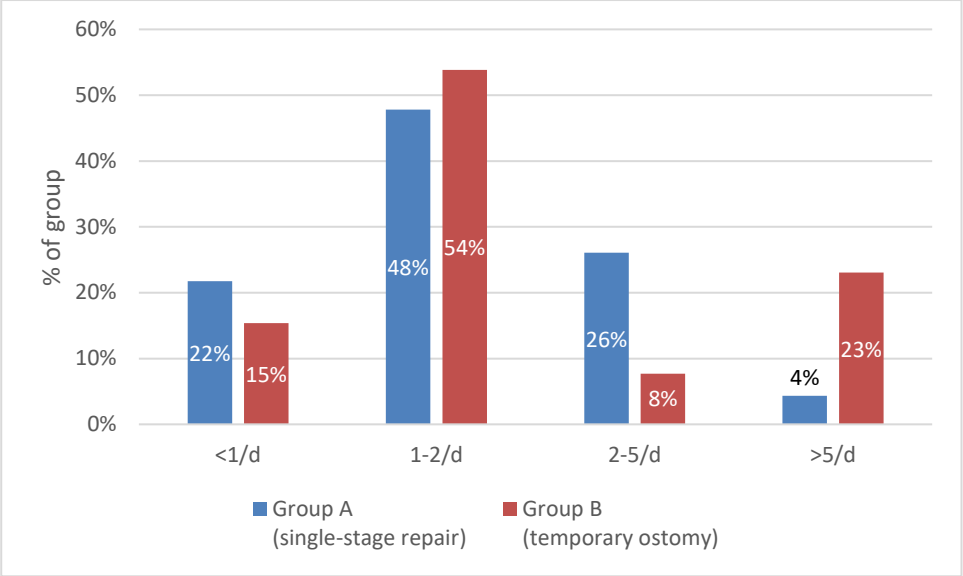

Fig. 20 Reported stool frequency Groups A and B

Accompanying urinary incontinence was present in 35% of Group A patients (18% occasionally, 17% regularly) and in 31% of Group B patients (8% occasionally, 23% regularly. Need for regular medication was expressed by 22% of Group A patients, all regularly taking medication to control stool consistency. In Group B in total 23% used medication but only 8% on a regular basis while 15% stated to occasionally use medication to control stool consistency. While the original item does not differentiate between laxatives and medication to counter diarrhea in our study patients exclusively stated laxatives as the medication used. Regular enema was needed by 1 patient in Group A (4%) and 3 patients in Group B (23%).

The necessity for diapers and panty pads was higher in Group B where only 46% stated to never use diapers while in Group A 70% of patients did not have that need (Fig. 21). Those who used diapers in Group A used them more than 5 times a week. In Group B 31% stated to use diapers more than 5 times per week and additional 8% used them occasionally less than 5 times per week. Panty pads were obsolete for 96% of Group A patients while only 77% of Group B patients did not use them. The comparison is however complicated by 2 Group B children being unable to make a statement due to still age-appropriate diaper wearing.

Considering erectile and ejaculatory function only few parents could state reliable answers in our interview: 2 male patients in Group A were reported to have impairment of erectile function. In Group B 2 male patients were reported to have normal erectile

function, one patient was reported to experience impairment. Regarding ejaculation 3 patients' parents answered that their son did not have normal ejaculation, one of them being part of Group A and 2 two of them being part of Group B.

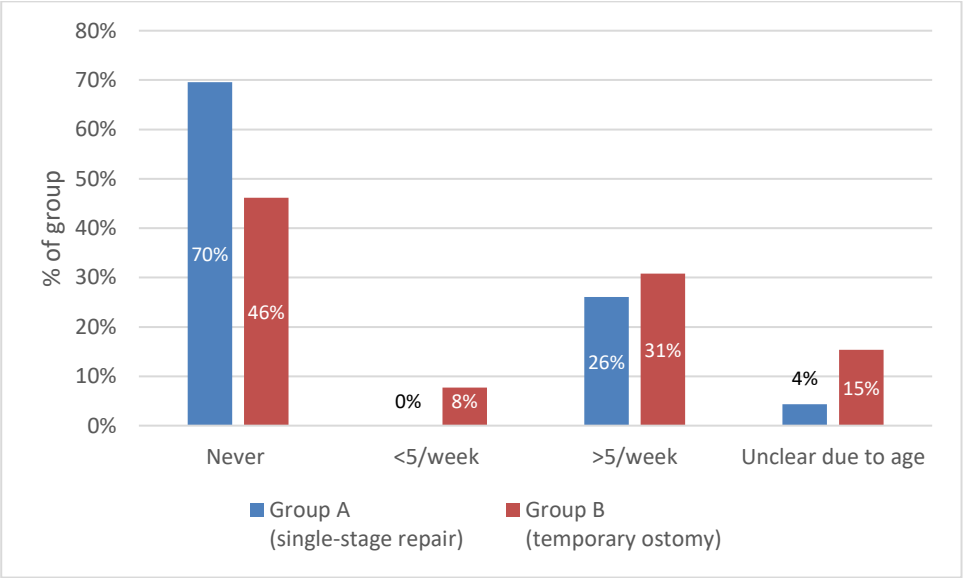

Fig. 21 Reported necessity for diapers in Groups A and B

3.3.1.1 Krickenbeck Score

Using the single items above to calculate the scores we used our study we could show a slight difference in favor of Group A (one-stage repair) (Fig. 22). While by the modified Krickenbeck criteria 52% of patients in Group A scored a "good" outcome, only 46% of patients in Group B reached the same category. 54% of patients in Group B scored a "poor" outcome with none of the patients in the "fair" category. In Group A 44% of patients scored a "poor" outcome and 4% were categorized as "fair". None of the differences could be proven to be statistically significant (p=0.73).

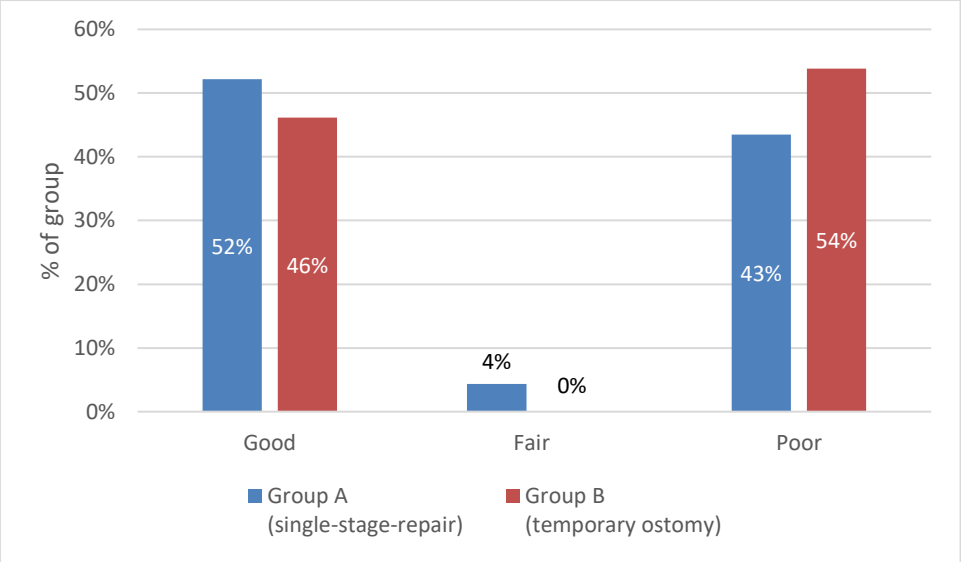

Fig. 22 **Functional results according to Krickenbeck Score**

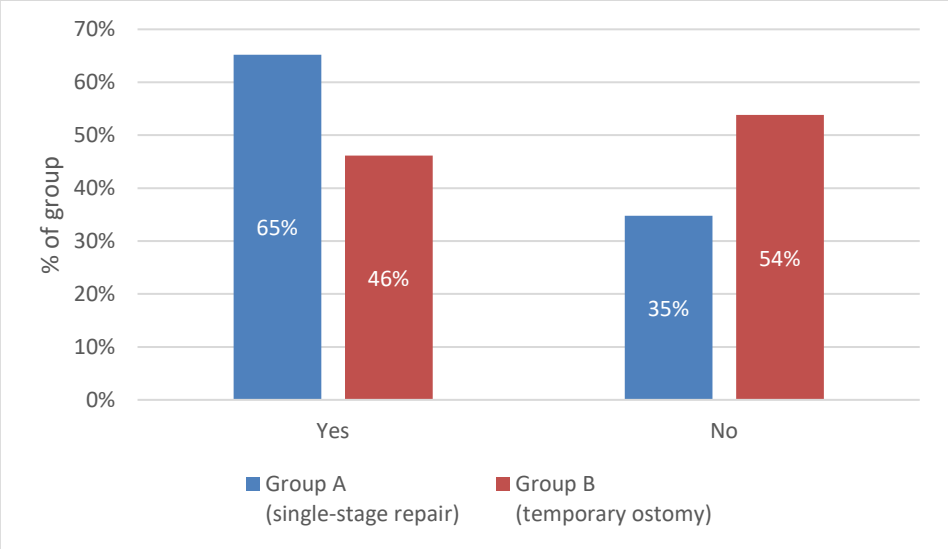

Fig. 23 **Voluntary bowel movement in Groups A and B**

Voluntary bowel movement (VBM) as defined by the Krickenbeck criteria was present in 65% of patients in Group A and 46% in Group B (Fig. 23).

Functional outcome according to the Krickenbeck criteria comparing female and male patients was slightly better in the female group of which 57% had a good outcome, 43% scored poor. In the male group 45% scored good, 5% fair and 50% were attributed a poor outcome (good vs fair and poor p=0.73) (Fig. 24).

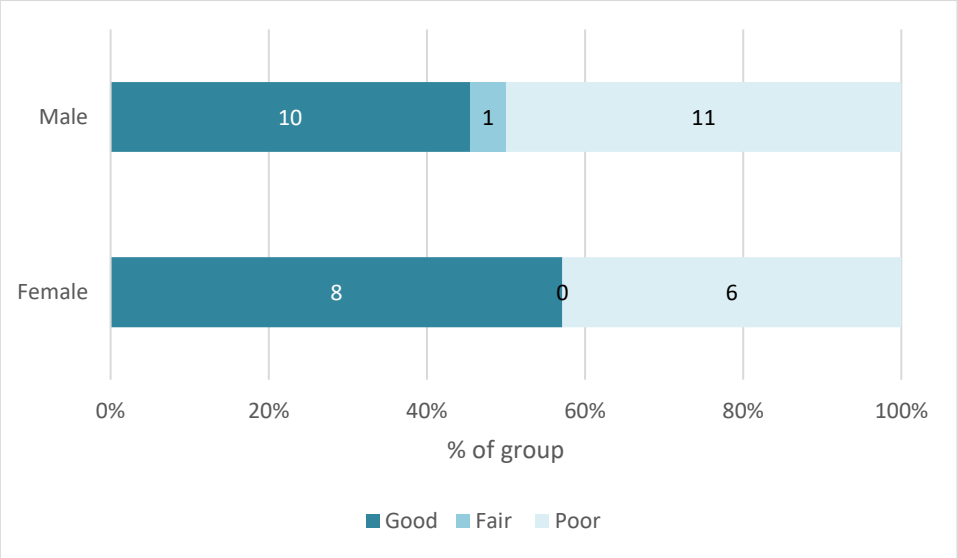

Fig. 24 **Krickenbeck score comparing female and male patients (% of group and total number of patients)**

3.3.1.2 Wildhaber Score

Evaluation of the Wildhaber Score showed no difference between Group A and B regarding those patients with a "good" outcome (52% in Group A and 54% in Group B). However, in Group B 23% of patients scored a "poor" outcome according to the Wildhaber Score while in Group A the "poor" outcome was only attributed to 9% of the patients. (Fig. 25). In Fisher's exact test p was 0.32 showing no statistical significance of this finding.

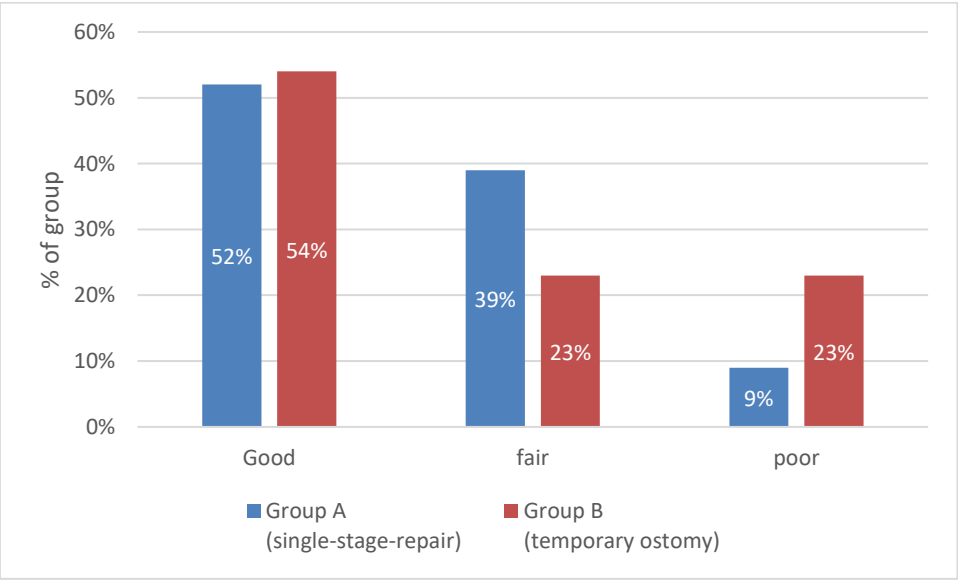

Fig. 25 **Functional results according to Wildhaber Score**

Also, according to the Wildhaber Score when comparing females and males there was a slightly better outcome in the female group (good vs fair and poor p=0.409) (Fig. 26). While 64% of female patients had a good outcome only 46% of males made the same category. Among females 29% had a fair, 7% a poor outcome while among the male group more patients had fair (36%) and poor (18%) outcomes.

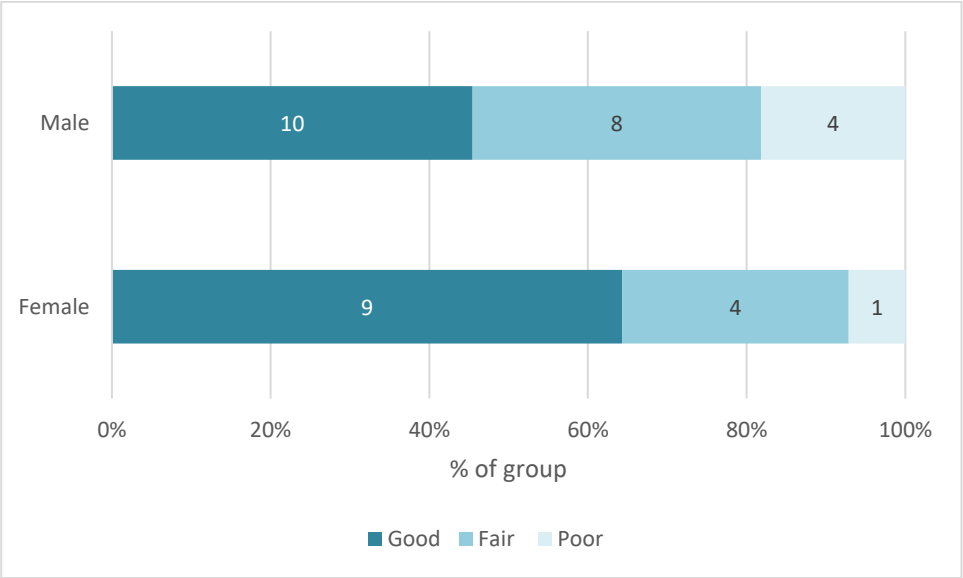

Fig. 26 **Wildhaber Score comparing female and male patients (% of group and total number of patients)**

3.3.2 Quality of life

All of the patients in our study were following age-appropriate daily activities such as kindergarten, school or employment. In Group A as well as in Group B each one patient (one ARM and one HD patient) stated to sometimes miss out on school or kindergarten due to their illness, all others stated to never be absent due to bowel related reasons. Two patients from Group B (or their parents) stated their illness had a negative effect on their education, they were each one ARM and one HD patient. All the others saw no negative impact of their disease on their education. Regarding a negative influence on their career choice the majority stated it was yet too soon to tell (Group A 78 % (18) Group B 62 % (8)) or saw no negative influence (Group A 22% (5) Group B 31% (4)). Only one HD patient from Group B stated a career limitation due to his illness. One patient from each Group (each one ARM and one HD patient) stated further to experience limitations in physical activity due to the disease and its symptoms. Stomachache was distributed similarly among Groups A and B while being entirely absent in the majority of the patients (Group A 57%, Group B 69%).

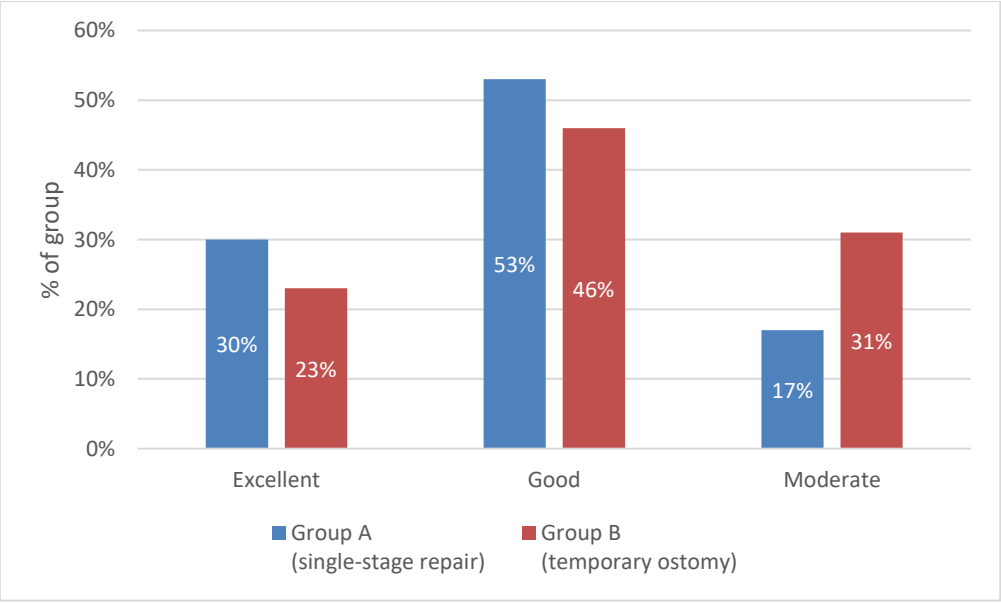

Fig. 27 Overall health in Groups A and B

Being asked to state the patients' level of overall health all participants gave answers between excellent and moderate with a tendency towards better health in Group A where 31% stated excellent overall health level (Group B 23%), 52% reported a good

level of overall health (Group B 46%) and only 17% chose moderate to describe their health status while there were almost twice as many (31%) in Group B (Fig. 27). Asked for their level of satisfaction with their bowel function 30% (Group A) and 30% (Group B) were entirely satisfied, 48% (Group A) 54% (Group B) were mostly satisfied 18% of Group A patients were mostly dissatisfied (0% in Group B) and 4% in Group A and 15% of Group B patients stated to be entirely dissatisfied with their bowel function (Fig. 28). The diseases' negative impact on overall well-being was also higher in Group B than in Group A while no relevant difference could be shown between ARM and HD patients. 15% of patients in group B stated a severe negative impact of the disease on their well-being while the same was true for only 4% of Group A patients (Fig. 29). No impact was stated be 53% of Group A patients and 46% of Group B patients.

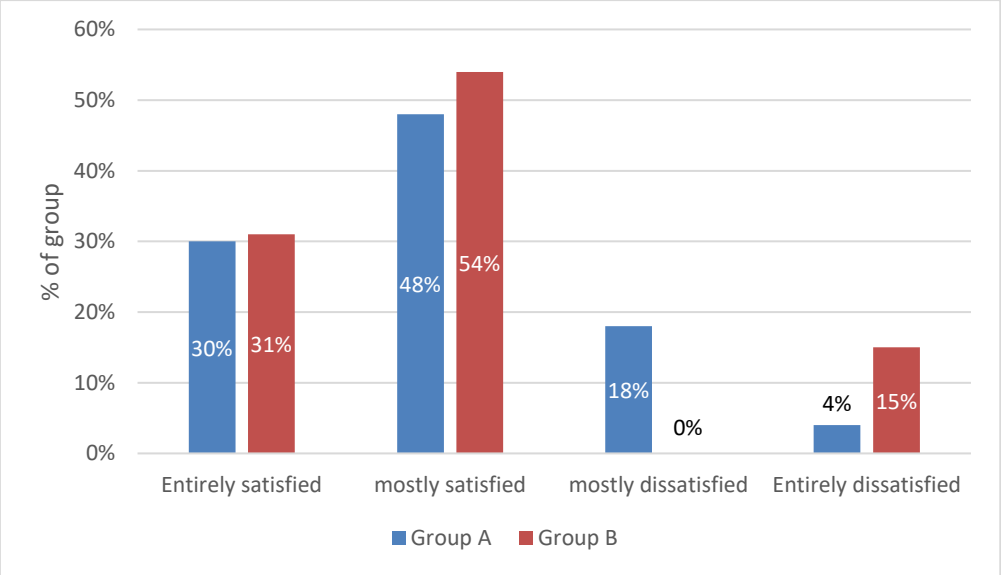

Fig. 28 **Level of satisfaction with patient´s bowel function**

The diseases' negative impact on everyday life was assessed separately and answered similarly by Groups A and B. The majority stated no influence (Group A 61%, Group B 54%), barely any or mild negative influence felt 34% (Group A) and 30% Group B). Severe negative influence was stated more often by Group B (15%) than Group A (4%) patients. Between the Group of ARM and HD patients, however, the impact on everyday life was stated to be more severe in HD patients than ARM (Fig. 30). While in both groups the majority stated no negative impact on everyday life (ARM 59%, HD 58%). Among those who did experience negative influence from the HD group 26% reported it to be mild and 16% felt severe negative influence. In com-

parison in the ARM group 6% reported mild influence and no one had severe negative influence on everyday life. None of the findings held statistical significance (p-values in Table 15).

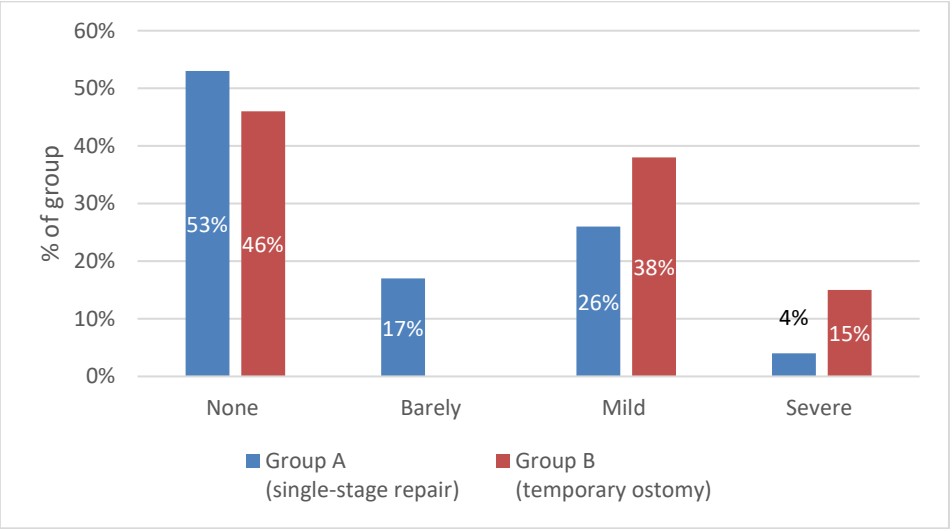

Fig. 29 Negative impact of disease on well-being

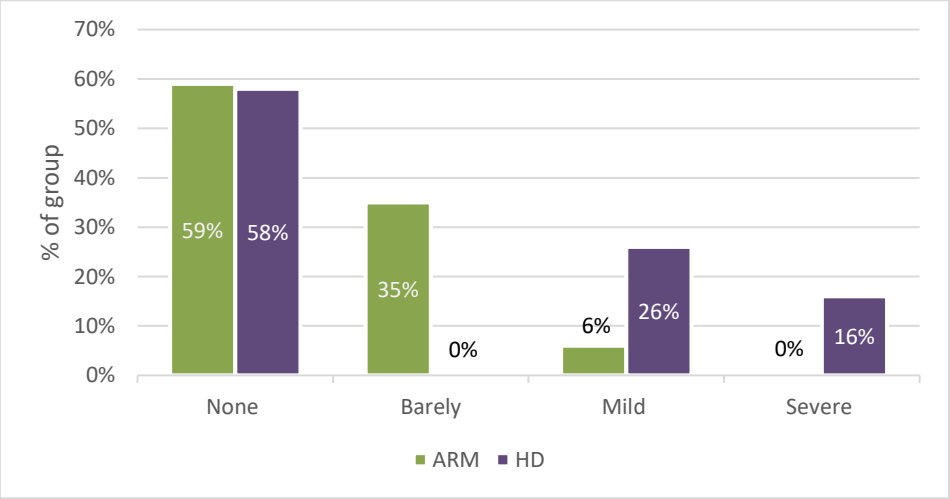

Fig. 30 Disease's negative impact on everyday life ARM and HD

Questions regarding rather staying at home or not eating outside of home due to their disease the answers were quite evenly distributed when comparing Group A and Group B (Table 15). The great majority (80-90%) stated no or rather no limitations in these fields. Also, finding friends was something that the vast majority of all groups did not perceived as a problem (Group A 87%, Group B 92%) (Table 15).

When asked for worries about incontinence patients and their parents of all groups found this to be not or rather not true in about 90% of the cases (Table 16). Worries about stool when outside of home were reported more frequently in Group B were 15% found this to be rather true 8% even found it to be entirely true. Group A in comparison both answers were given by each only 4% while 91% stated no worries in this matter (Group B 62%) (Fig. 31).

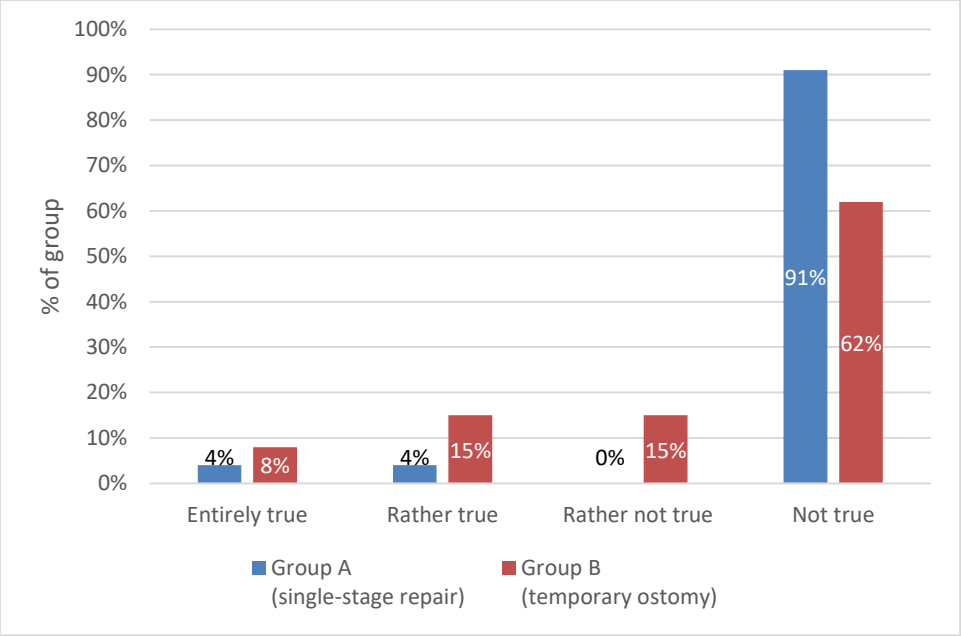

Fig. 31 Worry about stool when outside of home

Item	Category	Group A (n=23)	% of Group A	Group B (n=13)	% of Group B	p=	ARM (n=17)	% of ARM	HD (n=19)	% of HD	p=
Overall health	Excellent	7	30%	3	23%		3	18%	4	21%	
	Good	12	53&	6	46%	0.421	8	47%	10	53%	0.726
	Moderate	4	17%	4	31%		6	35%	5	26%	
Disease's impact on overall well-being	None	12	53%	6	46%	1	7	41%	11	58%	0.505
	Barely	4	17%	0	0%		4	24%	0	0%	
	Mild	6	26%	5	38%		6	35%	5	26%	
	Severe	1	4%	2	15%		0	0%	3	16%	
Disease's negative influence on every-day life	None	14	61%	7	54%	0.735	10	59%	11	58%	1
	Barely	4	17%	2	15%		6	35%	0	0%	
	Mild	4	17%	2	15%		1	6%	5	26%	
	Severe	1	4%	2	15%		0	0%	3	16%	
Would rather stay at home because of disease	Entirely true	1	4%	2	15%		1	6%	2	1%	
	Rather true	1	4%	1	8%	0.328	0	0%	2	11%	0.342
	Rather not true	1	4%	2	15%		1	6%	2	11%	
	Not true	20	87%	8	62%		15	88%	13	68%	
Would rather not eat outside of home	Entirely true	1	4%	1	8%		0	0%	2	11%	
	Rather true	2	9%	0	0%	1	2	12%	0	0%	1
	Rather not true	1	4%	0	0%		0	0%	1	5%	
	Not true	19	83%	12	92%		15	88%	16	84%	
Finds it hard to find friends due to the disease	Entirely true	0	0%	1	8%		1	6%	1	5%	
	Rather true	1	4%	0	0%	1	0	0%	0	0%	1
	Rather not true	2	9%	0	0%		0	0%	2	11%	
	Not true	20	87%	12	92%		16	94%	16	84%	

Table 15 **Long-term outcome QOL items (I)**
(items above stated p-value vs. items below)

The need to always have a toilet nearby was rather similarly distributed regarding Groups A and B (Table 16) while it showed to be present more often in ARM patients than in HD patients according to our findings (Fig. 32).

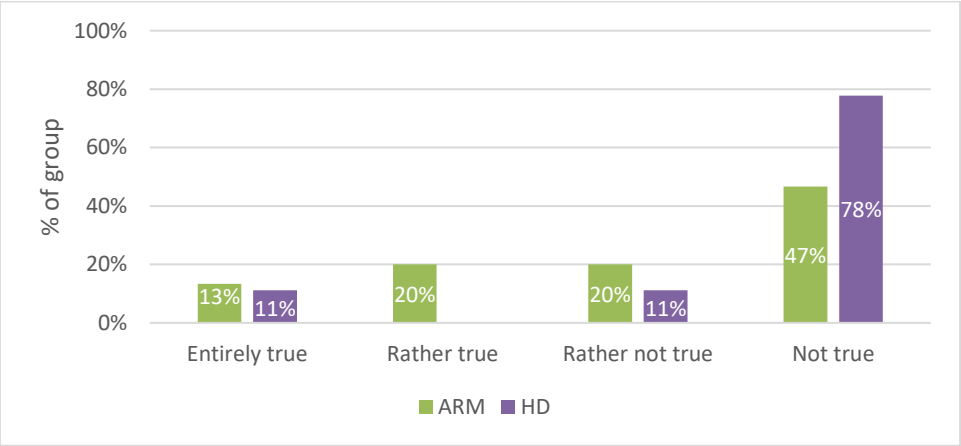

Fig. 32 Need for toilet nearby in ARM vs. HD patients

When asked if they needed to adjust their daily activities to bowel function patients from Group B stated to be more restricted as 15% each totally or partly agreed to the statement whereas in Group A patients either totally disagreed (74%) or mostly disagreed (26%) (Fig. 33,Table 16).

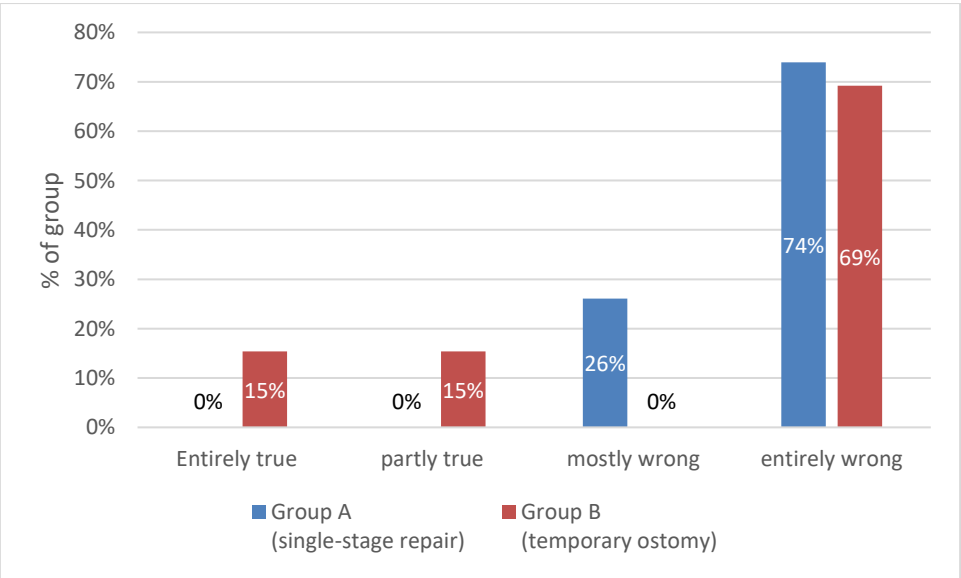

Fig. 33 Need to adjust daily activities to bowel function

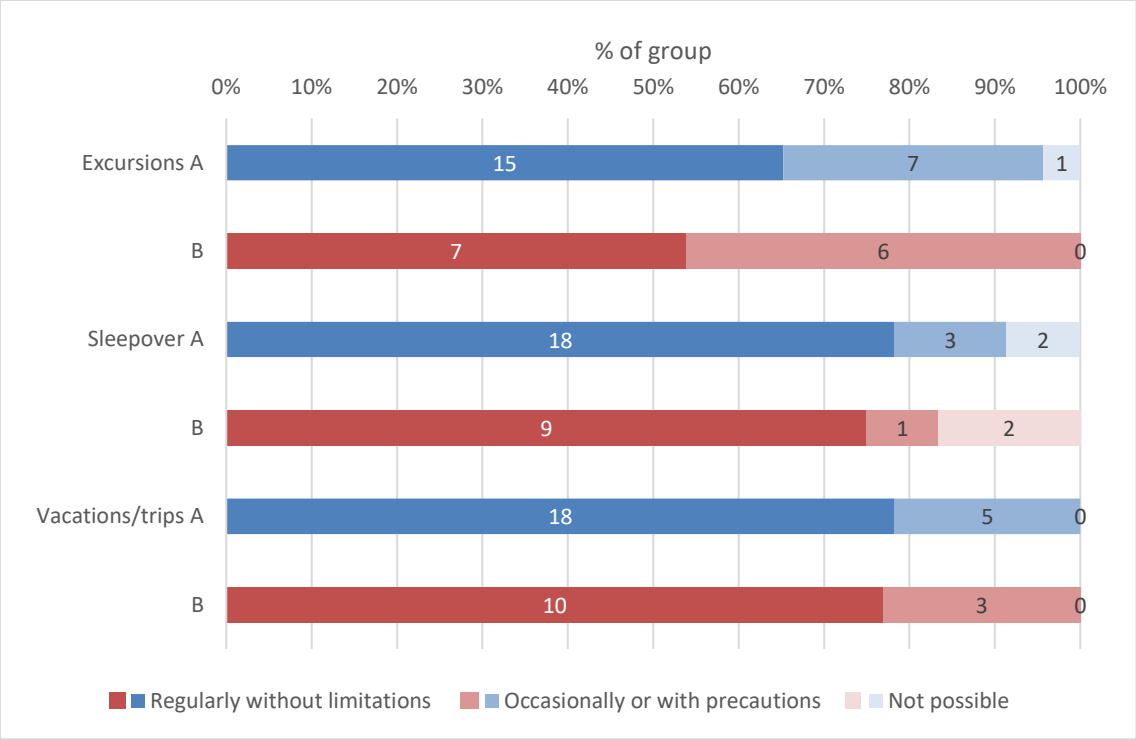

Fig. 34 **Excursions, sleepovers and vacations Groups A and B (% of group and total number of patients)**

The disease's influence on the patients' personality development in Group B was more often rated to be severe (15%) than in Group A (4%). Moderate influence again was more often present in Group B with 38% (Group A 13%) and no influence was reported by 83% of Group A patients but only by 46% of Group B (Fig. 35). P-value for no influence versus moderate and severe influence combined was 0.056 (Table 16).

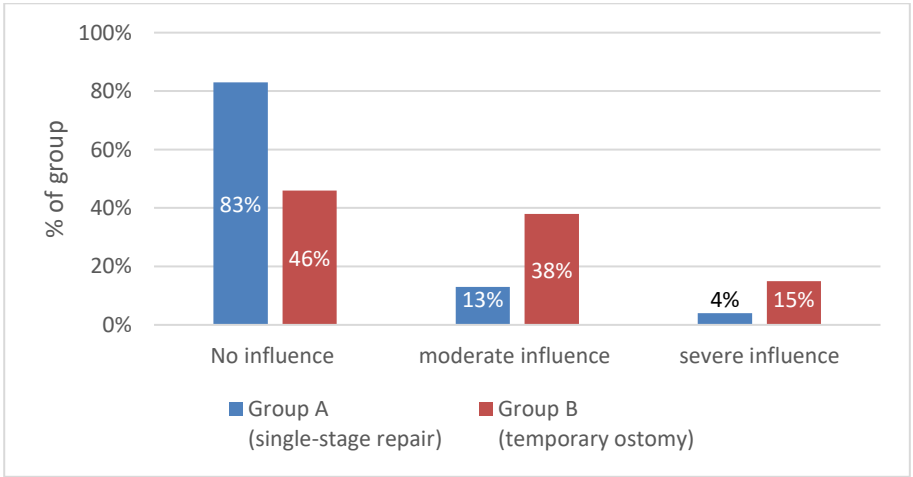

Fig. 35 **Disease's influence on patients' personality development**

Item	Category	Group A (n=23)	% of Group A	Group B (n=13)	% of Group B	p=	ARM (n=17)	% of ARM	HD (n=19)	% of HD	p=
Worries about stool when outside of home	Entirely true	1	4%	1	8%	n.s.	0	0%		11%	n.s.
	Rather true	1	4%	2	15%		3	18%		0%	
	Rather not true	0	0%	2	15%		1	6%		5%	
	Not true	21	91%	8	62%		13	76%		84%	
Is worried about incontinence when outside home	Entirely true	0	0%	1	8%	n.s.	1	6%		0%	n.s.
	Rather true	2	9%	0	0%		1	6%		5%	
	Rather not true	2	9%	2	15%		3	18%		5%	
	Not true	19	83%	10	77%		12	71%		89%	
It is important to always have a toilet nearby	Entirely true	3	13%	1	8%	n.s.	2	12%		11%	n.s.
	Rather true	2	9%	1	8%		3	18%		0%	
	Rather not true	2	9%	3	23%		3	18%		11%	
	Not true	15	65%	6	46%		7	41%		74%	
	Too young to tell	1	4%	2	15%		2	12%		5%	
Must adjust activities to bowel function	Entirely true	0	0%	2	15%	n.s.	0	0%		11%	n.s.
	Partly true	0	0%	2	15%		1	6%		5%	
	Mostly wrong	6	26%	0	0%		4	24%		11%	
	Entirely wrong	17	74%	9	69%		12	71%		74%	
Disease's influence on personality development	No influence	19	83%	6	46%	0.056	11	65%		74%	n.s.
	Moderate influence	3	13%	5	38%		6	35%		11%	
	Severe influence	1	4%	2	15%		0	0%		16%	

Table 16 **Long-term outcome QOL items (II)**

(items above stated p-value vs. items below, n.s. = not statistically significant, >0.05)

Hobby restrictions were not a problem for about 80% of patients from all groups (Table 16). Regarding the possibility of excursions in Group A 65% reported no problems whatsoever while a slightly smaller amount of 54% from Group B stated the same (Fig. 34). The remaining participants mostly stated to be able to go on excursions with precautions (Group A 30%, Group B 46%) while only one patient from Group A (4%) was unable to take part in excursions due to bowel issues. Sleepovers were not a problem for 78% (Group A) and 69% (Group B) of the participants while Group B had a slightly higher percentage of patients being unable to sleep over outside their home (Group A 9%, Group B 15%). The ability to go on vacation trips without problems or precautions was very similar with 78% in Group A and 77% in Group B. The remaining 22% / 23% of patients could go on trips with precautions (Table 17).

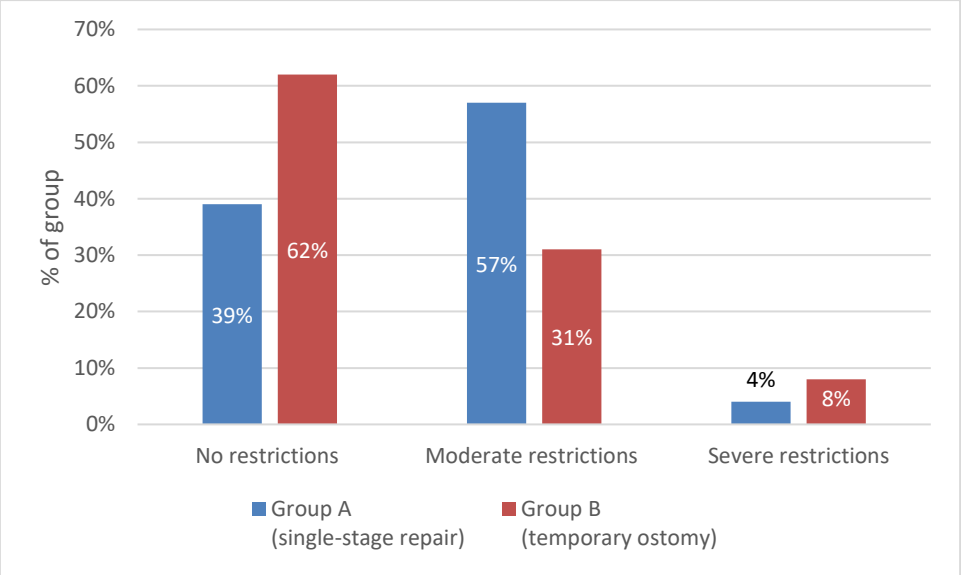

Fig. 36 Alimentation restrictions Groups A and B

Looking at alimentation and restrictions in the choice of foods severe restrictions were similarly rare (Group A 4% Group B 8%) while moderate restrictions were more common in Group A patients with 57% (Group B 31%). No restrictions were stated by 62% of Group B and 39% of Group A patients (Fig. 36). Alimentation restrictions were more equally distributed regarding the groups of ARM and HD patients (Table 17).

Item	Category	Group A (n=23)	% of Group A	Group B (n=13)	% of Group B	p=	ARM (n=17)	% of ARM	HD (n=19)	% of HD	p=
Hobby restrictions because of disease	Entirely true	0	0%	1	8%	n.s.	0	0%	1	5%	n.s.
	Rather true	1	4%	1	8%		1	6%	1	5%	
	Rather not true	2	9%	1	8%		1	6%	2	11%	
	Not true	19	83%	9	69%		13	76%	15	79%	
	Too young to tell	1	4%	1	8%		2	12%	0	0%	
Excursions	Regularly without limitations	15	65%	7	54%	n.s.	12	71%	10	53%	n.s.
	Occasionally or with precautions	7	30%	6	46%		4	24%	9	47%	
	Not possible	1	4%	0	0%		1	6%	0	0%	
Sleepover	Regularly without limitations	18	78%	9	69%	n.s.	13	76%	14	74%	n.s.
	Occasionally or with precautions	3	13%	1	8%		1	6%	3	16%	
	Not possible	2	9%	2	15%		2	12%	2	11%	
	Too Young to tell	0	0%	1	8%		1	6%	0	0%	
Vacations/trips	Regularly without limitations	18	78%	10	77%	n.s.	14	82%	14	74%	n.s.
	Occasionally or with precautions	5	22%	3	23%		3	18%	5	26%	
	Not possible	0	0%	0	0%		0	0%	0	0%	
Alimentation	No restrictions	9	39%	8	62%	n.s.	9	53%	12	63%	n.s.
	Moderate restrictions	13	57%	4	31%		7	41%	6	32%	
	Severe restrictions	1	4%	1	8%		1	6%	1	5%	
Negative impact on familiy life	No influence	15	65%	8	62%	n.s.	12	71%	11	58%	n.s.
	worsened	8	35%	4	31%		4	24%	8	42%	
	destroyed	0	0%	1	8%		1	6%	0	0%	

Table 17 **Long-term outcome QOL items (III)**
(Items above stated p-value vs. items below,
n.s. = not statistically significant, >0.05)

The social impact on family life caused by the disease was reported to be very similar in Groups A and B (Table 17). A slight difference could be observed comparing ARM and HD patients. Here 71% of ARM patients considered their family life unaltered by the disease while 58% of HD stated no impact on family life. In Group B 42% stated family life had been worsened (Group A24%) and one patient in Group A stated family life had been destroyed by the child's disease (Group B 0%).

87% among Group A patients as well as 85% of patients from Group B stated to never be unhappy because of the disease. 13% of Group A and 8% of Group B felt unhappy occasionally and one patient from Group B was regularly unhappy because of the disease (Fig. 37,Table 18).

Regarding the participants character traits, the vast majority of both groups (Group A 74%, Group B 85%) were reported to not be timid because of their disease. The remaining participants (Group A 26%, Group B 15%) stated to occasionally behave more timidly when compared to healthy peers (Table 18).

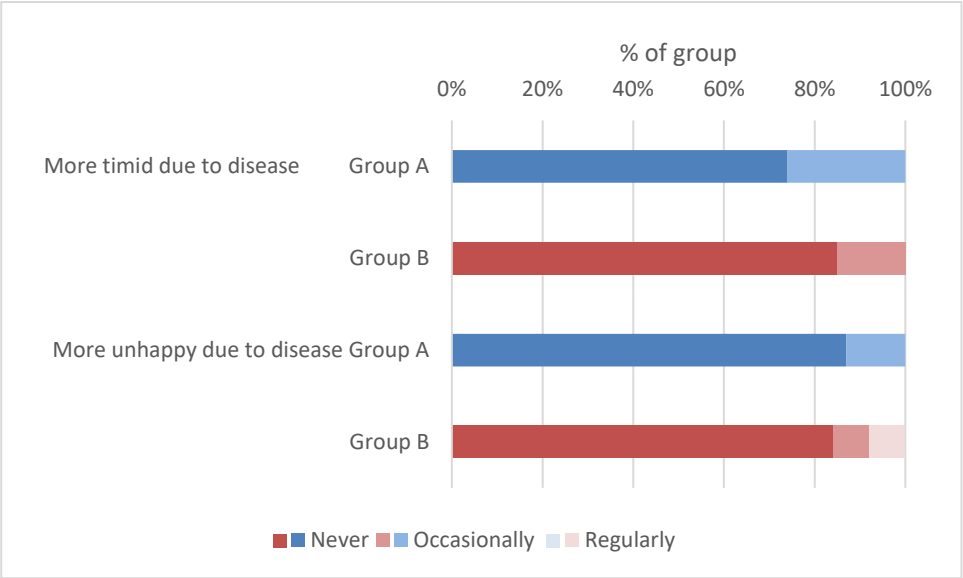

Fig. 37 **Feeling timid or unhappy because of disease**

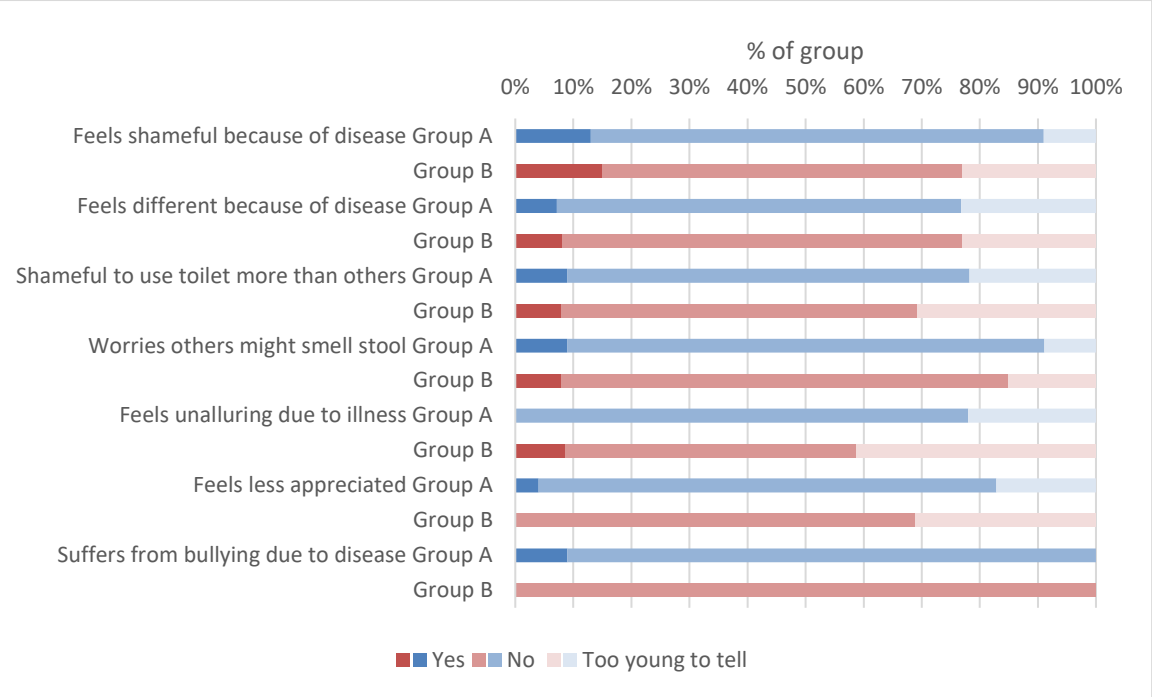

Fig. 38 Negative feelings and social discrimination due to illness

Feeling shameful or different due to the disease, being ashamed to leave the classroom to use the toilet more often than others as well as worries that others might smell stool was nearly equally distributed comparing Groups A and B with the majority not stating a relevant problem (Fig. 38, Table 18). In Group A none of the patients stated to feel unalluring due to the illness while in Group B 1 patient (8%) experienced this kind of difficulty. This question was not answered by 22% of Group A and 38% of Group B patients due to a young age (Fig. 38, Table 18). One patient (4%) from Group A felt less appreciated because of the disease while no patient from Group B reported this problem. 2 patients from Group A additionally reported bullying due to their disease while again no patient in Group B stated the same. (Table 18)

Social life in general was considered affected by the disease by 13% of Group A patients and similarly by 23% of Group B. the remaining 87% (Group A) and 77% (Group B) stated no influence (Table 18).

As a social factor outside the patient's home peer rejection was not an issue for more than 90% of both groups (Group A 91%, Group B 92%) while each one patient reported peer rejection on a regular basis in Group A (4%) and B (8%). Likewise, one patient in Group A reported occasional peer rejection (Table 18, Fig. 38).

Item	Category	Group A (n=23)	% of Group A	Group B (n=13)	% of Group B	p=	ARM (n=17)	% of ARM	HD (n=19)	% of HD	p=
Unhappy because of disease	Never	20	87%	11	85%	n.s.	14	82%	17	89%	n.s.
	Occasionally	3	13%	1	8%		3	18%	1	5%	
	Regularly	0	0%	1	8%		0	0%	1	5%	
Timid because of disease	Never	17	74%	11	85%	n.s.	11	65%	17	89%	n.s.
	Occasionally	6	0%	2	15%		6	35%	2	11%	
	Regularly	0	0%	0	0%		0	0%	0	0%	
Negative impact on social life	No	20	87%	10	77%	n.s.	15	88%	15	79%	n.s.
	Yes	3	13%	3	23%		2	12%	4	21%	
Feels different	Yes	1	4%	1	8%		12	71%	16	84%	
	No	19	39%	9	69%	n.s.	4	24%	2	11%	n.s.
	Too young to tell	3	13%	3	23%		1	6%	2	11%	
Feels unalluring due to illness	Yes	0	0%	1	8%	n.s.	1	6%	0	0%	n.s.
	No	18	78%	6	46%		11	35%	13	68%	
	Too young to tell	5	22%	5	38%		5	29%	6	32%	
Peer rejection	Never	21	91%	12	92%	n.s.	17	100%	16	84%	n.s.
	Occasionally	1	4%	0	0%		0	0%	1	5%	
	Regularly	1	4%	1	8%		0	0%	2	11%	
Suffers from bullying due to disease	Yes	2	9%	0	0%	n.s.	0	0%	2	11%	n.s.
	No	21	91%	13	100%		17	100%	17	89%	
Feels less appreciated	Yes	1	4%	0	0%	n.s.	0	0%	1	5%	n.s.
	No	18	78%	9	69%		13	76%	14	74%	
	Too young to tell	4	17%	4	31%		4	24%	4	21%	

Table 18 **Long-term outcome QOL items (IV)**

(Items above stated p-value vs. items below, n.s. = not statistically significant, >0.05)

3.3.2.1 QOL Score according to Bai et. al.

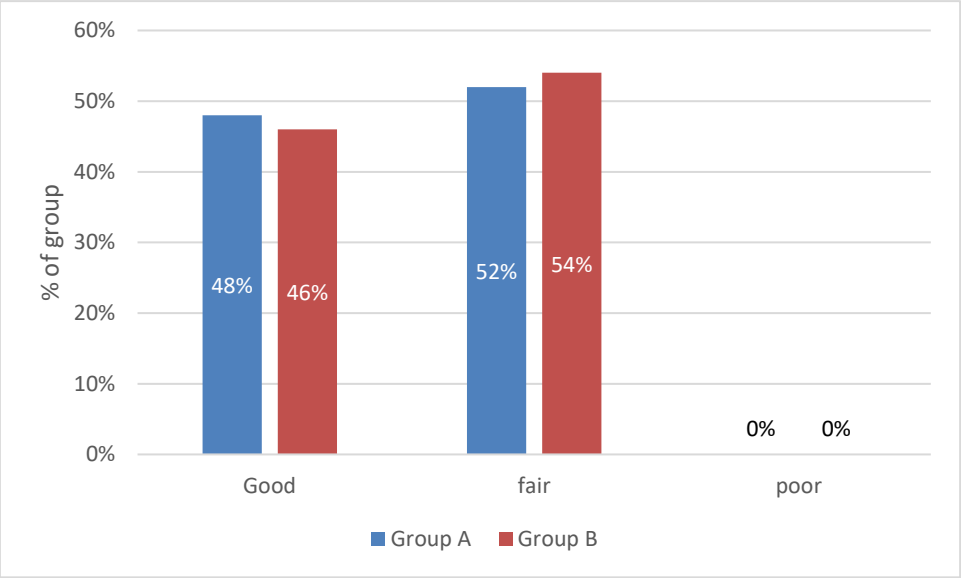

Fig. 39 Results according to Quality-of-Life Score from Bai et al.

When calculating the score according to Bai et. al. [140] for our patients it was striking that no patient scored “poor” while ”good” and “fair” outcomes were almost exactly equally distributed within each group as well as in comparison. In Group A 48% scored a “good” outcome while in Group B there were 46% patients with that outcome. A “fair” outcome was attributed to 52% of Group A patients and to 54% of Group B patients (Fig. 39).

Also, when taking the median of this numerical score without dividing it into the categories good fair and poor, no relevant difference between the groups could be identified as the mean was 8.9 points in Group A and 8.7 points in Group B (Fig. 40).

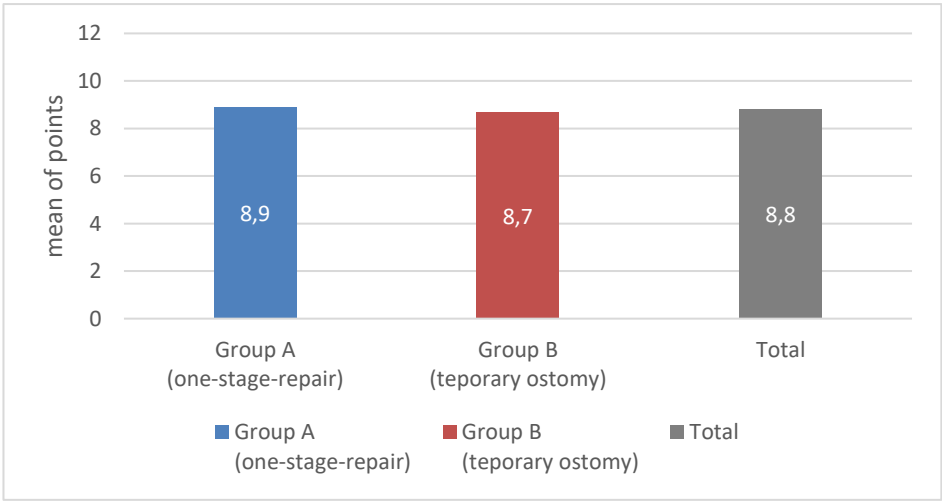

Fig. 40 Mean of Bai QOL Score ARM and HD patients

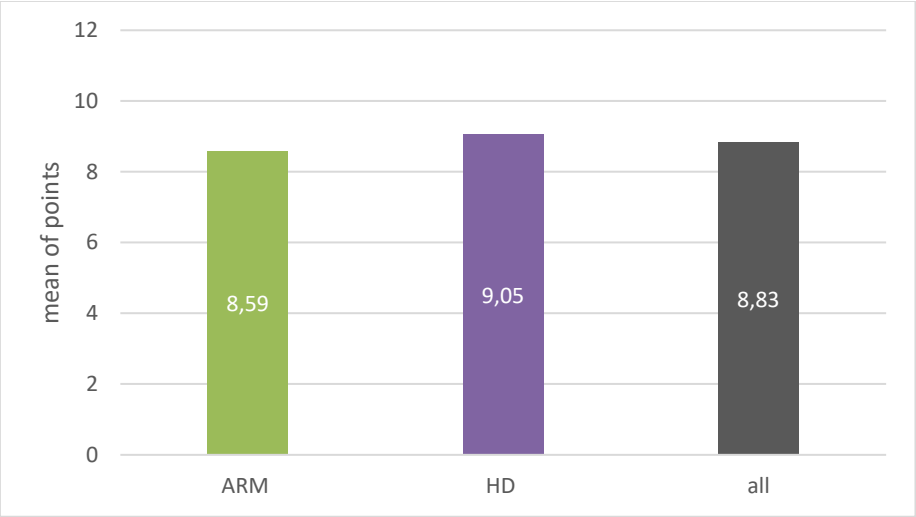

Fig. 41 Mean of Bai QOL Score ARM and HD patients

The difference between ARM and HD groups was slightly larger with a mean of 8.59 points in ARM and 9.05 points in HD patients (Fig. 41). The difference was not statistically significant with p=0.214. Likewise, without statistical significance (p=0.617) was the difference between the mean of points between male (8.68 points) and female (9.07 points) patients (Fig. 42).

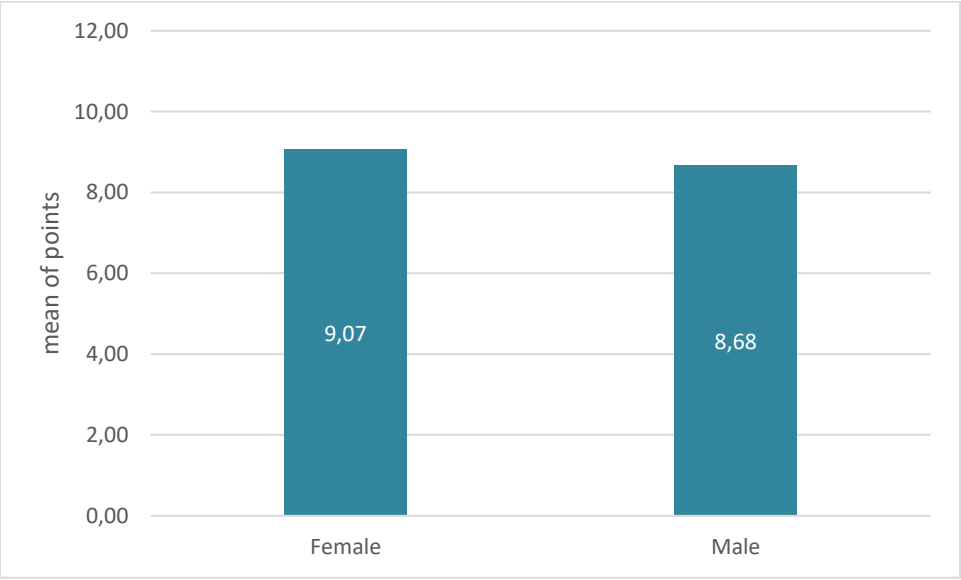

Fig. 42 Mean of Bai QOL Score female and male patients

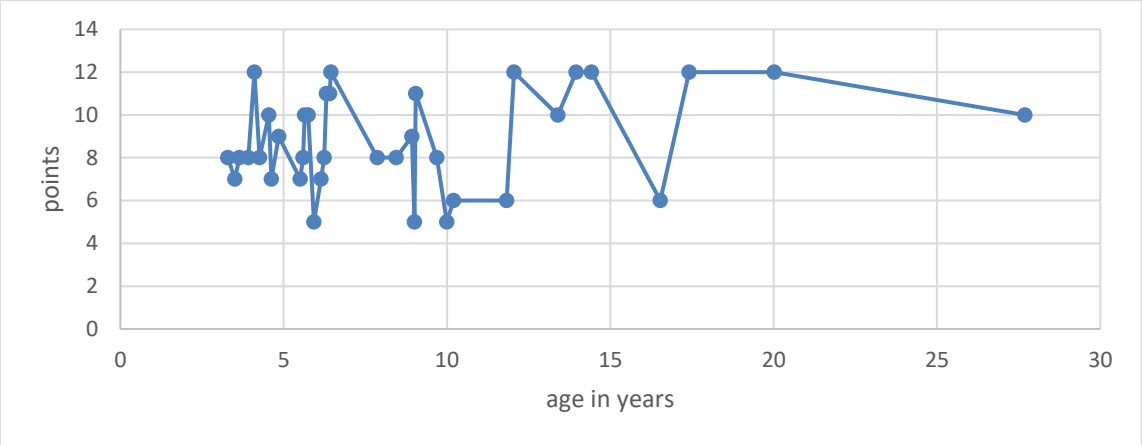

Fig. 43 **Correlation age at interview and points in Bai QOL score**

No correlation was found between age at interview and the points our patients collected in the score (Fig. 43).

3.3.2.2 QOL Score according to Barrena et. al.

Comparing QOL outcomes of our patients using the QOL Score suggested by Barrena et. al. [127] did not provide us with a large differentiation between the groups. 100% of patients from Group A scored a "good" outcome according to this score as did 92% of Group B patients. Only 8% of Group B patients scored a "fair" outcome while also in this score no patient was attributed a "poor" outcome in terms of their QOL (Fig. 44).

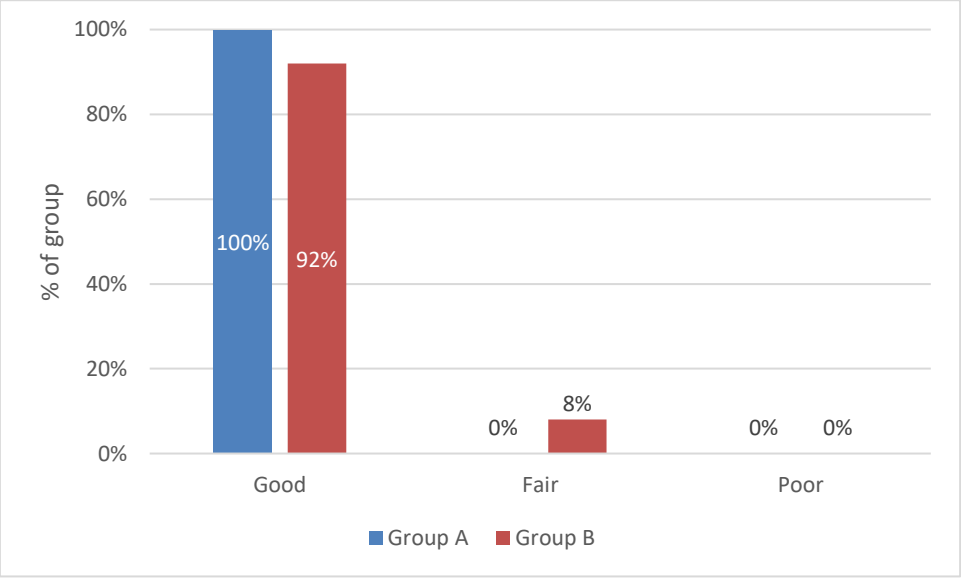

Fig. 44 **Results according to Quality-of-Life-Score from Barrena**

Comparing mean of points between Group A (13.52) and Group B (12.92 points) a slight but not statistically significant (p=0.284) difference could be shown (Fig. 45).

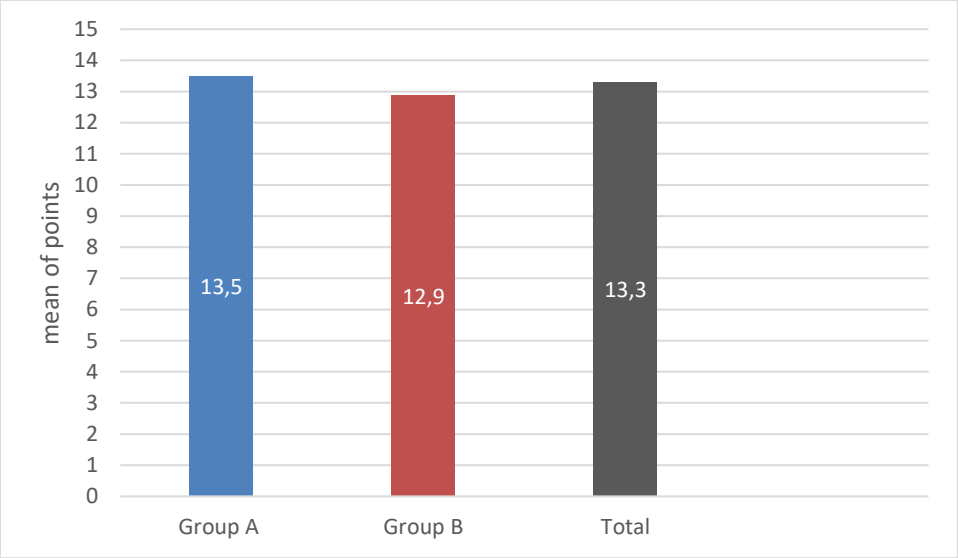

Fig. 45 **Mean of Barrena QOL Score ARM and HD patients**

Mean of points between ARM (13.47 points) and HD (13.15 points) patients revealed nearly no difference (p=0.804) (Fig. 46). Also, no difference was to be found between female and male patients regarding their long-term QOL outcome (Fig. 47). Likewise, no correlation could be found between the age at our interview and the points scored (Fig. 48).

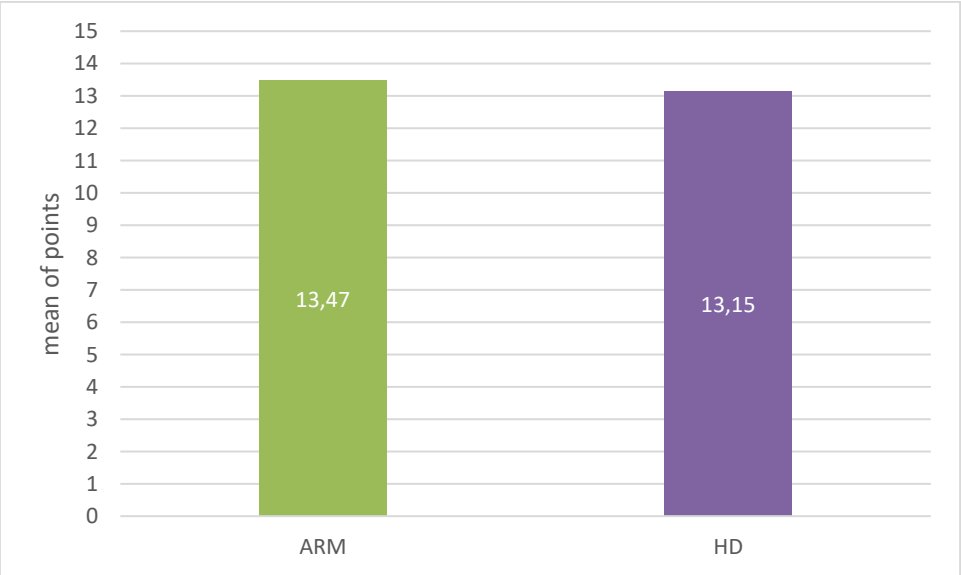

Fig. 46 **Mean of Barrena QOL Score ARM and HD patients**

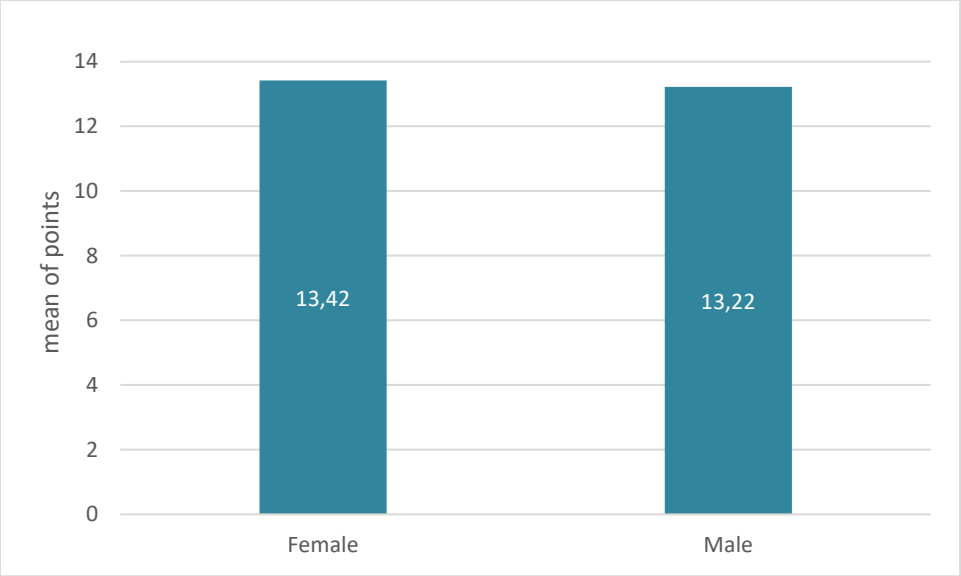

Fig. 47 **Mean of Barrena QOL Score female and male patients**

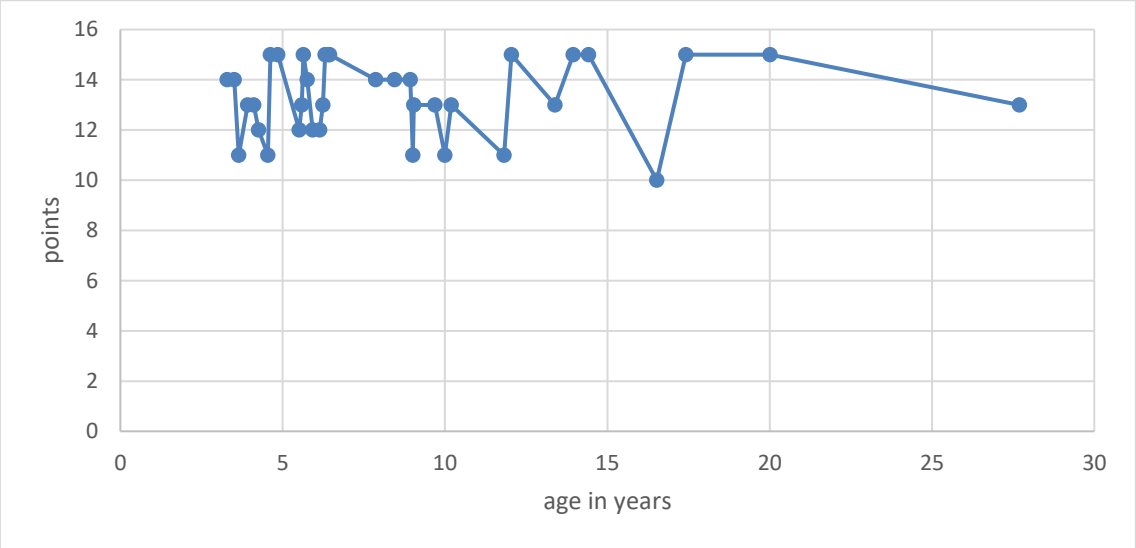

Fig. 48 **Correlation age at interview and points in Barrena QOL score**

3.4. Drop-out analysis

48 patients met the initial inclusion criteria and were invited but not included in the study because they could not be contacted. When comparing these patients to the study's participants a significantly higher age in the drop-out group (p=0.026) was registered.

The mean age in the group of participants was 8.96 years (range 3.5 years to 27.7 years) while the drop-out group showed a mean age of 11.66 years (range 1.9 years to

31.9 years). Gender ratio was comparable in both groups with the group of participants having a larger male proportion (61% male vs 39% female) (Fig. 49).

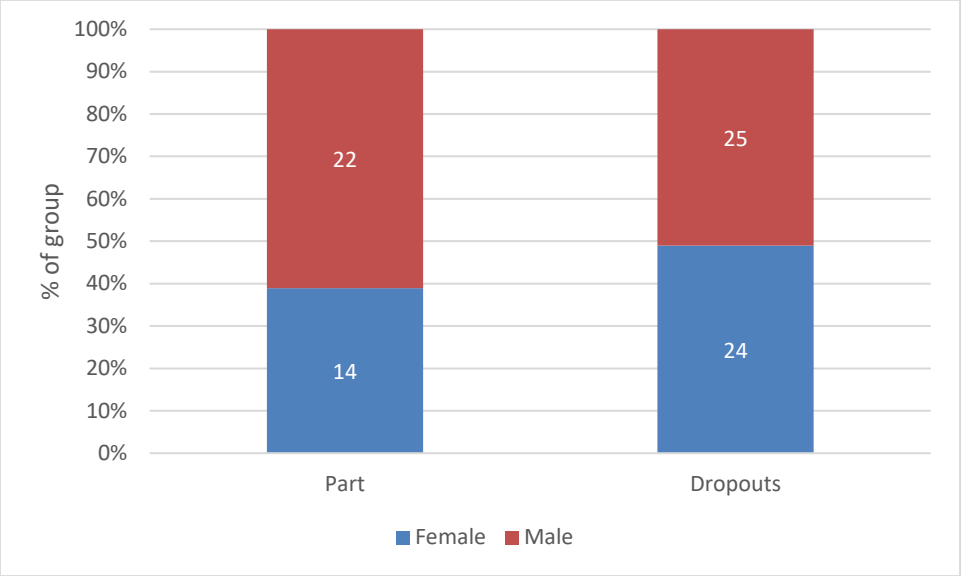

Fig. 49 **Gender proportion drop-outs vs participants**

Associated malformations were equally distributed among both groups with a presence of 51% in the participants and 52% in the drop-out group (p=1).

The proportion of patients receiving a primary repair in the drop out group was 57% while 43% received a temporary ostomy (Fig. 50).

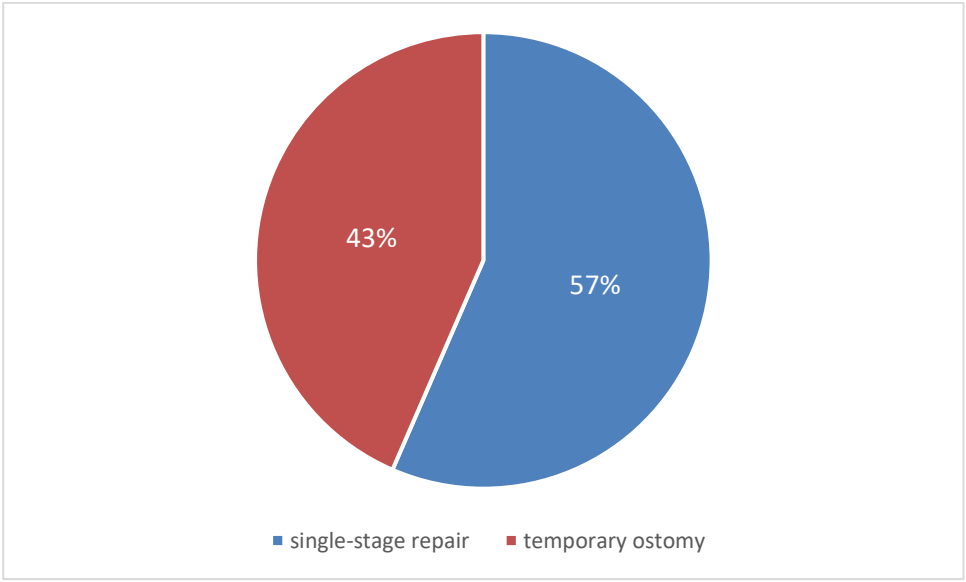

Fig. 50 **Single-stage repair and staged approach in drop-out group**

4. Discussion

The objective of this study was to verify if a single-stage repair is generally superior to a three-stage repair with a temporary ostomy measured at the patients' long-term outcome in terms of bowel function and quality of life.

Although our results could not prove a general and statistically significant superiority of the single-stage-approach a clear tendency towards more favorable results in this group was shown in almost all of our sub results. There is yet no similar study comparing the two approaches by focusing on the patients' long-term outcome. Studies comparing single and multiple-staged approaches usually focus on the preoperative period, those evaluating long-term outcome do not compare the two approaches. All of our findings did not hold statistical significance but support a growing cumulation of evidence showing advantages of a single-stage repair.

Sulkowski et.al. compared single and multiple-staged repairs regarding short-term outcome and likewise found the single-stage repair to be superior in almost all subitems [145]. The growing number of results showing superiority of the single-stage repair can be considered the reason why over the last two decades the single-stage repair has increasingly become the strategy of choice for HD patients supported by the evolvement of minimally invasive surgery. Since the PSARP technique was introduced, long-term outcome in ARM patients has continuously been improving [21] and the rates of single-stage repair have been rising. Giuliani et. al. state that single-repair is suitable for 90-95% of HD patients and strongly advocate for its preferred choice over multiple-staged approaches [85]. They reported a percentage of primary repair of 65,5% in their study [85] which almost exactly concurs with our 64% of primary repairs.

Functional outcome

Regarding the functional long-term-outcome we could show that in the single-stage repair group (Group A) the percentage of patients reporting incontinence, constipation, soiling of severe extend, necessity for diapers as well as a high frequency of bowel movements were smaller than in the three-stage repair group (Group B). Also, we found that patients after single-stage repair less often reported problems holding stool. Objectifying the long-term outcomes with the help of the Krickenbeck criteria we could show a slightly better outcome in the single-repair group. Raman et. al. showed a presence of

voluntary bowel movement (VBM) as defined by the Krickenbeck criteria in 45% of their patients [117]. This almost exactly matches our numbers for the multiple-staged repair group (46%) while the result was better in the single-stage repair group (65%). A normal bowel function – defined as VBM without soiling – was present in 12.1% of patients in the study by Raman et. al. and Rintala et. al. showed a percentage of 7.5% of normal bowel function in their patients in 1991 [146]. Our results showed higher percentages with 22% in Group A and 31% in Group B. Rintala et. al. reported a socially problematic bowel disfunction in 20-40% and normal bowel habits in 15% of their patients in 2002 [114]. Our study showed a rate of 31% (multiple-repair group) vs 17% (single-stage repair group) of socially problematic soiling (Grade 3). Our results evaluating Wildhaber Score showed a slightly higher percentage of "poor" outcome in the three-stage repair group.

Comparing the numerical score Barrena et. al. [127] found a mean score of 11 points in their patients while our results were lower but comparable and without relevant difference with a mean of 10.1 points in Group A and 9.8 points in Group B.

QOL outcome

Concerning the QOL outcome we could not show a relevant difference when using the Scores by Bai and Barrena to compare the outcomes between single-stage and multiple-staged repair. However, regarding the single items a clear tendency towards better QOL after single-stage repair was present throughout our findings. Overall health experienced by patients and their parents was reported to be excellent more often in the single-stage group. Dissatisfaction with bowel function, negative impact on the child's wellbeing and on their personality development, having to adjust activities to their bowel function as well as worrying about stool outside of home were all factors, we could show to be less frequent in patients after single-stage repair.

Bai et. al. for their patients reported feelings of shame about having to leave the classroom more often than others to go to the toilet. For our cohort this was not a frequent problem which was reported by 2 patients (9%) in Group A and 1 patient (8%) in Group B. Further Bai et. al. reported fear of peer rejection while in our study 8% of patients in each group stated to have occasional or regular experience with peer rejection due to the disease. Bullying was reported to not be a problem by any patients from

the multiple-stage repair group and by the vast majority of the primary repair group. 2 Patients (9%) after primary repair reported to have suffered from bullying due to their disease.

As Barrena et. al. [127] found in 2008 we can likewise state that of our patient cohort most live normal lives with few limitations in diet and all had normal daily activity (kindergarten, school or work).

We suggest that international studies in the future should additionally explore the cultural aspect possibly influencing social impairment for patients with defective stooling one or the other way.

Findings on the correlation between functional impairment and QOL are contradicting in the literature. Goyal et. al. for example found that defective stooling had no impact on QOL outcome in children under 10 years of age [147]. Bai et. al. reported patients with poor functional outcome also scoring worse regarding QOL [140]. Hassink et. al. showed a direct impact of incontinence on the patients' educational level as well as their social relationships [141]. In our cohort one patient of each group (4% of Group A and 8 % of Group B) answered it to be rather true or entirely true that finding friends was more challenging due to the disease compared to other children their age. Rintala even showed that more than by constipation and incontinence the QOL was affected by psychological functioning [148] and Raman et. al. found QOL outcome to be unaffected by the patients' age at interview, the surgical approach, the type of malformation or stooling outcomes[117].

Several studies have shown that bad functional outcome does not necessarily correlate with an impaired QOL when compared to a healthy control group [117]. Therefore, it is essential to not just collect data concerning the functional outcome and draw conclusions in terms of QOL but to inquire QOL separately ideally with a widely used score instrument.

Perioperative findings

Besides our focus on long-term outcome regarding bowel function and QOL we found relevant and highly significant differences between the single-stage and the multiple-stage repair group concerning perioperative factors.

The most significant differences were the longer hospitalization length (20 days vs. 84.8 days, p=0.002) as well as the higher mean of surgical procedures per patient (1.3 vs. 5.4, p=0.008) in favor of the primary repair. Our findings match the results of Sulkowski [145] while Giuliani et. al. found no difference in duration of hospitalization between patients with single and multiple-staged repair [108]. In pediatric care hospitalizations lead to attendance time lost in school or kindergarten for the patients but also absence time from work for the parent(s) taking care of the hospitalized child. The social and economic impact of these factors have not yet been explored in detail but must not be underestimated in clinical practice. Preferring single-stage repair over multiple-staged approaches these impairing factors can be minimized no longer putting the patients at an unnecessary disadvantage.

Consequently, more surgical procedures imminently hold a higher risk of complications. When evaluating complications secondary to surgical intervention it sometimes proofs hard to differentiate between complications caused by the operation and the unfortunate but natural course of disease. We could however prove a higher occurrence of more severe complications in the three-stage repair group (Grade 3 complications in 50% of Group B vs 4% in Group A, p=0.002) while no statistically significant difference could be shown between the general occurrence or non-occurrence of complications between the groups. Our findings support what Giuliani et. al. stated in their study from 2020 about finding a high rate of complications such as wound-dehiscence, prolapse and infection which also matches the complication profile in our study [108]. Complications of ostomy are reported to lie around 20-30% [100, 108] we found 50% of complications in our staged group to be stoma related (out of 13 patients 3 had no complication, 5 had non-stoma related complications and 5 suffered from stoma-related complications). In addition, our cohort presented more complications in patients with an associated malformation as 74% of patients with associated malformations presented complications (Grade 1-3) vs. 41% in those patients without associated malformations.

Further, we found a statistically highly significant difference between reoperations needed to control complications in more than half of our patients after three-stage-repair. These findings agree with Sulkowski et. al. finding higher percentages of readmission (58.5 vs 37.9%) as well as higher numbers of unplanned secondary surgeries (38.7 vs 26%) after multiple-staged repair compared to primary repair [145]. Our findings were even less balanced as more than half the patients (54%) in the three-stage

repair group needed reoperation while in the primary repair group it was only 4% (p=0.001).

Our cohort showed an earlier definite repair in the single-stage group (188 vs. 277 days of age), we could however not show a correlation between earlier repair and better long-term outcome. Moore and Albanese et. al. amongst others stated a favorable "training effect" of brain-defecation reflexes after early repair [13, 95]. Even though our study was not designed to examine such reasons for this finding, an earlier creation of the definite physical situation is expected to have advantages of several kind.

Another perioperative finding which was not explored by us in detail but should not be underestimated is the psychological challenge for parents and family when taking care of a newborn or toddler with an ostomy that also has also been discussed by Giuliani et. al. [85]. By preferring a primary repair where clinically possible such psychological burden can be lessened. With the single-stage repair there is no need for a colostomy, turning away the psychological hardship for the parents that comes with a colostomy of their own child. In older patients the psychological burden for the patients themselves is one more reason to avoid a colostomy whenever possible.

Several studies have shown that long-term outcome regarding continence and QOL should not be understood as a static but a fluid state that undergoes changes with time. Mills et. al. found that continence in HD patients does improve with age quoting several longitudinal studies supporting their findings [122]. Järvi et. al. found a decline in bowel function with rising age as well as an increasing constipation [138]. As our study is a cross-sectional study by design, we could not examine such a development, but neither could we find a correlation between age at follow up and outcome according to the different scores we employed. However, such changes in continence and QOL can naturally be expected taking into consideration the fact that even many long-term follow up interviews take place before puberty. Not only physical changes pose a factor for change of outcome, but also young adults might reevaluate their psychological QOL challenges and come to different conclusions than they did as a child e.g., considering mild soiling in their new adult context.

Lastly, economic reasons which we did not explore in our study should be considered as a potentially strong advantage of a single-stage procedure as hospitalization and

number of surgeries can be decreased significantly. Readmission and complication in the multiple-staged approach add to costs. Other studies have been able to proof these economic advantages of a primary repair as described by Giuliani et. al. [85]. The economic difference may be no primary point of interest to countries with a highly functional health care system and wide health insurance coverage. In countries with less assured health systems this aspect can however be the reason a patient cannot be treated at all or not sufficiently. Therefor the single-stage repair offers great potential to optimize therapy for ARM and HD patients worldwide.

Limitations

Our study's limitations were of several kinds. First and foremost, our small number of complete data sets causes our cohort to not represent the entire spectrum of ARM and HD variations as is the case for many other studies in this field [111]. Most importantly however it severely limits statistical power and thus restrains our ability to create statistical evidence that holds generalized implication. This problem is a common one when exploring rather rare malformations that present in various forms (e.g., Mills et. al. [122]), which is why we proceeded despite the small number of participants. A main reason for this in many studies as well as in ours is the long-term follow-up problem of establishing contact many years after the surgical repair. In our case almost half of the possible participants could not be reached due to missing contact in formation.

It was striking that patients with especially complex medical history and exceptionally incomplete files more often than others could not be contacted during the recruiting phase. On the other hand, patients with complicated courses of disease but a regular follow-up history, were easier to track in some cases due to frequent checkup contacts. Patients with milder malformations were less likely to attend follow-ups for many years like some patients with more severe malformations did. We can only suspect that due to a favorable outcome the parents did not see the need for extended check-ups. This is in line with reports from many studies in this field. As So stated in 1980: "Parents do not bring children back for follow-up care when they are healthy." [65]. This might explain why we could show a longer follow-up time for patients after multiple-staged repair in our study.

Additionally the patient charts did not provide solid information on Enterocolitis which is why we were not able to evaluate the prevalence of this important complication.

Due to the small number of patients, statistical analysis of subgroups and correlations of surgical procedures and outcome was severely limited. Similar problems are repeatedly described by many authors such as Catto-Smith and Mills et. al. [84, 122]. This of course leaves us unsure about as to which extend those patients' inclusion would have affected our results. Considering the ratio of single-stage and multiple-stage operated patients was similar comparing our participants (64% single-stage vs. 36% multiple-staged) and those patients who could not be reached (57% single-stage vs. 43% multiple-staged) we do not suspect relevant confounding in this ratio.

Because of the rareness of the diseases, we combined ARM and HD patients into one group knowing it would increase heterogenicity of the study's cohort. However, we succeeded to balance Groups A and B with almost exactly 50% ARM and HD patients each (Group A Group B). Since both malformations have a similar set of challenges in the long-term outcome, we decided to use this way to enlarge our cohort. Sulkowski et. al. [145] succeeded to conduct a longitudinal study on a large patient collective using a national health care data base (Pediatric Hospital Information System by the American Children's Hospital Association) , which can be a way also for other researchers to form patient cohorts large enough to reveal relevant differences in outcome according to the surgical strategy.

A further limitation of our study is the cross-sectional design and the non-randomized choice of surgical procedure. As found in other studies before this fact leads to the bias of sicker patients with preoperative decompensation or associated malformations that complicate surgical repair more often receiving a multiple-staged repair with an initial ostomy. The same problem has been described by Sulkowski et. al. [145] and surely is a reoccurring challenge in many studies as well as in ours. These patients have a higher risk for complications already due to their comorbidities and thus such preselection can possibly bias study outcomes to the disadvantage of the three-stage repair.

Further, the choice of initial surgical approach is often reported to depend on the surgeons' personal experience, preference and many situational factors. Giuliani et. al. stated that often the surgeons' training and their mentors' preference play a role in the decision [85]. Additionally, in multicenter studies the surgical repair will differ between centers and surgeons even if intended to produce comparable results [53]. The choice of the procedure (single-stage or multiple-staged) was repeatedly reported to depend on the center operated in [145]. Likewise, in our study 80% of patients recruited from UKD had undergone single-stage repair while for MBT the percentage of multiple-staged procedures was higher ((43% Group A, 57% Group B).

We did not explore the explicit reasons for the surgeons' decision to choose single or multi-staged repair. Sulkowski et. al. [145] made use of propensity score matched grouping to balance this potential bias, this however is not applicable for our small patient group. We believe that the growing body of evidence in favor of the single-stage repair which this study is a part of should lead to a consistent training that considers research evidence as well es clinical practice to provide a reliable guideline for consistent patient care. The reasons for the surgeons' preference for one or the other procedure should be explored in further detail in the future.

A long-term confounder is the fact that surgical technique develops and evolves over time, in the surgical field in general as well as for each surgeon individually [21].

As Mills stated in 2008 long-term outcome of newly developed surgical techniques take their time to show results in our research [122]. In addition, the physicians involved in the process of collecting the data might individually interpret or rank outcomes differently as reported by Langer et. al. [53]. In our study this confounder at least could be ruled out since all interviews were carried out by the same physician. Others report the limitation of adult physicians with a lack of experience with pediatric malformations performing the follow-up and Gustafson et. al. call for an aftercare team involving adult surgeons to transfer knowledge for better care for patients in adult life [112]. As aftercare for our patients was exclusively attended in pediatric surgery departments of the included clinics, we do not suspect confounding due to this aspect.

One more general limitation is that the scoring outcome “good” can never be seen as equivalent to a normal bowel function as seen in control groups as Rintala already stated in his study in 2002 [114]. Additionally, when interviewed using a Likert Scale a relativity bias can bias the answer. A sick child whose symptoms improved with time will be more likely to state a “good” satisfaction, even though compared to a healthy child the gap will be obvious if measured objectively. A special challenge of evaluating QOL and functional outcome in patients born with a malformation will always be the relativity bias due to the fact that they have never been entirely healthy bowel wise. This problem has been mentioned before by Rintala [114] as well as Raman [117]. Heij et. al. concluded on the functional issue to only attribute a “good” outcome if “the ability to hold back feces until the proper place and time for complete evacuation” is given. [78].

Another difficulty may be attributed to a feeling of shame and hierarchical thinking. Both can lead to underreporting of unfavorable symptoms such as soiling, incontinence or any other outcome that is expected to be perceived negatively. This is valid for patients holding back information regarding their symptoms in front of their parents as well as underreporting from parent to physician. This can be caused by feelings of shame, lack of trust or even fear of further diagnostic procedures. In the communication with the surgeon an unwillingness to confront the physician with his “failure” can be the cause of underreported complications as Rintala already stated in 2002 [114]. Heij et. al. shared these thoughts on the problem and additionally stated it was questionable, if the evaluation of the outcome by the operating surgeon can always be considered reliable [78]. Ludman et. al. showed that surgeons underestimated and underreported what to them seemed to be “minor” complications while the symptom might pose a substantial problem in the patient’s everyday life [149]. This can at least partly be explained by the bias of “having seen worse” which leads to a relativity bias. However, literature differs on whether a standardized questionnaire can solve the problem of underreporting or will further obstruct expedient communication [149] We see an opportunity in a questionnaire completed by the patient and parents that can be a guideline to discussion when meeting the physician.

We were faced with the general challenge of assessing the QOL in children mostly by interviewing not the patients themselves but interviewing their parents as a proxy.

In the evaluation of children proxy bias cannot always be avoided. The child's experience with bowel function, symptoms and complications can differ greatly from the parents' perception due to various filters that disturb communication as has been found by Rintala [114]. Wigander et. al. in paired questioning could show that children reported more physical symptoms as well as more psychological impairment when compared to their mothers' answers [111]. Mills et. al. however stated to have found a satisfying correlation between the patients' and the proxies' answers [122].

The socioeconomic situation of the patients' family might likewise lead to a different perception and judgement of the same situation due to resilience factors making it easier to cope with the situation. Therefore, in future studies this factor should be considered to gain a broader picture of the social implications.

Heterogeneity poses a challenge that also applies to the choice of tool to objectively evaluate long-term outcome, concerning both functional and QOL. Until now studies have shown to be heterogenous in that matter and therefore hard to compare and there has yet to be found a consensus on which score to use internationally to enable a faster advancing research progress. Many attempts have been made to categorize functional and QOL outcome into score systems to make studies comparable. Scoring systems have been adapted to suit patients with gastrointestinal impairments and focus has been on the social aspects of defective stooling and its' impact on everyday life. Additionally, measures have been taken to further adapt the scores and questionnaires to the different age groups concerned [117, 140, 147].

For evaluation of our patients' functional long-term outcome, we decided to use a scoring system originally designed for ARM patients by Holschneider et. al. in the 2005 Krickenbeck conference. [4] The Krickenbeck criteria are an international consensus on evaluation of postoperative continence under no therapy in patients of 3 years of age or older which was designed to provide a tool to make follow-up studies comparable [4]. As mentioned above the criteria were originally created for the evaluation of postoperative continence outcome of ARM patients but has been increasingly used also for the evaluation of continence in post-repair HD patients [110, 150-152]. This is reasonable as post-repair HD patients often suffer from very similar problems as ARM patients

and the Krickenbeck criteria provide a standardized tool to evaluate follow-up data [110]. In our study we also applied the criteria for patients over 3 years of age who had not yet reached full stool continence (not fully potty-trained).

As the Krickenbeck classification is not designed to differentiate incontinence and overflow incontinence from constipation we see a limiting factor in this. Stensrud et. al. [110] stated that their patients still suffered from soiling after constipation was treated. Due to our study's design, we did not have the possibility to treat and reevaluate the patients' symptoms. We chose to additionally employ the scoring system proposed by Wildhaber et. al. [74] to enable later comparison with a broader spectrum of studies. As it is designed as a linear score, we expected it to hold possibilities for further statistical analysis which we however could not make use of in the end due to the small patient collective. For QOL evaluation we made use of the scores proposed by Barrena and Bai [127, 140] as they are applicable for our cross-sectional study design as well as for the telephone interview. Both are numerical scores which we hoped to make use of for further statistical evaluation which lastly was not possible due to the small cohort.

Conclusion

Despite its many limitations our study joins the growing body of evidence proofing single-stage repair surgery to be feasible, safe and producing equally good or better functional results while resulting in less short-term complications and reoperations when compared to the multiple-staged approach in HD and ARM patients. By preferring the single-stage-repair the psychological trauma that often comes with a colostomy is avoided and absence times in kindergarten, school and work (parents) can be reduced. Additionally, economical and organizational advantages make the single-stage-repair a chance for patients in health care systems with less broadly available resources. A remaining group of more severely ill patients, however, might still profit from the multiple-stages repair.

In the heterogenous and therefore challenging field of research of functional and QOL long-term outcome in ARM and HD patients, larger studies are needed to draw solid conclusions with the help of complex statistical models that depend on larger numbers of patients from all life stages.

Our findings are congruent with many earlier studies, among others a large study by Giuliani et. al. from 2020 who strongly advocates for an abandonment of the staged approach whenever clinically possible [85]. Our study confirms their study and adds a long-term perspective on functional and QOL outcomes in favor of the primary repair.

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Appendix

A. Klinischer Fragebogen

Anorektale Malformation und Hirschsprung'sche Krankheit:
Vergleich der Ergebnisse bei Patienten mit Operation ohne Stoma vs. Patienten mit primärer Stomaversorgung in Bezug auf Kontinenz und Patientenzufriedenheit

Angaben zur Person (Patient/in)

Pseudonym:

Alter bei Befragung:
aktuelle Größe
und Gewicht:
(BMI:
HD □ ARM □

Answering: □ Patient □ Parent

Die Antworten auf folgende Fragen sollten sich auf die letzten drei Monate beziehen.

1. Mein Kind ist altersbedingt noch nicht trocken/ (Krickenbeck nicht anwendbar)
Zu jung, um Stuhlgang selbstständig zu kontrollieren ja □ nein □
< 3 Jahre (bis 5)

2. Mein Kind hat aktuell ein dauerhaftes Stoma ja □ nein □

Thema Willkürliche Darmentleerung

3. Verspürt ihr Kind, wenn es groß zur Toilette muss?
Dranggefühl ja □ nein □
(Wenn unsicher dann Nein.)

Dranggefühl
2 normal □
1 unsicher □
0 nicht vorhanden □

4. Meldet ihr Kind sich, weil es zur Toilette muss?
Fähigkeit zur Verbalisierung ja □ nein □

5. Kann Ihr Kind den Stuhlgang ggf. bis zum Toilettengang einhalten?
Zurückhalten der Darmbewegung ja □ nein □

6. Frequenz des Stuhlgangs
Wie häufig hat Ihr Kind Stuhlgang?

*	seltener als 1/d	□
2:	1-2/d	□
1:	2-5/d	□
0:	> 5/d	□

Stuhlinkontinenz (grob orientierend)

7. Hat Ihr Kind:

unkontrollierten Windabgang	Ja □	Nein □
Stuhlabgang bei Diarrhö	Ja □	Nein □
Stuhlabgang unkontrolliert	Ja □	Nein □
Stuhlabgang bei körperlicher Aktivität	Ja □	Nein □
Stuhlabgang in emotionalen Momenten	Ja □	Nein □
Stuhlabgang beim Husten oder Niesen	Ja □	Nein □
Stuhlinkontinenz isoliert tagsüber	Ja □	Nein □
nachts	Ja □	Nein □
tageszeitenunabhängig	Ja □	Nein □

8. Wie häufig hat ihr Kind unkontrollierten Stuhlabgang?

nie		□
versehentlich	(gelegentlich bei Diarrhö, Stress)	□
regelmäßig	(konsistenzunabhängig)	□

9. Besteht die Notwendigkeit von Windeln?

2	nie	□
1	manchmal <5/Woche	□
0	immer > 5/woche	□

10. Einlagen in Unterwäsche □ nein □ tagsüber □ nachts □ immer

11. Zeitpunkt des Erreichen der Stuhlkontinenz (Datum):
Alter:
Abstand 1. OP:

12. Stuhlschmieren - Wir häufig hat ihr Kind stuhlverschmutzte Unterwäsche?

0	nie	□
Grad 1	gelegentlich 1-2x/Woche	□
Grad 2	jeden Tag, kein soziales Problem	□
Grad 3	jeden Tag, soziales Problem	□

13. Stuhlschmieren - Konsistenzabhängig?

2	nie	□

1 bei Stress/ Diarrhö □
0 Immer /regelmäßig □

14. Wie ist die überwiegende Stuhlkonsistenz ihres Kindes?
2 normal □
1 lose/breiig □
0 flüssig □

15. Muss Ihr Kind stark pressen um den Stuhlgang einzuleiten?

nie □
manchmal (< 50% der Toilettengänge) □
regelmäßig □

16. Kann Ihr Kind unterscheiden zwischen flüssigem/festen Stuhl?
(Diskrimination)
2 normal □
1 unsicher □
0 nicht vorhanden □

17. Hat Ihr Kind Probleme Urin zu halten, bis es die Toilette erreicht?
Nie □
Gelegentlich □
Regelmäßig □

In emotionalen Momenten	Ja □	Nein □
Beim Husten/ Niesen	Ja □	Nein □
Bei körperlicher Aktivität	Ja □	Nein □

Chronische Obstipation
18. Leidet Ihr Kind unter chronischer Verstopfung? (Kein Stuhlgang > 48h)
Wenn ja, wie ist diese behandelt?
0 nie □
Grad 1 durch Änderung der Diät behandelbar □
Grad 2 Notwenigkeit von Laxanzien □
Grad 3 Therapieresistent gegen Laxanzien und Diät (regelm Einläufe = Grad 3) □

Langzeit Medikation (Einläufe, Medikamente)
19. Ist Ihr Kind langfristig angewiesen auf Medikation oder Einläufe?
2 keine □
1 manchmal (bis 1 /Woche) □
0 immer /regelmäßig □

Regelmäßige Einnahme Laxativa (Movicol etc.) □
Regelmäßige Einläufe notwendig □
regelmäßige Einnahme von Loperamid
oder ähnliche orale Medikation bei Diarrhöen □

20. Leidet Ihr Kind unter Bauchschmerzen?
Nie □ gelegentlich (< 1/Woche) □ regelmäßig (>= 1/woche) □

21. Leidet ihr Kind unter Schmerzen beim Stuhlgang
Nie □ gelegentlich (< 1/Woche) □ regelmäßig (>= 1/woche) □

17+* (22.) Gibt es Probleme bei der Sexualfunktion bzw. beim Geschlechtsverkehr?
Regelmäßige Errektionsprobleme Ja □ Nein □
Regelmäßige Ejakulationsschwierigkeiten Ja □ Nein □

QUALITY OF LIFE

0. Insgesamt würde ich die Gesundheit meines Kindes als … beschreiben.
ausgezeichnet □
gut □
mittelmäßig □
schlecht □

1. Die Erkrankung HD/ARM hat einen negativen Einfluss auf mein generelles Wohlbefinden keinen
□
kaum □
leichten □
großen □

2. Die Erkrankung HD/ARM hat einen negativen Einfluss auf mein Alltagsleben
keinen □
kaum □
leichten □
großen □

3. Ich bin mit meiner / der Darmfunktion meines Sohnes/meiner Tochter zufrieden (score 1–4, 4 = very satisfied)
Völlig zufrieden □
meistens zufrieden □
meistens unzufrieden □
völlig unzufrieden □

4. Zustimmung zu den Aussagen:
Mein Kind muss seine Aktivitäten nach seiner Darmfunktion ausrichten.
Trifft vollkommen zu □
Eher zutreffend □
Eher unzutreffend □
Gar nicht zutreffend □

5. Mein Kind bleibt lieber zu Hause, als bei Freunden zu spielen.
Trifft vollkommen zu □
Eher zutreffend □

Eher unzutreffend □
Gar nicht zutreffend □

6. Mein Kind isst nicht gern außerhalb von zu Hause
Trifft vollkommen zu □
Eher zutreffend □
Eher unzutreffend □
Gar nicht zutreffend □

7. Ich finde schwerer Freunde als andere in meinem Alter.
Trifft vollkommen zu □
Eher zutreffend □
Eher unzutreffend □
Gar nicht zutreffend □

8. Mein Kind macht sich sorgen, versehentlich Stuhl zu verlieren
Trifft vollkommen zu □
Eher zutreffend □
Eher unzutreffend □
Gar nicht zutreffend □

9. Mein Kind macht sich Sorgen um seinen Stuhlgang wenn er/sie außerhalb von zu Hause ist.
Trifft vollkommen zu □
Eher zutreffend □
Eher unzutreffend □
Gar nicht zutreffend □

10. Mein Kind hat Beschäftigungen, die ihm gefallen wegen der Erkrankung aufgeben müssen
Trifft vollkommen zu □
Eher zutreffend □
Eher unzutreffend □
Gar nicht zutreffend □

11. Es ist wichtig, immer zu wissen, dass eine Toilette in der Nähe ist.
Trifft vollkommen zu □
Eher zutreffend □
Eher unzutreffend □
Gar nicht zutreffend □

12. Ernährungsgewohnheiten
keine Ernährungseinschränkungen 3 □
leichte Ernährungseinschränkungen 2 □
ausgeprägte Ernährungseinschränkungen 1 □

13. Schule und Arbeit
Normale tägliche Aktivitäten 3 □
Keine regelmäßigen Aktivitäten 2 □
Keine Aktivitäten möglich (handlungsunfähig durch Erkrankung) 1 □

14. Hat ihr Kind Schulfehlzeiten durch die Erkrankung zu verzeichnen ?
keine □
manchmal □
regelmässig □

15. Die Schullaufbahn meines Kindes wurde negativ beeinflusst durch Erkrankung
Ja □ Nein □

16. Meine Berufswahl war durch die Erkrankung beeinflusst/ eingeschränkt?
Ja □ Nein □

Freizeit

17. Die Körperliche Betätigung ist durch die Erkrankung eingeschränkt
Ja □ Nein □

18. Regelmäßig Sport, Ausflüge etc. 3 □
Nur gelegentlich und unter besonderen Vorkehrungen 2 □
Keine regelmäßigen Freizeitaktivitäten 1 □

19. Auswärts Übernachten ist…
… problemlos möglich. □
… nur eingeschränkt und mit Vorkehrungen möglich □
… nicht möglich □

20. Aufgrund der Erkrankung…
…fahre ich nicht in den Urlaub □
…fahre ich seltener in den Urlaub/eingeschränkte Ziele □
…fahre ich problemlos in den Urlaub □

21. Einfluss der Erkrankung auf die Persönlichkeit

Die Erkrankung hat
…keinen Einfluss auf die Persönlichkeitsentwicklung 3 □
… einen leichten Einfluss 2 □
… einen starken Einfluss (handlungsunfähig durch Erkrankung) 1 □

22. Die Erkrankung hat generell einen negativen Einfluss auf mein **Sozialleben**
Ja □ Nein (keinen Einfluss) □

Familienleben

23. Die Erkrankung hat
…keinen Einfluss auf unser Familienleben 3 □
… das Familienleben verschlechtert / negativ beeinflusst 2 □
… das Familienleben zerstört 1 □

Gleichaltrige

24. Ich habe das Gefühl, von Gleichaltrigen mehr ausgegrenzt oder zurückgewiesen zu werden
(Zurückweisung von Gleichaltrigen aufgrund der Erkrankung?)

Keine □
manchmal □
Häufig □

Emotionen

25. Mein Sohn/ Meine Tochter ist unglücklich

nie □
manchmal □
regelmäßig □

26. Mein Sohn/ Meine Tochter ist ängstlich

nie □
manchmal □
regelmäßig □

27. Ich schäme mich wegen meiner Erkrankung Ja □ Nein □

28. Ich schäme mich, wenn ich wegen meiner Erkrankung das Klassenzimmer häufiger als andere verlassen muss, um zur Toilette zu gehen.

Ja □ Nein □

29. Ich fühle mich anders als andere in meinem Alter auf Grund der Erkrankung

Ja □ Nein □

30. Ich fühle mich wegen der Erkrankung weniger attraktiv

Ja □ Nein □

31. Ich habe Angst, dass andere riechen könnten, dass ich inkontinent bin.

Ja □ Nein □

32. Ich fühle mich wegen der Erkrankung von anderen weniger wertgeschätzt

Ja □ Nein □

33. Ich werde wegen meiner Erkrankung häufiger geärgert als andere Kinder.

Ja □ Nein □

Ich versichere an Eides statt, dass die Dissertation selbständig und ohne unzulässige fremde Hilfe erstellt worden ist und die hier vorgelegte Dissertation nicht von einer anderen medizinischen Fakultät abgelehnt worden ist.

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