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PhD thesis

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Haemorrhoidal Disease – Minimal Open Haemorrhoidectomy, Symptoms and Health-related quality of life

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Contents

Studies included in the PhD thesis

The studies for this thesis were carried out at the Department of Surgery, Holbaek Hospital, Region Zealand, Denmark.

The thesis is based on the following studies:

Study I:

Rørvik HD, Styr K, Ilum L, McKinstry GK, Dragesund T, Campos AH, Brandstrup B, Olaison G. *The Haemorrhoidal Disease Symptom Score and Short Health Scale$_{HD}$: new tools to evaluate symptoms and Health-Related Quality of Life in Haemorrhoidal Disease.* Dis Colon Rectum. 2019;62(3):333-342.

Study II:

Roervik HD, Heiner Campos A, Ilum L, Styr K, McKinstry GK, Olaison G. *Minimal open hemorrhoidectomy.* Tech Coloproctol. 2019;23(1):73-77.

Study III:

Rørvik HD, Campos AH, Styr K, Ilum L, McKinstry GK, Brandstrup B, Olaison G. *Minimal Open Haemorrhoidectomy versus Transanal Haemorrhoidal Dearterialization: the effect on symptoms. An open-label randomized controlled trial.* Dis Colon Rectum [In Press].

Study IV:

Rørvik HD, Davidsen M, Gierloeff MC, Brandstrup B, Olaison G. *Quality of life in patients with Haemorrhoidal Disease* [submitted]

Throughout the thesis the studies will be referred to by their Roman numerals as indicated above.

Abbreviations

ASA	American Society of Anesthesiologists
AUC	Area under the curve
CI	Confidence interval
COSMIN	Consensus-based standards for the selection of health measurement instruments
DRG	Disease-related group
EQ-5D	EuroQol - 5 dimensions
HAL	Haemorrhoidal artery ligation
HD	Haemorrhoidal disease
HDSS	Haemorrhoidal disease symptom score
HRQoL	Health-related quality of life
ICC	Interclass correlation coefficient
MOH	Minimal open haemorrhoidectomy
PROM	Patient-reported outcome measure
RCT	Randomized controlled trial
ROC	Receiver operating curve characteristics
RFIS	Revised Fecal Incontinence Score
SDC	Smallest detectable change
SF-12v2	Optum® 12-Item Short Form Survey version 2
SF-36v2	Optum® 36-Item Short Form Survey version 2
SHS_{HD}	Short Health Scale adapted to haemorrhoidal disease
Spearman's rho	Spearman's ranked correlation coefficient
SUSY 2017	Danish Health Interview Survey 2017
THD	Transanal haemorrhoidal dearterialization

Background

Definition

Haemorrhoids (from ancient Greek: haema = blood and rhoos = flowing) is the term used to describe the enlargement of the anal cushions. Some degree of haemorrhoids localized intra-anally can be found in most adults.[5] Haemorrhoids first become pathologic when they cause symptoms, which will be referred to as haemorrhoidal disease (HD) in this thesis.

Anatomy

The anal canal from the rectum to the anus measures 2.5-4 centimeteres.[6] The inner lining of the anal canal changes from pink intestinal mucosa (columnar epithelium) in the upper part to the pale anoderm (squamous epithelium) in the lower part.[6] The transitional zone from columnar to squamous epithelium is referred to as the dentate line. The anal cushions are mucosa covered protrusion located just above the dentate line.[7–9] The anal cushions are part of the normal anal anatomy and have rather constant positions in the anal canal: the left lateral, right anterior and right posterior position (Figure 1).[7,9]

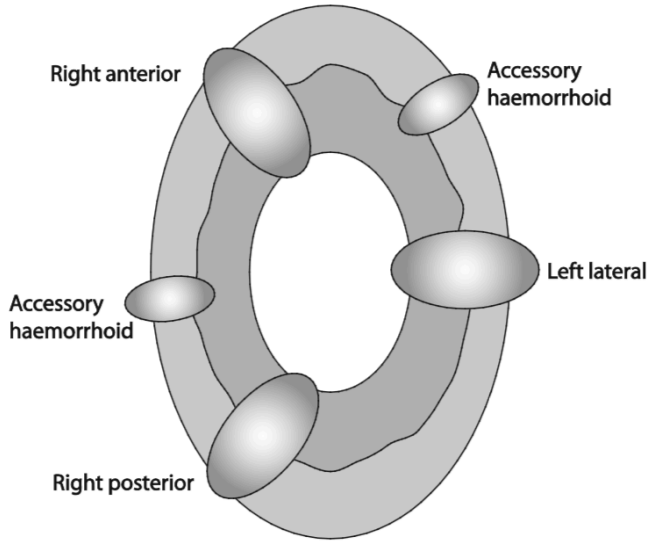
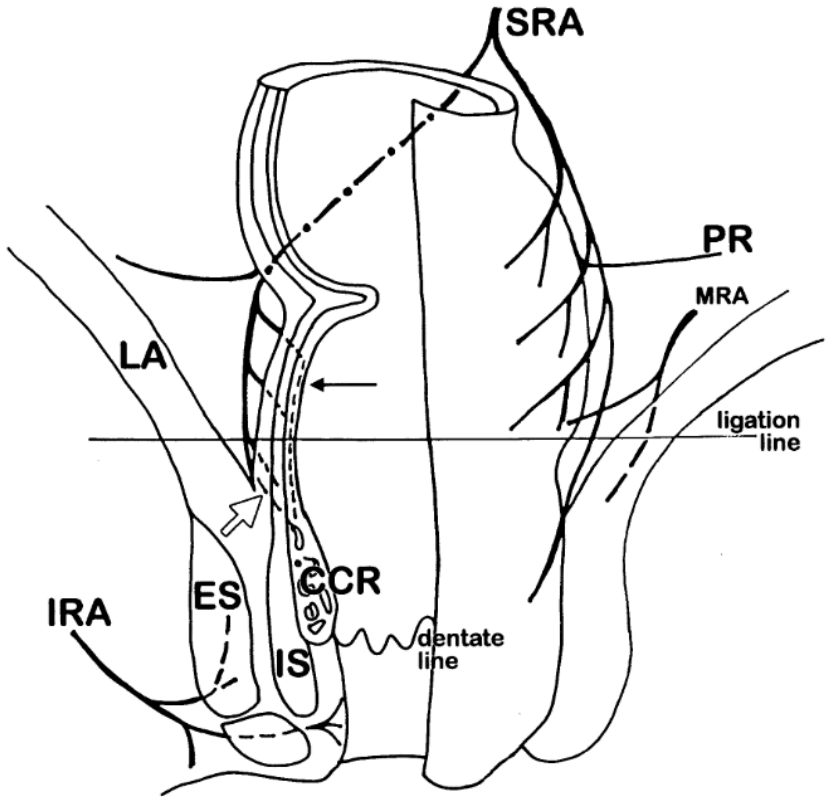


Figure 1: Schematic figure of the anal canal in the transverse plane and the position of the anal cushions. From Gerjy R. *Outcome after haemorrhoidopexy.* Medical dissertation No. 1064, Lindköping Univsersity, 2008. Reprinted with permission from the author.

The anal cushions are thought to function as a valve that contributes to anal continence.[10] The submucosa of the anal cushions contains vessels, muscle cells and connective tissue. The vessels form a plexus, called the internal haemorrhoidal plexus or the corpus cavernosum recti.[11] The haemorrhoidal plexus is a cavernous arteriovenous network without the interposition of a capillary system. The internal haemorrhoidal plexus receives blood supply from terminal branches of the superior rectal artery (branch of the inferior mesenteric artery). A study using transanal ultrasonography found that the majority of these branches transversed the rectal wall at a level of 0-3 cm above the anorectal junction.[12] A cadaver study had similar findings and was also able to demonstrate that some branches run longitudinally in the submucosa down to the internal haemorrhoidal plexus (Figure 2).[13]



SRA = Superior rectal artery; PR = Peritoneal reflection; MRA = Middle rectal artery; IRA = Inferior rectal artery; LA = Levator ani muscle; ES = External anal sphincter; IS = Internal anal sphincter; CCR = Corpus cavernousum recti.

Figure 2: Schematic figure of the distal rectum and anal canal showing the arterial blood supply to the internal haemorrhoidal plexus. The terminal branches of the superior rectal artery transverse the rectal wall and run longitudinally in the submucosa to the internal haemorrhoidal plexus (black arrow) or transverse the rectal wall nearly horizontally at the level of the internal haemorrhoidal plexus (white arrow).[13] Reprinted with permission from Elsevier.

The external haemorrhoidal plexus or perianal veins are located below the dentate line and are covered by anoderm and perianal skin.[14] The middle and inferior rectal arteries originating from the internal iliac arteries supply the lower part of the anal canal and the anus. The venous drainage of the haemorrhoidal plexus follows the arterial supply. The superior haemorrhoidal veins drain the internal haemorrhoidal plexus and return the blood to the portal venous system. However, a communication between the internal and external haemorrhoidal plexus does exist. The external haemorrhoidal plexus is drained by the middle and inferior rectal veins, which return the blood to the caval venous system.[14] This could explain why the incidence of haemorrhoids does not increase in patients with portal hypertension.[15,16]

Pathogenesis

Several pathologic changes have been described in the development of HD, but the exact pathophysiology is not fully understood.[17] The two most generally accepted theories are the *sliding anal canal theory* and the *vascular hyperplasia theory.* The *sliding anal canal lining theory* attributes the development of haemorrhoids to a weakening of the muscle and connective tissue of the anal cushions, which causes the dilatation of the internal haemorrhoidal plexus and prolapse (downward displacement) of the cushions.[9,18] The *vascular hyperplasia theory* is based on the observation of angiogenesis in the anal cushions and changes in the blood flow of the internal haemorrhoidal plexus. An increased diameter and blood flow of the terminal branches of the superior rectal artery have been demonstrated in patients with HD.[19] Also present are sphincter-like constrictions responsible for regulating the efferent and afferent blood flow of the internal haemorrhoidal plexus.[20] Dysfunction of this sphincter mechanism is suggested as a key mechanism in the pathogenesis of HD, causing progressive dilatation of the internal haemorrhoidal plexus and vascular hyperplasia. Enzymes responsible for connective tissue degeneration and angiogenesis are overexpressed in haemorrhoidal tissue, thereby supporting both theories.[21]

Prevalence

The prevalence of HD is unknown and many people with HD probably never seek medical advice. However, data from epidemiologic studies and public health registries indicate that HD is common in adults. In an Austrian study 17.4% of adults attending a colorectal cancer screening program had symptomatic haemorrhoids.[22] A cross-sectional study published in 1990 reported that approximately 10 million people in the United States suffered from HD, giving a prevalence of 4.4%.[23] In Germany whose population is approximately 80 million, 3.5 million people seek medical advice and 40-50 000 surgical procedures for HD are performed each year.[24] Similar numbers have been reported in other European countries (Table 1).

Table 1: Surgical procedures for haemorrhoidal disease in three European countries.

Country	Population	Surgical procedures	Surgical procedures /100.000
Germany	80 million	40-50,000[24]	50-63
France	66 million	27,600[25]	42
England	53 million	25,000[26]	47

Symptoms and clinical assessment

The five cardinal symptoms of HD are pain, perianal irritation or itching, bleeding, soiling and prolapse.[6,27] None of these symptoms are pathognomonic for HD and clinical examination including anoscopy is needed to set the diagnosis. Sigmoidoscopy or colonoscopy is recommended to exclude colorectal malignancy and inflammatory bowel disease. According to the Danish guidelines for the detection and treatment of colorectal cancer, all patients >40 years with rectal bleeding should be referred for endoscopy.[28]

Goligher's classification is the most widely used grading of anatomical pathology in HD.[27] Based on this classification the internal haemorrhoids are graded on a scale of I to IV according the degree of prolapse:

Grade I haemorrhoids do not prolapse during straining but "*project slightly into the lumen of the anal canal when the veins are congested at defaecation".*
Grade II haemorrhoids prolapse during straining but "*return spontaneously to the anal canal when the motion has been passed and the defaecation effort has ceased."*
Grade III haemorrhoids prolapse during straining and "*remain prolapsed afterwards until they are digitally replaced within the anus."*
Grade IV haemorrhoids cannot be completely reduced into the anal canal and "*remain as a permanent projection of anal mucosa".*

Treatment

Different treatment pathways for HD exist, including conservative treatments, office procedures and operations. In Denmark, the Danish Surgical Society has published treatment guidelines for HD. The guidelines recommend that treatment be tailored to the grade of haemorrhoidal prolapse (Table 2).[29] Fibre supplements reduce symptoms in HD and is recommended for all patients.[30] Conservative options include symptomatic treatment with topical ointments and suppositories. Grade I-II haemorrhoids (Goligher's classification) with persistent symptoms can be treated with office procedures such as rubber band ligation and sclerotherapy. Operations are generally preserved for patients with high grade of prolapse (Grade III-IV haemorrhoids).

Table 2: Treatment recommendations in the Danish National Guidelines published by the Danish Surgical Society.[29] Reprinted with permission from the Danish Medical Journal.

Goligher's classification	**Treatment**				
	Conservative	Office procedures	HAL / THD	SH	CH
Grade I	+	-	-	-	-
Grade II	+	(+)	(+)	(+)	-
Grade III	+*	-	+	+	+
Grade IV	+*	-	+	-	+

* Supplement to surgical treatment

THD = Transanal Haemorrhoidal Dearterialization; HAL = Haemorrhoidal Artery Ligation; SH = Stapled haemorrhoidopexy; CH = Conventional haemorrhoidectomy.

Traditionally, operations for HD have been ablative with excision of the haemorrhoids (haemorrhoidectomy). The excision can be performed using knife, scissors, diathermy or a vessel-sealing device (e.g. LigaSure or Harmonic Scapel).[31,32] The wounds in the anal canal can be left open (open haemorrhoidectomy) or closed (closed haemorrhoidectomy) without any difference in long-term results.[33,34] Haemorrhoidectomy is considered the gold standard for the surgical treatment of HD and has the lowest recurrence rate.[29,35] However, postoperative pain after haemorrhoidectomy can be severe and last for several weeks. During the last few decades, non-ablative methods have been introduced. With these methods no wounds are left in the anal canal, with the aim of reducing postoperative pain and the risk of local complications. What these non-ablative methods all have in common is that they require the use of new instruments, which increase operative costs. In stapled haemorrhoidopexy the haemorrhoidal prolapse is reduced using a circular stapler in the distal rectum.[36] In haemorrhoidal artery ligation/transanal haemorrhoidal dearterialization (HAL/THD) procedures, the terminal branches of the superior rectal artery that supply the internal haemorrhoidal plexus are ligated and the haemorrhoidal prolapse reduced using a running suture (mucopexy).[37,38]
The patients included in this thesis who were treated with an operation mainly received a modified open haemorrhoidectomy, which we named minimal open haemorrhoidectomy (MOH) or THD. These operations will therefore be presented in more detail.

Minimal Open Haemorrhoidectomy

The operative technique in open haemorrhoidectomy, developed at St. Marks Hospital in London, was first described by Milligan and Morgan in 1937.[39] Milligan and Morgan described how the anoderm, the internal and external haemorrhoidal plexus were dissected off the external subcutaneous sphincter and the internal anal sphincter with scissors. The haemorrhoidal pedicle in the rectal mucosa was ligated before the haemorrhoid was excised. The ligature was sutured to the lower edge of the internal sphincter. Most surgeons today do not perform open haemorrhoidectomy as described by Milligan and Morgan. The operation has been modified to reduce postoperative pain. Loder and Phillips described the open diathermy haemorrhoidectomy without pedicle ligation.[40] In their experience, the use of high current diathermy instead of

scissors improved anatomical exposure during dissection. During dissection they encountered small muscle fibres passing from the internal anal sphincter into the anal cushions, and highlighted the importance of dividing these close to the cushions in order to leave an intact surface of the internal anal sphincter. Similarly, Gerjy and Nyström described how the subdermal fascia continued on to a fascia covering the internal anal sphincter, which could be identified and left unharmed during dissection of the haemorrhoid.[41] Leaving the internal sphincter unharmed was postulated to reduce postoperative pain. Clinical trials revealed that diathermy dissection resulted in less postoperative pain compared with scissor dissection and that pedicle coagulation caused less postoperative pain compared to pedicle ligation.[42,43]

MOH was developed by the group of surgeons participating in the present study. We adopted the principles of diathermy dissection, pedicle coagulation and dissection in an anatomical plane leaving the internal anal sphincter unharmed. The excision of skin and haemorrhoid is minimized leaving a proximal part of the haemorrhoid intra-anally in order to preserve anal continence. The operative technique is described and illustrated in Study II:

"The external components are grasped by clamps using gentle traction. Diathermy is used for dissection and hemostasis. The skin is incised midway to one-third of the distance from the top of the pedicle. The subdermal fascia continuing into a submucosal fascia covering the internal anal sphincter is identified as are fibers passing between the hemorrhoid and this fascia. The hemorrhoid is dissected free from the underlying internal sphincter in this plane, leaving the sphincter unharmed. The anal mucosa is incised at the transition from anal mucosa to hemorrhoidal mucosa and only anal mucosa overlying the hemorrhoid is excised. Only the caudal part of the hemorrhoid is excised. With the hemorrhoid held with gentle traction it is divided at the anal orifice. There will thus be a residual part of the hemorrhoid intra-anally with its caudal end 1–2 cm proximal to the anal orifice".

Transanal Haemorrhoidal Dearterialization

HAL and THD are in principal the same operation but use equipment from different distributors. The haemorrhoidal arteries are ligated and the haemorrhoidal prolapse reduced by means of performing mucopexies. The THD proctoscope (G.F Medical Division, Correggio, Italy) is used in the THD procedure. With the patient in the lithotomy position the proctoscope is introduced into the anal canal and the haemorrhoidal arteries usually found at the 1,3,5,7,9 and 11 o'clock positions are located using Doppler ultrasonography.[38] The arteries are ligated with a Z-stich at these six positions where the strongest Doppler signals are identified. Anatomical variations of the haemorrhoidal arteries exist and more than six ligations might be necessary.[44] The ligation-suture is not cut but used as fixation point for the mucopexies performed as running sutures in the mucosa ending at least 5 mm above the dentate line.[45] The mucopexies can be performed circumferentially (1,3,5,7,9 and 11 o'clock positions) or targeted in patients with non-circumferential haemorrhoidal prolapse.

HAL/THD have gained increased popularity since their introduction in the mid-nineties.[37] Initial studies reported limited postoperative pain, fast recovery and low recurrence rates.[46] However, evidence on the long-term effect of THD from RCTs is limited. Higher recurrence rates after HAL/THD compared with stapled haemorrhoidopexy have been reported.[47] Eight RCTs have compared HAL/THD with haemorrhoidectomy using various outcomes (Table 3).[45,48–54] Most studies were small and were designed to study postoperative pain. Only two studies have presented long-term follow-up of symptoms using patient-reported questionnaires.[45,51] Both studies reported similar symptom control, but are limited by the use of non-validated questionnaires. Evidence is largely lacking concerning the long-term effect of THD on symptoms compared with haemorrhoidectomy.

Table 3. Randomized controlled trials comparing ligation procedures with haemorrhoidectomy.

Author (year)	N	Grade	Procedures	Follow-up (months)	Outcomes					Conclusion
					Postoperative pain	*Symptoms*	*HRQoL*	*Recurrence*	*Complications*	
Bursics et al. (2003)[48]	30 vs. 30	II-IV	DG-HAL vs. CH	12	Use of analgesics.	Patients asked about symptoms	No measurement	Symptom recurrence: N = 6 vs. 5.	3 anal fissures (DG-HAL) No long-term complications.	Less use of analgesics after DG-HAL. No difference in symptom control.
Denoya et al. (2013)[49]	20 vs. 20	III-IV	THD vs. CH	3	Use of analgesics **BPI***	No measurement	Short Form 12 FIQoL	Not reported	Urinary retention more frequent after CH.	Less use of analgesics after THD. Better BPI score from POD 7 after THD No difference in Short Form 12 and FIQoL
Elmer et al. (2013)[45]	20 vs. 20	II-III	THD vs. OH	12	**VAS***	Symptom questionnaire	No measurement	Recurrent prolapse: N = 9 vs. 4 Reoperation: N= 1 vs. 1	No difference in short-term complications. No long-term complications.	Less pain after THD the first week postoperatively. Pain, itching, bleeding and prolapse improved in both groups. Soiling improved only after OH. Non-significant trend towards inferior anatomical result after THD.
De Nardi et al. (2014)[50]	25 vs. 25	III	THD vs. OH	24	**VAS***	Yes/no questionnaire	No measurement of HRQoL. Patient satisfaction (ordinal scale 1-4)	Symptom recurrence: N = 5 vs. 4 Reoperation: N = 1 vs. 1	No long-term complications	No difference in postoperative pain, symptom control, or patient satisfaction.
Elshazly et al. (2014)[51]	100 vs. 100	II-III	LA vs. OH	24	VAS	Symptom questionnaire	Included in symptom questionnaire: Impact on QoL (ordinal scale 0-4)	Recurrence: N = 5 vs. 3	No difference in short or long-term complications.	Less postoperative pain and faster recovery after LA. No difference in symptom score 1 and 2 years postoperatively.
Tsunoda et al. (2017)[52]	22 vs. 22	III	THD vs. VSH	Median (range): 33 (12-46)	**NRS*** Use of analgesics	Patients asked about symptoms	Short Form 36 Patient satisfaction (ordinal scale 0-10)	Reoperation: N = 1 vs. 1.	No difference in short-term complications. No long-term complications.	Less postoperative pain after THD. No difference in symptom control and HRQoL.
Lópes et al. (2019)[53]	20 vs. 20	III-IV	DG-HAL vs. OH	Median (range): 15 (12-27)	**VAS***	Symptom questionnaire (6 months follow-up)	Short Form 36	Symptom recurrence: N = 1 vs. 1	No difference in short-term complications	Less postoperative pain after THD until POD 15. No differences in postoperative morbidity, symptom control and recurrence.
Trenti et al. (2019)[54]	39 vs. 41	III-IV	THD vs. VSH	1	NRS **Use of analgesics***	Symptom questionnaire	Short Form 12	Not reported	No difference in short-term complications	Less use of analgesics after THD from POD 8. No difference in symptom score and HRQoL at 1 month follow-up.

*** Primary outcome**. N = Number of patients; Grade = Goligher's classification; DG-HAL = Doppler-guided haemorrhoidal artery ligation; THD = Transanal haemorrhoidal dearterialization; LA = Ligation anopexy; CH = Closed haemorrhoidectomy; OH = Open haemorrhoidectomy; VSH = Vessel sealing devise haemorrhoidectomy; HRQoL = Health-related quality of life; BPI = Brief Pain Inventory; FIQoL = Fecal Incontinence Quality-of-Life score; POD = Postoperative day; VAS = Visual analogue scale; NRS = Numeric rating scale.

Outcome measures after surgical treatment for haemorrhoidal disease

HD is a benign disease and the long-term goal of treatment is the resolution of symptoms and improvement of patient wellbeing. In 2012, when we started planning this thesis, no validated outcome measures for symptoms in HD existed.

Figure 3: Patient self-reported symptoms of haemorrhoids as presented by Nyström et al.[55] Symptoms are graded based on their frequency (never = 0, less than once a week = 1 etc., the maximum score is 15 points). Reprinted with permission from John Wiley and Sons.

The following questions deal with haemorrhoids. Your answers should reflect the latest 2-week period

1	How often do you have pain from the haemorrhoids?	☐ Never	☐ Less than once a week	☐ 1–6 times weekly	☐ Every day (always)
2	How often do you have itching or discomfort of the anus?	☐ Never	☐ Less than once a week	☐ 1–6 times weekly	☐ Every day (always)
3	How often do you have bleeding when passing a motion?	☐ Never	☐ Less than once a week	☐ 1–6 times weekly	☐ Every day (always)
4	How often do you soil your underclothes (soiling from the anus)?	☐ Never	☐ Less than once a week	☐ 1–6 times weekly	☐ Every day (always)
5	How often do you reduce a prolapsing haemorrhoid with your hand when passing a motion?	☐ Never	☐ Less than once a week	☐ 1–6 times weekly	☐ Every day (always)

Nyström et al. had introduced a non-validated symptom score used in a few clinical trials (Figure 3).[45,55,56] Later, new symptoms scores were presented but important properties such as reliability and responsiveness have not been tested.[57,58]

The lack of standardized outcome measures has led to a heterogeneity of outcome measurements in studies on HD. A review of clinical trials identified 59 different types of outcomes and wide variation in the definitions of outcomes.[59] As a consequence, comparison of results across studies is difficult. Short-term outcomes such as postoperative pain are often used as the primary outcome. However, when asked about preferences for an operation method, patients seem to consider long-term outcomes such as the risk of recurrence and complications to be more important.[26] To reduce the heterogeneity of outcomes in future trials, a working group of the European Society of Coloproctology has recently suggested a core outcome set in HD (Table 4).[60] The primary outcome in this set is patient-reported symptoms. A validated instrument for the assessment of haemorrhoidal symptoms would therefore be required. In this thesis we included and evaluated the symptom score presented by Nyström et al. with minor modifications, the Haemorrhoidal Disease Symptom Score (HDSS) (Figure 4).

Table 4. European Society of Coloproctology core outcome set for haemorrhoidal disease.[60] Reprinted with permission from John Wiley and Sons.

Core outcome set	
Primary outcome	
Patient reported symptoms	Patient reported outcome measure (PROM)
Blood loss	
Pain	
Prolapse	
Itching	
Soiling	
Secondary outcome	
Complications	
Incontinence	Wexner Fecal Incontinence Score
Abscess	Physical examination
Fistula	MR imaging after inconclusive physical examination
Urinary retention	Ultrasonography
Anal stenosis	Physical examination
Recurrence	The reappearance of initial symptoms
Patient satisfaction	This end-point will be included in the PROM

Measurements of HRQoL are intended to capture the impact of disease and its treatment on the wellbeing of an individual.[61] HRQoL measures are divided into generic and disease-specific instruments. Generic instruments are designed to assess HRQoL in individuals with and without active disease, while disease-specific instruments more closely assess the impact of a specific disease or treatment on HRQoL. The Short Health Scale is a disease-specific HRQoL measurement in patients with inflammatory bowel disease.[62,63] The questionnaire includes only one question in each of its four dimensions (symptom burden, functional status, disease-specific worries and general wellbeing). No disease-specific HRQoL measure in HD has previously been presented. In this thesis, we included and evaluated an adaption of the Short Health Scale for the use in patients with HD (SHS_{HD}) (Figure 4).

Figure 4: The Haemorrhoidal Disease Symptom Score and Short Health Scale$_{HD}$.[1] Reprinted with permission from Wolters Kluwer.

Hemorrhoidal Disease Symptom Score

The following questions deal with symptoms caused by hemorrhoids. Your answers should reflect your symptoms during the last 3 months (1 answer per question).

1, How often do you feel pain from your hemorrhoids?
□ Never □ Less than once a month □ Less than once a week □ 1–6 days per week □ Every day (always)

2. How often do you feel itching or discomfort of the anus?
□ Never □ Less than once a month □ Less than once a week □ 1–6 days per week □ Every day (always)

3. How often do you bleed when passing stool?
□ Never □ Less than once a month □ Less than once a week □ 1–6 days per week □ Every day (always)

4. How often do you soil your underwear (soiling from the anus)?
□ Never □ Less than once a month □ Less than once a week □ 1–6 days per week □ Every day (always)

5. How often do you feel a swelling or a prolapsing hemorrhoid?
□ Never □ Less than once a month □ Less than once a week □ 1–6 days per week □ Every day (always)

Short Health Scale$_{HD}$

The following questions deal with how your symptoms caused by hemorrhoids affect your daily life (one answer per question).

1, In your view, how severe are your symptoms caused by hemorrhoids? Please grade your symptoms on a 7-point scale, where 1 is "no symptoms" and 7 is "severe symptoms."

No symptoms						Severe symptoms
1 □	2 □	3 □	4 □	5 □	6 □	7 □

2. Do your symptoms interfere with your daily activities? Please grade your answer on a 7-point scale, where 1 is "not at all" and 7 is "interfere to a very high degree."

Not at all						Interfere to a very high degree
1 □	2 □	3 □	4 □	5 □	6 □	7 □

3. Do your symptoms cause much concern? Please grade your answer on a 7-point scale, where 1 is "no concerns" and 7 is "constant concerns.".

No concerns						Constant concerns
1 □	2 □	3 □	4 □	5 □	6 □	7 □

4. How is your general feeling of well-being? Please grade your answer on a 7-point scale, where 1 is "very good" and 7 is "very bad."

Very good						Very bad
1 □	2 □	3 □	4 □	5 □	6 □	7 □

Complications after operations for haemorrhoidal disease

The most common short-term complications after operations for HD are prolonged postoperative pain, bleeding, urinary retention, and anorectal abscess and/or fistula.[6] Serious, life-threatening complications are extremely rare, but cases of Fournier's gangrene after haemorrhoidectomy and stapled haemorrhoidopexy have been reported.[64–67] Apart from one case report of cerebral abscess after THD,[68] no life-threatening complications after HAL/THD have been reported.

Anal incontinence and stenosis are the most feared long-term complications as they can be difficult to treat and have substantial impact on quality of life. After haemorrhoidectomy the frequency of anal incontinence varies from 0-28% depending on definition and length of follow-up.[69] In randomized controlled trials with a follow-up of 1-2 years 3.6% of patients report anal continence or hygiene problems after

haemorrhoidectomy.[70] In particular, patients with preoperative impaired anal continence seem to be at risk of further deterioration after haemorrhoidectomy.[69,71]
The Wexner Fecal Incontinence Score is one of the most widely used measurement tools for anal incontinence.[72] The Wexner score does not measure fecal urgency and therefore a new Revised Fecal Incontinence Score (RFIS) has been suggested.[73] Anal stenosis is a rare complication after haemorrhoidectomy (≈ 1%) and is usually caused by excessive excision of anoderm.[6,74]
The reported frequency of anal incontinence after HAL/THD is very low (0.4%) and the risk of anal stenosis is virtually absent (0%).[46] One study found no changes in anal manometry measures or signs of damage to the anal sphincter on transanal ultrasonography after THD.[75]

Aims and hypotheses

The aims of this thesis were

- To develop and validate a measurement instrument for symptoms in HD (Haemorrhoidal Disease Symptom Score) (Study I).
- To validate a disease-specific measurement instrument for HRQoL in HD (SHS_{HD}) (Study I).
- To investigate the feasibility of a modified, less invasive operation method for open haemorrhoidectomy: Minimal Open Haemorrhoidecomty (Study II).
- To compare short – and long-term outcomes of Minimal Open Haemorrhoidectomy with Transanal Haemorrhoidal Dearterialization (Study III).
- To investigate HRQoL in a cohort of patients referred for treatment of HD (Study IV).

The hypotheses tested were

- A valid, reliable and responsive outcome measure can be constructed based on the five cardinal symptoms pain, itching, bleeding, soiling and prolapse.
- The Short Health Scale is a valid, reliable and responsive measure of HRQoL when adapted to the use in HD (SHS_{HD}).
- MOH is a safe operation
- MOH can be performed with a similar postoperative course as s non-ablative operation (THD).
- Haemorrhoidectomy offers better long-term control of symptoms compared with THD.
- HRQoL is impaired in patients with HD and improves after treatment with an operation.

Materials and Methods

Patients:

All patients included in this thesis were patients referred to the proctologic outpatient clinic at the Department of Surgery, Holbaek Hospital in Denmark. Adult patients diagnosed with HD were eligible for inclusion. Exclusion criteria were acute HD (bleeding requiring admission, strangulated internal haemorrhoids and thrombosed external haemorrhoids), concomitant proctologic disease (active anal fistula, fissure, stenosis, anorectal prolapse), inflammatory bowel disease, or colorectal or anal cancer. Patients were included prospectively and registered in a local database. In October 2013, we started registration of patients operated for HD (Figure 5). From January 2015, all patients whether treated conservatively or surgically were registered. All patients were assessed at inclusion. Patients operated for HD were reassessed at planned 3- and 12-month follow-up postoperatively.

We gathered the patients in two cohorts:

- *Cohort I:* Patients diagnosed with HD regardless of treatment, included from January 2015 to August 2017.
- *Cohort II:* Patients operated for HD with a follow-up period of 12 months, included from November 2013 to August 2016.

Patients in Cohort I who were scheduled for an operation could be included in both cohorts.

Study I included patients from Cohort I and II.

Study II included patients from Cohort II, those operated for HD before the start of Study III and patients excluded from Study III due to exclusion criteria or patient refusing randomization.

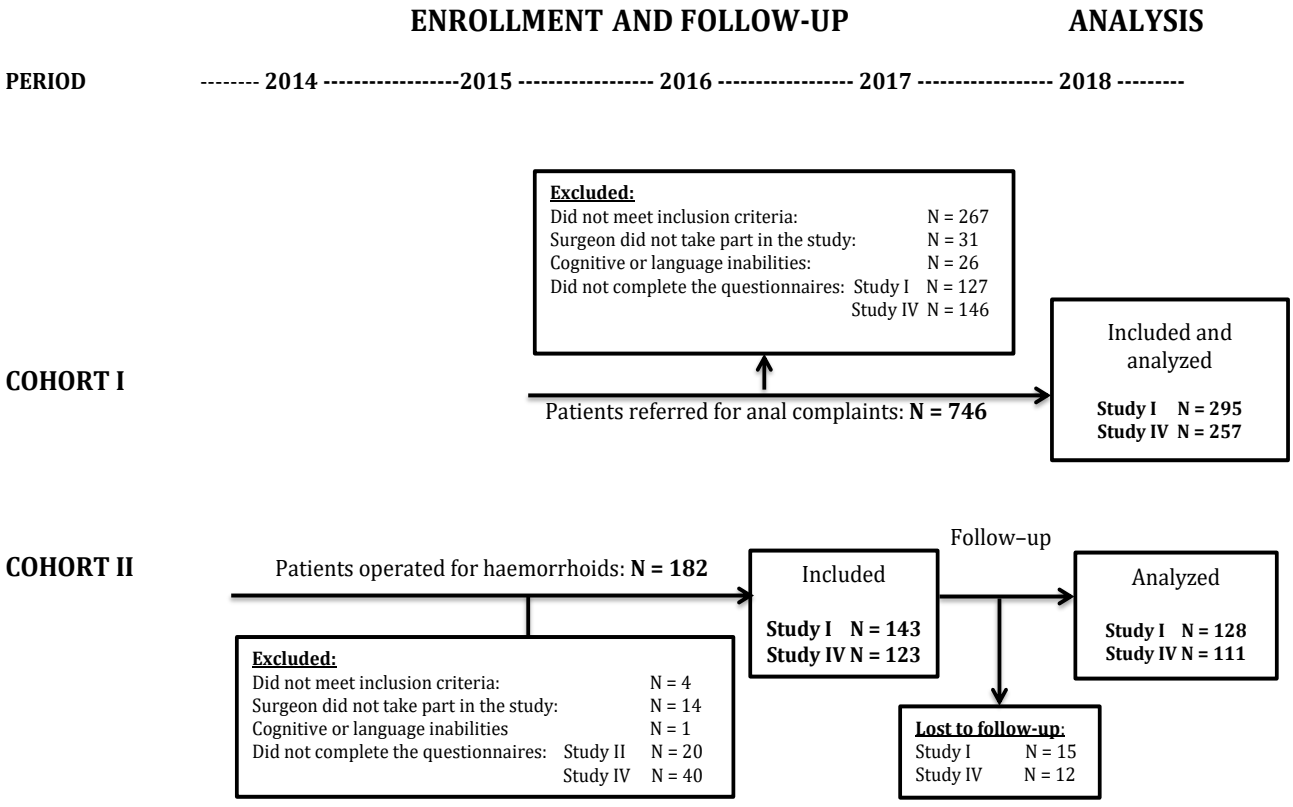
Study III included patients from Cohort II. The study was a randomized controlled trial. Patients included were randomly allocated to MOH or THD. Additional

exclusion criteria in Study III were ASA score >2, previous operation for haemorrhoidal disease within 2 years, anal incontinence to solid stools or previous operation for anal incontinence.

Study IV included patients from Cohort I and II.

The studies were approved by the Regional Committee on Health Research Ethics (SJ-348 and SJ-430) and The Danish Data Protection Agency (REG-71-2013). In Study I, II and IV patient treatment was not altered. The patients were informed about the study and they consented by completing the questionnaires. In Study III patients were included after written informed consent.

Figure 5: Inclusion of patients in Cohort I and II. Cohort I included all patients diagnosed with haemorrhoidal disease treated conservatively and surgically. Cohort II included only patients treated with an operation.



Outcomes

Table 5 presents an overview of the outcome measurements and assessment points for the studies in this thesis.

Table 5. Outcome assessment.

Outcomes	Inclusion	Peri-operative	1-14 days	3 monhts	12 months
Patient reported					
Symptoms (HDSS)	X			X	X
Anal continence (Wexner and RFIS)	X			X	X
HRQoL (SHS_{HD}, SF36v2, EQ-5D)	X			X	X
Postoperative pain (NRS)			X		
Analgesic consumption (Number of tablets)			X		
Recovery (return to daily activities)			X		
Patient satisfaction (Likert scale)				X	X
Global impression of change (Likert scale)				X	X
Perioperative					
Blood loos		X			
Operative time		X			
Total time in operation theatre		X			
Immediate adverse events		X			
Anatomical assessment					
Goligher's classification	X			X	X
Global assessment of pathology (Likert scale)	X			X	X
Complications					
Reported in study records		X		X	X
Reported in hospital records		X		X	X
Costs					
Perioperative costs		X			
Postoperative costs (DRG rates of adverse events and recurrence)				X	X

HDSS = Haemorrhoidal Disease Symptom Score; Wexner = Wexner Fecal Incontinence Score; RFIS = Revised Fecal Incontinence Score; HRQoL = Health-related quality of life; SHS_{HD} = Short Health Scale adapted to haemorrhoidal disease; SF36v2 = Short Form 36 version 2; EQ-5D = EuroQoL 5-dimension; NRS = Numeric rating scale; DRG = Disease related group.

Patient-reported outcomes

At inclusion, patients completed a questionnaire including measurements of symptoms, anal continence and HRQoL:

- Symptoms: HDSS[1]
- Anal continence: Wexner Fecal Incontinence Score and Revised Fecal Incontinence Score.[72,73]
- HRQoL: $SHS_{HD,}$[1] SF36v2,[76] and EQ-5D.[77]

The questionnaires included questions on duration of symptoms, previous treatments for proctologic diseases, marital status, educational status, and occupation.
The patients operated for HD completed the same questionnaire at postoperative follow-up. Patients graded their global impression of change and satisfaction with the operation on a 7-point Likert scale at postoperative follow-up.

Anatomical assessment:

The attending surgeon at the outpatient clinic determined the diagnosis and grading of HD based on patient history and clinical examination including anoscopy. According to local guidelines, endoscopy was performed as part of the primary workup in all patients ≥40 years. In patients <40 years the indication for endoscopy was left to surgeon's discretion. Endoscopic examination was mandatory for inclusion in Study III. Haemorrhoids were graded using Goligher's classification.[27] In addition, the surgeon provided a global assessment of haemorrhoidal pathology on a 7-point Likert scale.

Perioperative outcomes:

The operating surgeon registered perioperative data (anaesthesia, operation method, number of excisions/mucopexies, skin tag excision, estimated blood loss, operative time, total time in the operation theatre, and any adverse events) immediately after the operation. Postoperative pain, analgesic consumption and recovery were recorded daily in a patient diary the first 14 days postoperatively. The patients were asked to

report average pain during the day, peak pain and pain during defecation on a 0 to 10 numeric rating scale (0 = no pain; 10 = worst pain imaginable). Recovery was recorded with a question on patient wellbeing (1 = normal, 2 = slightly decreased, 3 = feeling ill). The postoperative pain treatment included a perioperative anal block using 40 mL of ropivacaine 5 milligrams per milliliter.[78] Paracetamol (1 gram 4 times daily), ibuprofen (400 mg 3 times daily), a local anaesthetic gel (xylocaine), and a laxative (magnesium oxide 1 gram 2 times daily) were given the first 7 days postoperatively with reduction as needed. Tablets of morphine 10 mg or tramadol 50 mg were prescribed to be used if needed.

Complications:

The ward nurses recorded immediate postoperative complications and length of hospital stay. Short- and long-term complications were recorded by the surgeon at 3- and 12-month follow-up. In addition hospital patient records were screened for any adverse events within the first year postoperatively. In Denmark the electronic patient record system enables access to records from other public hospitals, but not from private hospitals or general practitioners. The Clavien-Dindo classification was used to grade complications.[79]

Costs:

Cost analysis was planned from the health care provider's perspective (i.e. hospital treatment costs). The costs of surgical equipment (cost per unit) were calculated for each procedure. Estimates of the costs attributed to the use of the operating theatre, the surgical ward and personnel were obtained from the hospital administration (cost per time unit). To quantify the costs of complications and re-interventions, we used the Danish DRG rates obtained from the Danish National Patient Registry.[80]

Measurement properties:

Study I evaluated the measurement properties of two patient-reported outcome measures (PROMs). PROMs are questionnaires used to assess patients' own view of their health status.[81] The phenomena that the PROM measures are referred to as

constructs. In a PROM where the construct is the patients' own view or experience of a disease, the construct can not typically be measured objectively.[82,83] However, to be useful in clinical practice or trials the same properties are necessary for PROMs as for any test or measurement.[84] The PROM must be valid (measures the construct it is intended to measure), reliable (has low measurement error), and responsive (able to the detect changes in the construct).[82] These properties can be evaluated and hypotheses to assess the validity, reliability and responsiveness of a PROM can be tested. Recently, the COSMIN initiative has suggested guidelines for assessing the measurement properties of PROMs in medical research.[85,86]

The COSMIN initiative defines validity as the "*degree to which an outcome measure measures the construct it purports to measure"*.[85] Face validation (content validity) is often the first step of validity assessment. Face validation does not include statistical testing but is the initial evaluation of to what degree the questions in the PROM *"indeed look[] as though they are an adequate reflection of the construct to be measured"*.[85] Preferably, both medical experts and patients should assess face validity.

Validity can be tested by comparing the new PROM to an established gold standard measurement (criterion validity).[83] When a new PROM is developed, a gold standard measurement is usually not available. In this case, validity can be assessed by testing hypotheses supporting the theory that the PROM measures the construct it intended to measure (construct validity).[83] Frequently, this comes down to testing hypotheses of the ability of the PROM to discriminate between two populations with different amounts of the construct measured by the PROM.[83] The more hypotheses confirmed, the more confident one becomes that the PROM truly measures the construct of interest, i.e. the more confident one becomes that the PROM is valid.

Reliability is defined as *"the degree to which the measurement is free of measurement error"*.[85] If the construct remains unchanged the measurement should also remain unchanged. A test-retest analysis can be used to assess the reliability of PROMs. Two repeated measurements are compared. The interval between the measurements should be short to limit the possibility of changes in the construct, but long enough to prevent recall from the first measurement. An interval of approximately 2 weeks is often recommended, but no agreement on the optimal time interval exists.[86,87] In test-rest

analyses the interclass correlation coefficient (continuous data) and kappa statistics (ordinal or nominal data) are recommended.[88] The ICC assesses the consistency and agreement between measurements and gives a measure of the reliability of the PROM when used in a patient population.[89] However, the ICC is of limited value in interpreting the scores of a single patient.[82,90] Smallest detectable change (SDC) is a more useful measure in clinical practice (Figure 6). SDC is the difference in scores an individual patient must exceed to demonstrate change above measurement error with 95% certainty.[91]

Figure 6. Interclass correlation coefficient (absolute agreement).

$$ICC_{agreement} = \frac{\sigma_\alpha^2}{\sigma_\alpha^2 + \sigma_p^2 + \sigma_r^2}$$

$$\sigma_{error}^2 = \sigma_p^2 + \sigma_r^2$$

$$SEM_{agreement} = \sqrt{(\sigma_{error}^2)}$$

$$SDC = SEM_{agreement} \times 2.77$$

σ_α^2 = Variance due to systematic differences between patients (true variance in the population).

σ_p^2 = Variance due to systematic differences in between measurements (PROM).

σ_r^2 = Residual variance (random error variance).

σ_{error}^2 = Variance of measurement error

SEM = Standard error of measurement

SDC = Smallest detectable change

Internal consistency is considered a measure of reliability.[85] Given that the questions (items) in the PROM measure the same construct, the items should be correlated.

Cronbach's alpha is most commonly used to assess internal consistency.[92] Internal consistency is not applicable for all measurement instruments. In instruments designed on a formative model the items define the construct and are not necessarily correlated.[93,94]

Responsiveness is the ability of the PROM to detect changes in the construct.[85] Assessment of responsiveness is similar to the assessment of criterion and construct validity. In responsiveness analysis the validity of changes in scores is tested and a longitudinal study is therefore needed.[95,96] If no gold standard measurement is available, global rating scales of perceived change such as patient global impression of change are often used as comparator.[82]

Presentation of studies

Study I

The Hemorrhoidal Disease Symptom Score and Short Health Scale$_{HD}$: new tools to evaluate symptoms and Health-Related Quality of Life in Hemorrhoidal Disease.

Aim

The aim was to assess the validity, reliability and responsiveness of the HDSS and the reliability and responsiveness of the Short Health Scale$_{HD.}$ The HDSS measures the patient-reported frequency of pain, itching, bleeding, soiling and prolapse (Figure 4). The HDSS was developed from a non-validated symptom score used in previous trials (Figure 3).[45,55,56] The Short Health Scale is a simplified HRQoL measure originally developed for patients with inflammatory bowel disease.[62,63] The Short Health Scale was adapted for use in patients with HD (SHS_{HD})(Figure 4).

Methods

Cross-sectional (Cohort I) and longitudinal (Cohort II) observational study. Patients diagnosed with HD, treated both conservatively and surgically, were eligible for inclusion in Cohort I. Cohort I was used to test validity and reliability. Cohort II included patients operated for HD. The patients in Cohort II were followed 12 months postoperatively to assess responsiveness.

The patients completed a questionnaire including the HDSS and SHS_{HD} twice at inclusion. The patients received a letter that included the questionnaires and were asked to return the completed questionnaires by mail. When the patients attended the outpatient clinic, they were asked to complete the questionnaire a second time (test-retest). In Cohort II, patients completed the questionnaire at 12 months postoperative follow-up. At follow-up, patients also reported global impression of change (PGIC) and satisfaction with the operation.

We assessed face validity by asking 50 patients to report additional complaints related to HD not included in the HDSS. Patient-reported symptom load (graded 1 to 7: 1 = no symptoms; 7 = severe symptoms) was used as comparator to assess construct validity of the HDSS. ROC-curve analysis tested the ability of the HDSS to

discriminate between patients reporting a high and low symptom load (minimum criteria AUC > 0.70). Spearman's rho tested correlations and logistic regression assessed the importance of each individual symptom in the HDSS related to patient-reported symptom load. Test-retest analysis with an interval of 10 to 25 days assessed reliability using $ICC_{2.1}$ (minimum criteria ICC > 0.70). Cronbach's alpha assessed internal consistency (minimum criteria alpha > 0.70). ROC-curve analysis assessed responsiveness: the ability to discriminate between patients with and without improvement 12 months after surgery using PGIC as anchor (minimum criteria AUC > 0.70). Significance level was 0.05 (two-sided).

Results

In Cohort I, 295 patients were included (Figure 5). Of these, 60 patients had test-retest scores for reliability analyses. Cohort II included 143 patients. Complete data at 12 months postoperative follow-up were obtained in 128 (HDSS) and 121 (SHS_{HD}) patients.

Face validation did not identify additional symptoms to be included in the HDSS (3 different symptoms in 3 different patients). The HDSS was able to discriminate between patients reporting a high and low symptom load (AUC [CI95%] = 0.786 [0.725-0.848]). Pain and itching showed the strongest correlations to patient-reported symptom load at baseline (Spearman's rho [CI95%] of 0.467 [0.364-0.565] and 468 [0.367-0.562]). At postoperative follow-up prolapse had the strongest correlation (Spearman's rho [CI95%] of 0.604 [0.459-0.728]). The HDSS and the SHS_{HD} showed adequate reliability. The SHS_{HD} had a Cronbach's alpha [CI95%] of 0.773 [0.728-0.813]. The HDSS was based on a formative model and internal consistency was not tested. The HDSS had an $ICC_{2.1}$ [CI95%] of 0.822 [0.715-0.891] and the SHS_{HD} an $ICC_{2.1}$ [CI95%] of 0.763 [0.634-0.851]. Smallest detectable change was 5 points for the HDSS and 7 points for the SHS_{HD}. The HDSS and the SHS_{HD} demonstrated adequate responsiveness with AUC [CI95%] of 0.843 [0.756-0.929] and 0.840 [0.752-0.929], respectively. HDSS and SHS_{HD} both demonstrated good correlations with patient global impression of change and patients satisfaction at postoperative follow-up (Table 6). In patients with postoperative HDSS of ≤ 5 points 94% of the patients were satisfied with the operation, and if postoperative HDSS was 0, all (100%) patients were satisfied.

Table 6. Responsiveness assessed 12 months postoperatively.[1] Reprinted with permission from Wolters Kluwer.

	PGIC	PS
Measurement	CC [CI95%][a]	CC [CI95%][a]
Change in HDSS (absolute)	0.521* [0.370 – 0.650]	-
Change in SHS_{HD} (absolute)	0.581* [0.440 – 0.697]	-
Change in HDSS (relative)	0.658* [0.551 – 0.747]	-
Change in SHS_{HD} (relative)	0.656* [0.529 – 0.753]	-
HDSS at follow up	-0.680* [-0.769 to -0.569]	-0.660* [-0.754 to -0.541]
SHS_{HD} at follow up	-0.654* [-0.752 to -0.527]	-0.622* [-0.731 to -0.487]

[a]Data include the correlation coefficient (Spearman's rho) with 95% bootstrapping CI (bias corrected and accelerated, 5000 iterations).

*$p < 0.001$.

PGIC = Patient global impression of change; PS = Patient satisfaction with the operation.

Conclusion

The results suggest that the HDSS is valid, reliable and responsive, and that the SHS_{HD} is reliable and responsive.

Limitations

The single-centre design might reduce generalizability. Patient global impression of change was used as comparator to assess responsiveness. The use of global rating scales of perceived change is debated.[95,96] Global rating scales might be influenced by current disease status rather than the actual change in disease status.[97] The test-retest analysis had a relatively high rate of patients excluded from the analysis. Finally, we did not test the validity of the SHS_{HD} compared with other HRQoL measures. In Study IV the SHS_{HD} showed association with two validated generic HRQoL measures supporting the validity of the SHS_{HD}.

Study II

Minimal Open Hemorrhoidectomy.

Aim

The objective of this study was to examine the feasibility of MOH, describe the operative technique, and assess short-term outcomes compared with THD and LigaSure haemorrhoidectomy.

Methods

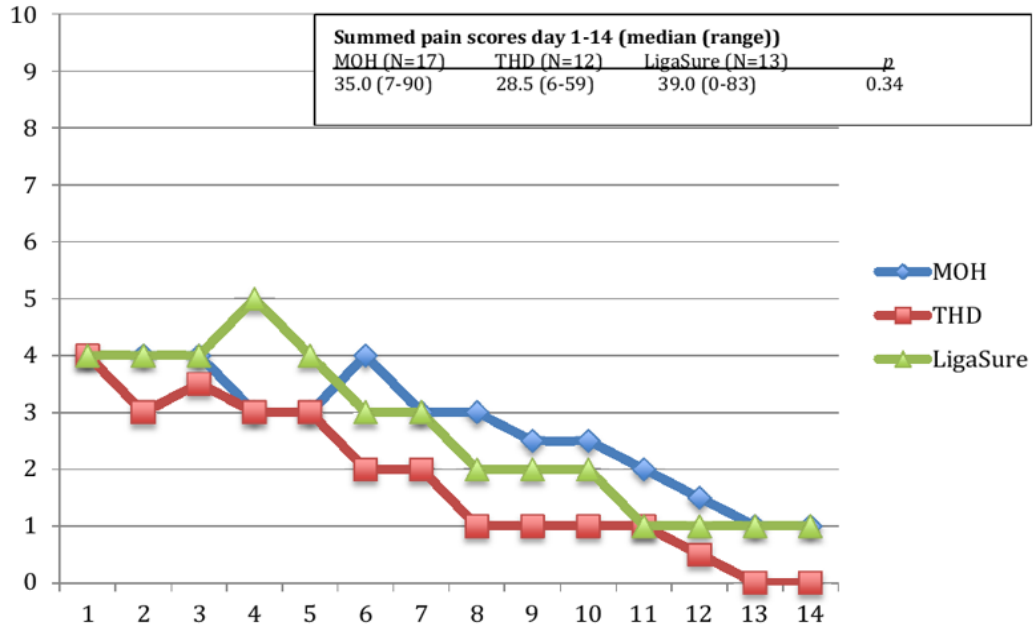
Patients operated for HD with MOH, THD or LigaSure haemorrhoidectomy were included. The study was observational. The indication for operation and choice of method was left to the surgeon's discretion. Patients were assessed at inclusion and at follow-up 3 months postoperatively. The patients registered postoperative pain (numeric rating scale 0-10), analgesic consumption and recovery the first 14 days postoperatively. The HDSS was used to assess symptoms and the SHS_{HD} to assess HRQoL. Anal continence was assessed using the Wexner score. Postoperative complications during the first 3 months were registered.
Fischer's exact test analysed frequencies and Kruskal-Wallis test by ranks analysed ordinal and continuous data. Significance level was 0.05 (two-sided).

Results

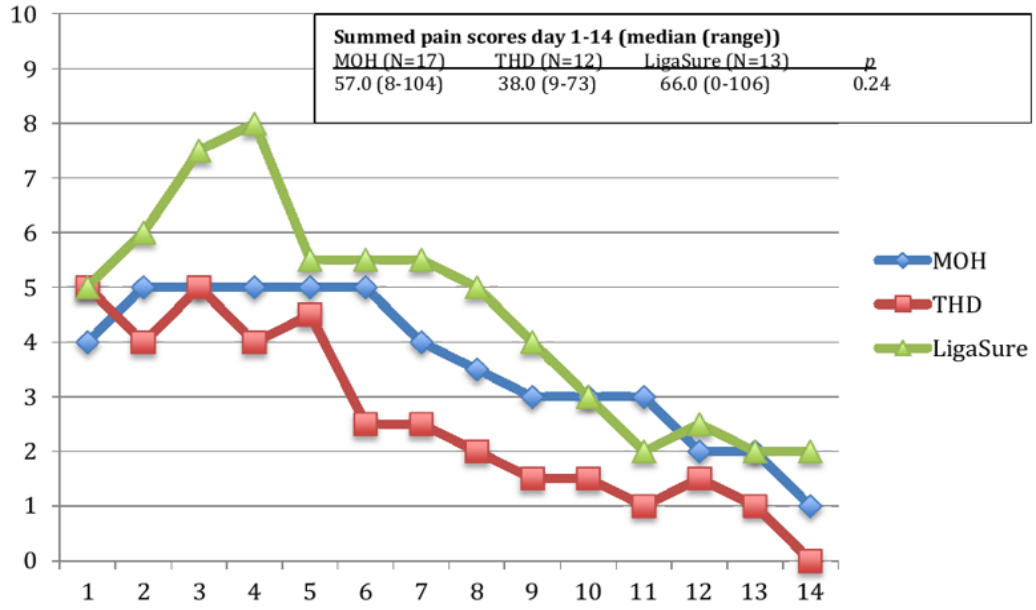
Seventeen patients were operated with MOH, 12 with THD and 13 with LigaSure haemorrhoidectomy. We found no difference in postoperative pain, analgesic consumption or recovery between the three groups ($p>0.05$) (Figure 7). Neither did we find a difference in symptom score, HRQoL, or anal continence at 3 months follow-up ($p>0.05$). MOH and THD had no serious short-term adverse events (Clavien-Dindo grade ≥3). Three patients in the LigaSure-group had a postoperative complication requiring reoperation (2 patients with postoperative bleeding and 1 patient who developed an anal fissure and submucosal fistula).

Figure 7. Average and peak pain postoperatively, registered on days 1-14 in patients operated on with minimal open haemorrhoidectomy (MOH), transanal haemorrhoidal dearterialization (THD), and LigaSure haemorrhoidectomy (LigaSure).[2] Reprinted with permission from Springer Nature.

Average Pain



Peak Pain



Conclusions

The results imply that MOH has a postoperative course (postoperative pain scores and recovery) similar to that of THD and LigaSure haemorrhoidectomy. The improvements of haemorrhoidal symptoms were in the same range. MOH had no serious adverse events. The findings suggest that MOH is a feasible technique for open haemorrhoidectomy. Larger studies are indicated.

Limitations

This was a small observational study. The type of operation was chosen based on the surgeon's and/or patient's preference which may have introduced selection bias. Due to the small sample size only large differences between the groups could be detected (type II error).

No firm conclusions could be drawn, but the results justified the initiation of a larger randomized controlled trial.

Study III

Minimal Open Hemorrhoidectomy versus Transanal Hemorrhoidal Dearterialization: the effect on symptoms. An open-label randomized controlled trial.

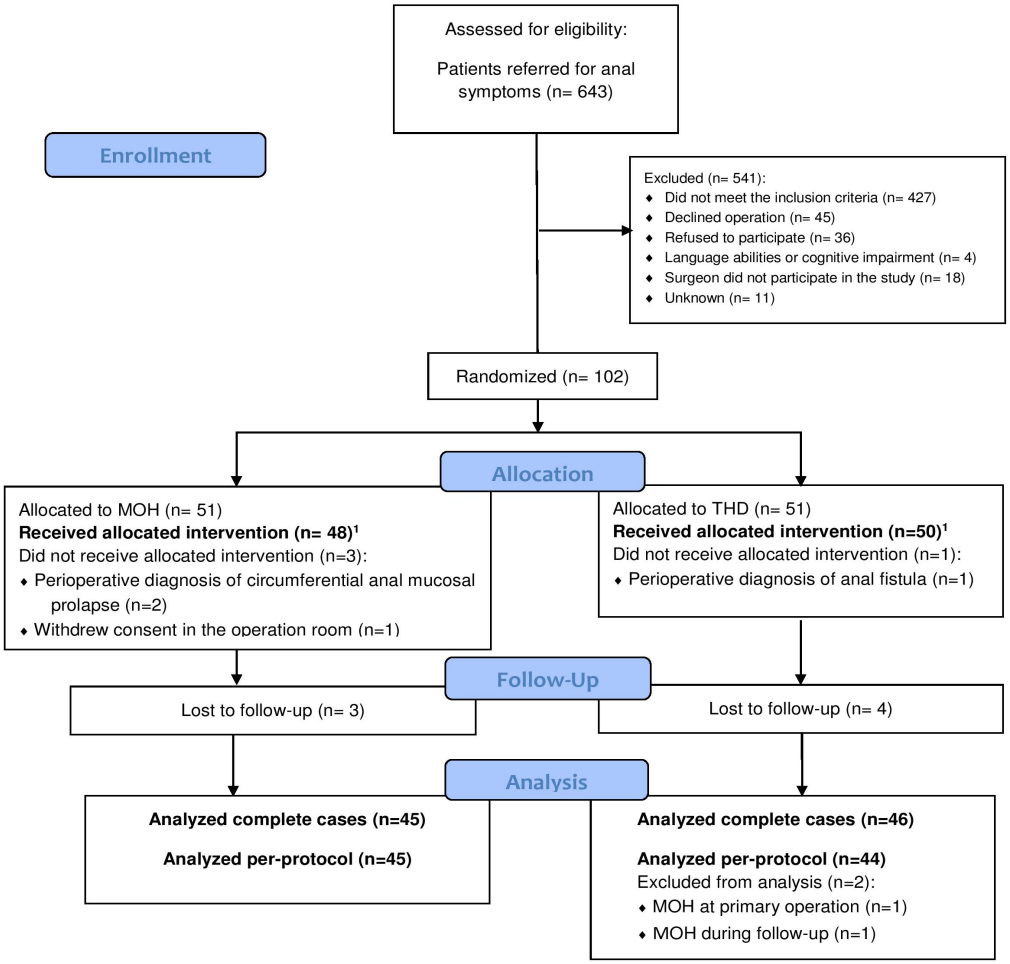
Aim

The aim was to compare the long-term effect of MOH and THD on patient-reported symptoms.

Methods

Single-centre, open-label randomized controlled trial. Patients with internal haemorrhoids grade III-IV, or grade II with bleeding despite previous RBL or sclerotherapy were eligible for inclusion. Exclusion criteria were ASA-score > II, active anal fissure or fistula, operation for haemorrhoids within two years before inclusion, anal incontinence to solid stool or operation for anal incontinence, colorectal cancer, or inflammatory bowel disease. Patients were randomly allocated (in a 1:1 ratio) to MOH or THD. The randomization was stratified by gender. There was no blinding of participants, surgeons, hospital, or research staff.

Figure 7. Study flow chart (Consort diagram). Reprinted with permission from Wolters Kluwer.



[1] Patients analyzed in *modified* intention-to-treat analyses (*m*ITT).

Patients were assessed at baseline and at 3- and 12-month postoperative follow-up. The primary outcome was patient-reported symptoms one year after surgery, assessed by the HDSS. Secondary outcomes included HRQoL, patient satisfaction, re-interventions for recurrence, postoperative pain and recovery, adverse events, and hospital treatment costs. The primary outcome was analysed with in a modified intention-to-treat analysis and per-protocol in patients operated for HD. Secondary outcomes were analysed per-protocol. Depending on the distribution Chi-square test or Fisher's exact test analysed frequencies and independent *t*-test or Mann-Withney U test analysed continuous data. Goodman and Kruskal's gamma analysed ordinal data. Significance level was 0.05 (two-sided). A sample size of 80 patients (40 vs. 40) was required to detect a difference in HDSS of 1.5 points with significance level of 0.05 and power of 80%.

Results

Figure 7 presents patient inclusion. Complete data for the primary outcome were obtained in 45 of 48 (MOH) and 46 of 50 (THD) patients. Median (range) HDSS at 12 months follow-up was 3 (0-17) after MOH and 5 (0-17) after THD (p=0.15). MOH had better anatomical result (p<0.001) and more patients reported symptoms of haemorrhoidal prolapse after THD (p=0.008) (Table 7). After THD, 7 patients had a re-intervention for recurrence compared to 0 patients after MOH (p=0.013). Patient satisfaction was higher after MOH (p=0.049).

No differences were found for HRQoL, average and peak postoperative pain, use of analgesics or recovery. There were no differences in postoperative anal incontinence scores or number of adverse events. In the MOH-group, 2 patients reported deterioration of anal continence. At the first postoperative follow-up, 3 patients in the MOH-group had signs of anal stricture. In 2 patients the stricture resolved after intervention with anal dilatation. One patient still used self-dilatations at one-year follow-up.

The median (range) hospital treatment costs of MOH was € 441 (253-7424) and of THD € 1006 (706-5401) (Median difference [CI95%]: € 555 [472-693], p<0.001).

Conclusion

Both MOH and THD have long-term effect on haemorrhoidal symptoms without a difference in symptom score one year postoperatively. MOH had better effect on symptoms of prolapse and more patients needed treatment for recurrence after THD. Patient satisfaction was higher after MOH. Postoperative pain and recovery after MOH and THD were within the same range.

Table 7. Per-protocol analysis of outcomes at one-year follow-up. Reprinted with permission from Wolters Kluwer.

Outcome		**MOH N = 45**	**THD N = 44**	**Effect size**	***P***
SYMPTOMS					
Hemorrhoidal Disease Symptom Score, median (range) (IQR)		3.0 (0-17) (5.0)	5.0 (0-17) (9.0)	Mdiff [CI95%] = -1.0 [-3.0 to 0.0]	0.18
Improvement in Hemorrhoidal Disease Symptom Score, mean (SD)		8.40 (4.65)	6.36 (5.34)	$\bar{x}$ diff [CI95%] = 2.04 [-0.07 to 4.14]	0.058
Patients reporting symptoms of					
Pain, N(%)	Yes	15 (33)	20 (45)	OR [CI95%] = 0.73 [0.43 to 1.24]	0.24
Itching, N(%)	Yes	28 (62)	26 (59)	OR [CI95%] = 1.14 [0.49 to 2.67]	0.76
Bleeding, (N%)	Yes	16 (36)	15 (34)	OR [CI95%] = 1.07 [0.45 to 2.55]	0.89
Soiling, N(%)	Yes	22 (49)	20 (45)	OR [CI95%] = 1.15 [0.50 to 2.64]	0.75
Prolapse, (N%)	Yes	14 (31)	26 (59)	OR [CI95%] = 0.31 [0.13 to 0.75]	**0.008**
ANAL CONTINENCE					
Wexner score, median (range) (IQR)		2.0 (0-12) (4.8)	3.0 (0-13) (4.0)	Mdiff [CI95%] = -1.0 [-2.0 to 0.0]	0.11
	Missing, N(%)	1 (2)	1 (2)		
Revised Fecal Incontinence Score, median (range) (IQR)		0.0 (0-7) (2.5)	0.0 (0-11) (2.0)	Mdiff [CI95%] = 0.0 [0.0 to 0.0]	0.43
	Missing, N(%)	0 (0)	3 (7)		
PATIENT SATISFACTION AND QUALITY OF LIFE					
Patient satisfaction,					
1= very dissatisfied to	1	1 (2)	2 (4)		
7= very satisfied, N%	2	1 (2)	6 (14)		
	3	2 (4)	3 (7)		
	4	3 (7)	2 (4)	γ = -0.32	**0.049**
	5	1 (2)	4 (9)		
	6	13 (29)	10 (23)		
	7	24 (53)	17 (39)		
Short Health Scale$_{HD}$, median (range) (IQR)		6.0 (4-19) (5.0)	7.0 (4-19) (6.0)	Mdiff [CI95%] = -1.0 [-2.0 to 0.0]	0.08
	Missing, N(%)	1 (2)	0 (0)		
POSTOPERATIVE ANATOMICAL ASSESSMENT					
Goligher's classification, N(%)	Grade I / Normal	38 (84)	20 (46)		
	Grade II	3 (7)	8 (18)		
	Grade III	1 (2)	2 (5)	γ = 0.79	**<0.001**
	Grade IV	0 (0)	9 (21)		
	Missing	3 (7)	5 (11)		
Surgeon's overall assessment of pathology (1-7), median (range) (IQR)		2.0 (1-6) (1.0)	2.0 (1-5) (2.0)	γ = 0.62	**<0.001**
	Missing	3 (7)	6 (14)		

OR = odds ratio; Mdiff = Hodges-Lehmann estimate of median difference; $\bar{x}$ diff = mean difference; γ = Goodman and Kruskal's gamma; IQR = interquartile range.

Limitations

The study is limited by the single-centre design and the lack of blinding. The single-centre design reduces generalizability. The same group of surgeons that operated the patients evaluated them at postoperative follow-up. Blinding of patients or surgeons was not possible, but an independent assessor could have limited the possibility for bias in the assessment of anal pathology and recurrence at follow-up. It could be criticized that the statistically insignificant result for the primary outcome is due to insufficient power (type II error). The power calculation was based on normally distributed data. Due to skewness of data we used a non-parametric test with potential loss of statistical power. If present, a difference in postoperative symptom score seems to be mainly driven by the difference in symptoms of prolapse, which we could demonstrate with the present sample size. The randomization was not stratified for grade of haemorrhoids and a slightly unequal distribution of grade III-IV haemorrhoids was present. A follow-up of one year might not be sufficient to predict the long-term effect of the operations and a 5-year follow-up is ongoing.

Study IV

Quality of life in patients with Haemorrhoidal Disease.

Aim

The aim of this study was to investigate the impact of HD on HRQoL by

- Comparing HRQoL measures in patients with HD to HRQoL measures in a background population.
- Investigating the associations between clinical characteristics of HD (symptom duration, symptom burden, anal pathology, etc.) and HRQoL measures.
- Investigating how and if HRQoL measures changed after surgical treatment of HD.

Methods

Cross-sectional (Cohort I) and longitudinal (Cohort II) observational study. Cohort I consisted of a consecutive series of patients diagnosed with HD at our outpatient clinic. Cohort II consisted of patients operated for HD with 12 months postoperative follow-up. Patients with missing data were excluded. HRQoL was assessed using three generic (SF-12v2, SF-36v2 and EQ-5D) and one disease-specific (SHS_{HD}) questionnaire. The primary outcome was the physical and mental component summary scores (SF-12v2) in patients with HD (Cohort I) compared with data from a background population obtained from the Danish Health Interview Survey (SUSY 2017).[98]

In addition, the EQ-5D utility index (Time-Trade-Off) in patients with haemorrhoids (Cohort I) was compared with published Danish population norms.[99,100] The associations between generic HRQoL measures (SF-36v2 and EQ-5D) and clinical characteristics (symptom duration, previous operation for haemorrhoids, HDSS, symptom load, SHS_{HD}, Goligher's classification, surgeon's global assessment of pathology, and allocated treatment) were tested (Cohort I). Changes in HRQoL measures after treatment were assessed in patients operated for HD (Cohort II). Independent *t*-test or one-sample *t*-test analysed normally distributed continuous data. Mann-Withney U test or Wilcoxon signed rank test analysed skewed continuous data. We used multiple linear regression analysis to adjust for confounding variables (age, sex, BMI and educational status). Significance level was 0.05 (two-sided).

Results

Patient inclusion is presented in Figure 5. Cohort I included 257 patients. Cohort II included 123 patients and complete data were obtained in 111 patients at follow-up. The physical component summary score (SF12v2) in patients with HD was similar to the score in the background population (calculated difference [CI95%] = -1.14 [-2.40 to 0.12], p=0.076). In patients with HD reporting a high symptom load (HDSS > 14) the physical component score was lower than in the background population (Table 8).

Table 8. HRQoL (SF-12v2) related to the severity of symptoms (HDSS) in patients with haemorrhoidal disease (Cohort I) compared with a general population (SUSY 2017).

		Calculated difference[b] [CI95%]	*p*
Mental Component Summary (SF-12v2)			
COHORT I[a]	HDSS 1-7	4.82 [2.10 to 7.54]	**0.001**
	HDSS 8-11	1.14 [-1.35 to 3.63]	0.6
	HDSS 12-14	1.35 [-1.09 to 4.21]	0.2
	HDSS 15-20	1.21 [-1.82 to 4.25]	0.4
SUSY 2017		Reference	
Physical Component Summary (SF-12v2)			
COHORT I[a]	HDSS 1-7	-0.12 [-2.52 to 2.29]	0.9
	HDSS 8-11	0.17 [-2.03 to 2.37]	0.9
	HDSS 12-14	-2.03 [-4.37 to 0.32]	0.09
	HDSS 15-20	-4.37 [-7.05 to -1.69]	**0.001**
SUSY 2017		Reference	

[a]Patients in Cohort I divided in quartiles based on HDSS. [b]Adjusted for age, sex, BMI and educational status excluding individuals <30 years. Negative difference indicates decreased HRQoL.

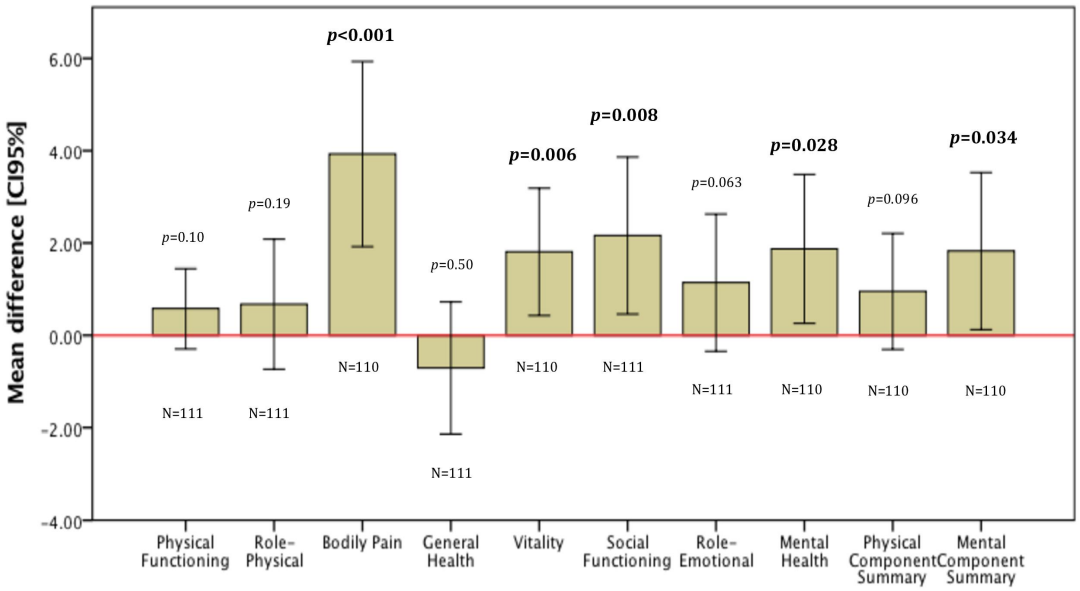
HRQoL = Health-Related Quality of Life; SF-12v2 = Optum® 12-Item Short Form Health Survey version 2; HDSS = Haemorrhoidal Disease Symptom Score; SUSY 2017 = Danish Health Interview Survey 2017

The mental component score (SF12v2) was higher in patients with HD compared with the background population (calculated difference [CI95%] = 2.01 [0.66 to 3.36], p=0.003).

The EQ-5D utility index in patients with HD was lower than the population average in men, women <50 years, and patients with higher education.

Patient-reported symptoms were associated with HRQoL measures, while the surgeon's grading of anal pathology had no association. The SHS_{HD} was associated with the EQ-5D utility index and all dimensions of the SF-36v2. HRQoL measures (SF36v2, EQ-5D utility index and SHS_{HD}) improved after surgical treatment (Figure 9).

Figure 9. The impact of surgery on HRQoL. Mean difference [CI95%] in Short Form 36 version 2 scores preoperatively and one year after surgery. A positive difference indicates improvement of HRQoL.



Conclusion

HD has a negative impact on HRQoL with regard to the degree of symptoms. HRQoL measures improved when HD was treated with an operation. Patient-reported symptoms were associated with HRQoL measures, whereas no association was found for the surgeon's grading of anal pathology.

Limitations

There was a relatively high rate of non-responders in the population of patients with HD (Cohort I = 34 %) and the background population sample (SUSY 2017 = 44 %). Some degree of selection bias is possible and might explain the finding of a higher mental component summary score in Cohort I compared with the background population. We studied a selection of patients with HD (patients referred to our outpatient clinic) and our results may not represent the whole population of patients with HD. On the other hand, the study population should represent the patients seen by most general and colorectal surgeons.

There was no untreated comparison group by which to study the impact of surgical treatment of HD.

Discussion

Principal findings

This thesis addresses three issues in HD: the assessment of patient-reported symptoms and disease-specific HRQoL, the short –and long-term outcomes of MOH a modified, less invasive technique for open haemorrhoidectomy compared with THD a non-ablative operation, and HRQoL in patients with HD and the possible impact of surgical treatment on HRQoL.

The primary goal of treatment of HD is the long-term resolution of symptoms and improvement of patient wellbeing. The assessment of these two outcomes has been hampered by a lack of validated measurement instruments. Study I evaluated two new questionnaires to assess patient-reported symptoms (HDSS) and disease-specific HRQoL (SHS_{HD}). The HDSS demonstrated adequate values for the three key measurement properties: validity, reliability and responsiveness. The SHS_{HD} demonstrated adequate reliability and responsiveness. The validity of the SHS_{HD} was not tested in Study I, but in Study IV associations with two validated, generic HRQoL measures (SF36v2 and EQ-5D) were found. These results support the validity of the SHS_{HD} as a simplified HRQoL measure in patients with HD.

Study II-III showed that MOH is a safe and efficient operation for patients with grade II-IV haemorrhoids. The immediate postoperative course after MOH was similar to that of THD. Both operations demonstrated reduction in symptoms, improvement of HRQoL and high patient satisfaction. We found, however, a higher frequency of recurrent haemorrhoidal prolapse and need for treatment of recurrence after THD. Patient satisfaction was higher after MOH. Moreover, MOH had lower hospital treatment costs compared with THD.

The results of Study IV suggest that haemorrhoidal symptoms have a negative impact on HRQoL and that HRQoL improves after surgical treatment of HD.

Assessment of symptoms and HRQoL

The value of symptom assessment in HD has already been mentioned. The risk of recurrence of symptoms is a main concern when patients are asked to choose between operation methods.[26] Patient-reported symptoms have a negative impact on HRQoL,[4] whereas the surgeon's anatomical grading of HD is poorly correlated to symptoms and not associated with HRQoL.[4,101]

Patients with HD usually present with more than one symptom and symptoms are known to fluctuate. Ideally, a symptom questionnaire gives an overview of the symptoms and reflects the total symptom burden that the patient experiences. In clinical practice an overview of symptoms is useful for guiding the surgeon on choice of treatment and monitoring the effect of treatment. In clinical trials a score reflecting the total symptom burden might be more useful when comparing groups of patients. The HDSS includes the five cardinal symptoms in HD, and a recall period of 3 months was chosen to cover spontaneous variations in symptoms. The symptoms can be evaluated separately or summarized to a symptom score. Study I showed that the HDSS was able to discriminate between patients reporting a high and low symptom load.[1] The result suggests that the summarized score is an adequate reflection of the total symptom burden. The HDSS was responsive to change after treatment and a low symptom score at postoperative follow-up is a good predictor of patient satisfaction.[1] These findings support the utility of the HDSS as outcome measure after treatment.

The HDSS was developed from a symptom score presented by Nyström et al (Figure 3).[55] The structure of the questionnaire was adapted from a previously validated questionnaire on bowel function and resembles that of other widely used scoring tools (e.g. the Wexner score and the low anterior resection syndrome score).[72,102,103] Like the HDSS, these questionnaires report how often the patient experiences symptoms or complaints. Whether symptoms are best measured by their frequency or intensity is unclear. It could be argued that frequency measures undermine the importance of less frequent but highly bothersome symptoms. On the other hand, the correlation between frequency and intensity measures is usually high and frequency measures have demonstrated favourable psychometric properties.[104–106] In the HDDS the items on bleeding and soiling showed weak correlations to overall symptom load.[1] A similar finding was reported by Pucher et al., who presented a symptom score for HD.[57] In

this questionnaire items were selected based on their impact on quality of life. The items on bleeding and soiling were non-significant factors and were excluded from the final score. The explanation could be that these symptoms are less important to the patients when they evaluate the overall symptom burden. However, we cannot rule out the possibility for improvements on the assessment of these symptoms. The notable improvement in anal incontinence scores after treatment for HD is an interesting finding which is attributed to the reduction of soiling.[56] Perhaps questions on problems with perianal hygiene or the use of protective pads would better capture the impact of this symptom. We considered eliminating the items with the lowest correlation coefficient (bleeding and soiling) from the HDSS. However, the majority of patients reported symptoms of bleeding (82%) and soiling (69%), indicating their clinical relevance and both items were kept in the score.

In agreement with previous findings, the HDSS showed a rather weak correlation with the grade of haemorrhoidal prolapse (Goligher's classification).[101] In the original symptom score presented by Nyström, patients were asked how often they needed to manually reduce prolapsing haemorrhoids (strictly catching Goligher's grade III haemorrhoids) (Figure 3).[55] We changed this question to "*How often do you feel a swelling or a prolapsing hemorrhoid?*" in order to assess grade II-IV haemorrhoids.[1] We noted an inconsistency between patient-reported symptoms of prolapse and haemorrhoidal prolapse at clinical examination. Some patients may report anal skin tags as haemorrhoidal prolapse. Misclassifications by the surgeon could have also contributed to the observed inconsistency. The original question presented by Nyström was included in the questionnaire used in this thesis. Differences in patient-reported symptoms of prolapse and anatomical assessment by the surgeon were also present for this item. The two different items on prolapse were strongly correlated (Spearman's rho = 0.707) and exchanging the items in the HDSS yielded results regarding validity (AUC = 0.786 vs. 0.789), reliability (ICC = 0.822 vs. 0.842), and responsiveness (AUC = 0.843 vs. 0.806).

Measurement of HRQoL complements a symptom score by assessing the impact of symptoms on the patient's daily life and wellbeing. Generic HRQoL questionnaires are most commonly used in clinical trials on HD.[26,49,52,53,56] Generic questionnaires are useful for comparing HRQoL among diseases or with healthy individuals.

However, some items might not be equally relevant to the complaints in HD. Generic questionnaires can be less sensitive to changes induced by treatment as some aspects of proctologic diseases are not reflected in the questionnaire.[24] The SHS_{HD} is a promising tool for assessing HRQoL in patients with HD. The questionnaire is responsive and like the HDSS, it correlates with patient satisfaction after the operation.[1] The association with other HRQoL measures supports its validity.[4] The briefness of the questionnaire is appealing. The questionnaire is simple to complete which should increase response rates and data completeness.[107] The potential disadvantage of having only one question in each dimension has to be weighed against the advantage of simplicity. The element of random error is more likely to be reduced with multiple questions.[108] A more detailed picture of the patient's HRQoL could be achieved with larger multi-item questionnaires, but probably with reduced usefulness in a busy clinical setting.[107,109] During the study period of this thesis new HRQoL measures for proctologic diseases have been presented.[110,111] Both questionnaires include items on the impact of disease on social relations and sexuality. As these items could be relevant problems to patients with HD but are not specifically addressed in the $SHS_{HD,}$ it might be useful to explore the value of adding these items.

Minimal Open Haemorrhoidectomy vs. Transanal Haemorrhoidal Dearterialization

Previous RCTs comparing THD with haemorrhoidectomy have reported similar results in regards to symptom resolution and recurrence,[45,48–54] but only a few studies presented long-term follow-up (≥1 year) of symptoms using a patient-reported questionnaire.[45,51] Study III is the first to report a difference in the effect on haemorrhoidal prolapse.[3] Elshazly found no difference in symptom score 1 and 2 years after surgery.[51] Elmer et al. used a symptom questionnaire similar to the HDSS.[45] At 1-year postoperative follow-up, pain, itching, bleeding, and prolapse were reduced in both groups, while soiling was reduced only after haemorrhoidectomy. Both studies included patients with grade II-III haemorrhoids. A relatively high proportion of the patients included in Study III had grade IV haemorrhoids, which might explain the difference in the results. Successful treatment of advanced haemorrhoids with THD has been reported.[112,113] However, data from previous studies

suggest inferior results and lower patient satisfaction in grade IV haemorrhoids.[47,114,115] A fear that the minimal resections in MOH would increase the risk of recurrent prolapse was not substantiated by the results of Study II-III.

Many patients fear postoperative pain after haemorrhoidectomy, and THD is a result of the search for a less painful operation. In RCTs lower postoperative pain scores are reported after THD compared with haemorrhoidectomy.[45,49,51–54] However, THD is not free of postoperative pain and pain increases when mucopexies are added.[116] Moreover, higher postoperative pain scores are not necessarily reflected in faster recovery or return to daily activities.[45,50,54] The anatomical dissection and minimal resection in MOH were aimed to reduce postoperative pain after haemorrhoidectomy. We observed low median pain scores after MOH not exceeding 3 for average pain and 5 for peak pain the first 14 days postoperatively, and found no difference in average and peak postoperative scores after MOH and THD. Pain during defecation was higher after MOH, but without a difference in analgesic consumption or recovery. The results are interesting and suggest that a postoperative course after haemorrhoidectomy comparable to that of a non-ablative procedure is achievable. Further reduction of postoperative pain after haemorrhoidectomy might be possible with improved pain treatment. Metronidazole and chemical sphincterotomy (glyceryl trinitrate or diltiazem) have both demonstrated a reduction of postoperative pain after haemorrhoidectomy.[117–120]

An advantage of THD is the low risk of complications and impact on anal continence.[46,75] We observed that most complications after both MOH and THD were mild and transient, and we found no difference in postoperative anal continence scores. However, 2 patients both middle aged females, reported deterioration of anal continence after MOH. A frequency of anal incontinence between 2% and 4% after haemorrhoidectomy is in line with previous reports.[70] The risk of anal incontinence might still be a concern even with the minimal excision of haemorrhoids in MOH. Patients with impaired preoperative anal continence are at risk of further deterioration after haemorrhoidectomy,[71] and a non-ablative operation could be a better option for these patients.[46,75] We had some cases of anal stricture in the MOH-group. We had a low threshold for intervention for stricture. Early recognition and treatment resolved symptoms in 2 of the 3 patients. As no excision is performed, this complication

should not to occur after THD. Some authors recommend non-ablative operations in patients with circumferential haemorrhoidal prolapse where preservation of adequate bridges between the excisions in haemorrhoidectomy can be difficult.[121]

Patient selection is probably the key to finding the balance between efficacy of treatment and the risk of harm. Like the vast majority of trials on HD, we used Goligher's classification to grade anal pathology.[27] The classification is used in treatment guidelines and the widespread use of Goligher's classification facilitates comparison across studies.[29,122,123] However, the classification has obvious limitations and might be too simple for the assessment of anal pathology in HD.[124] Goligher's classification is a grading of *internal* haemorrhoids and do not include an assessment of external skin tags.[101] Moreover, the classification describes the most prolapsed pile and fails to reflect the distribution of haemorrhoidal prolapse in the anal canal.[125] A patient with Goligher's grade III haemorrhoids can have one single prolapsing haemorrhoid, whereas another patient can present a circumferential grade III haemorrhoidal prolapse. The obvious difference in anal pathology between these two patients is likely to impact the effects of treatment. Finally, the inter-rater reliability of the Goligher's is unknown and inconsistency between raters (surgeons) is possible.[126] New grading systems for anal pathology in HD have been suggested, but to date none of them have replaced the widespread use of the Goligher's classification.[101,125–127]

Non-ablative operations for HD all have in common the use of new instruments and equipment that increases perioperative costs. The high prevalence of HD and the constant need to limit expenses in the health-care system have led to increased attention on the costs of treatment. Two RCTs have compared the cost-effectiveness of HAL/THD with other procedures. Rubber band ligation is showed to be more cost-effective than HAL in the treatment of grade II-III haemorrhoids.[56] In comparison with stapled haemorrhoidopexy, HAL had higher costs in the treatment of grade II-III haemorrhoids.[25] Haemorrhoidectomy is more cost-effective than stapled haemorrhoidopexy in the treatment of grade II-IV haemorrhoids.[26] Our results are in line with these findings. THD had higher hospital treatment costs, mainly due to the costs of instruments and longer operative time. Increased operative time in THD compared with haemorrhoidectomy is a consistent finding.[128] Even if the operative time in THD group was calculated to be 30 minutes, costs were substantially higher in

the THD-group.[3] Without any major advantages in short or long-term outcomes it seems unlikely that THD will be cost-effective compared to MOH. It could be argued that our cost analysis did not include cost of sick leave / days off work. However, our results did not suggest prolonged postoperative recovery after MOH compared with THD.

In summary, the findings support the view of haemorrhoidectomy as the gold standard when operating for HD, and with the limited excisions in MOH the immediate postoperative course seems comparable to that of non-ablative operations.

Conclusions

- HDSS is a valid, reliable and responsive measure of symptoms in HD.
- SHS_{HD} is a valid, reliable and responsive measure of HRQoL in patients with HD.
- Haemorrhoidal symptoms have a negative impact on HRQoL and HRQoL improves after an operation.
- MOH is a feasible and safe operation with postoperative pain and recovery comparable to THD.
- MOH and THD both offer a long-term reduction of patient-reported symptoms and improvement of HRQoL.
- MOH offers better control of symptoms of prolapse and higher patient satisfaction compared with THD.
- MOH requires less re-interventions due to recurrence.
- MOH has lower hospital treatment costs compared with THD.
- Haemorrhoidectomy remains the gold standard when operating for haemorrhoids and MOH may be a valuable option.

Perspective for future research

Despite the large number of trials on treatment of HD there is still debate on which treatment is the most appropriate in a given situation and strong recommendations in treatment guidelines are lacking.[29,122,123] A major obstacle in generating high-quality evidence from meta-analyses has been the high level of heterogeneity in outcome measurement.[59] The core outcome set for HD recently suggested by the European Society of Coloproctology is an important step in the right direction (Table 4).[60] Patient-reported symptoms are suggested as the primary outcome and the HDSS and SHS_{HD} could both be valuable tools in this outcome set. In this thesis, the questionnaires demonstrated adequate values for important measurement properties. Confirmation of these results and cross-language validation of the questionnaires could promote their use in clinical practice and the development towards more standardized outcome measurement in clinical trials. Validity is not "*demonstrated once and for all by a single study"*.[90] Rather, validation should be seen as a "*ongoing process of accumulating evidence"*.[129] There might still be room for improvement in symptom assessment. Items on hygiene problems and impact on social relations and sexuality can be explored. Data on the natural history of haemorrhoidal symptoms would be useful when evaluating the effect of treatments.

Haemorrhoidectomy is considered the "gold standard" operation for HD and has the lowest recurrence rate.[35] The results of this thesis will not change this statement. Haemorrhoidectomy offers a more definite treatment of HD compared with THD and when applying the technique of MOH the immediate postoperative course seems to be comparable. The majority of patients who need an operation for HD can be treated efficiently with haemorrhoidectomy with acceptable postoperative pain, limited risk of complications, low recurrence rate and high patient satisfaction. Perhaps more attention should be given to further limiting postoperative pain and improving outcomes after haemorrhoidectomy as opposed to continuously searching for new procedures that increase costs. However, the risk of local anal complications and incontinence after haemorrhoidectomy can probably not be eliminated even with minimal excisions and improved surgical technique. The HAL/THD procedures are less invasive and very safe. Some patients might prefer a higher risk of recurrence to

minimize the risk of long-term complications. HAL/THD could be a valuable option in patients with increased risk of complications after haemorrhoidectomy, and more knowledge on proper patient selection would be of great benefit in clinical practice.[130] Future studies should also explore patient expectations and preferences before surgery.[35] The development of an improved grading system for anatomical pathology in HD with good inter-rater reliability is needed. Long-term follow-up of anal continence with pre- and postoperative anorectal physiologic testing could identify the impact of haemorrhoidectomy on anal continence compared with non-ablative operations and the potential benefits of the minimal excision in MOH.

Summary

Background: Symptomatic haemorrhoids (haemorrhoidal disease) are prevalent in the adult population and operations for haemorrhoidal disease are frequent. Haemorrhoidal disease is a benign disease and the primary goal of treatment is the resolution of symptoms and the improvement of patient wellbeing. The assessment of these two outcomes has been hampered by the lack of validated measurement instruments. Operations for haemorrhoidal disease are ablative (haemorrhoidectomy) or non-ablative (e.g. stapled haemorrhoidopexy and transanal haemorrhoidal dearterialization (THD)). Previous studies indicate that ablative operations have better long-term results in regard to recurrence, but are associated with more postoperative pain than non-ablative operations.

The objectives of this PhD thesis were:

1. To develop questionnaires for the assessment of symptoms and quality of life in haemorrhoidal disease.
2. To describe a minimal invasive, ablative operation for haemorrhoidal disease (minimal open haemorrhoidectomy, MOH).
3. To conduct a randomized controlled trial comparing the effect of MOH with a non-ablative operation (THD) on postoperative symptoms and quality of life.
4. To study quality of life in patients with haemorrhoidal disease and the effect of surgical treatment on patient-reported quality of life.

Results:

Ad.1. Patient-reported outcome measures for symptoms and quality of life were constructed and their measurement properties assessed. A measure of symptoms, the Haemorrhoidal Disease Symptom Score, based on the frequency of the five cardinal symptoms (pain, itching, bleeding, soiling and prolapse) was found to be valid, reliable and responsive (able to detect change). The Short Health Scale, a simplified quality of life measure with just one question in each of its four dimensions, was found to be valid, reliable and responsive when adapted for the use in haemorrhoidal disease (Short Health Scale$_{HD}$).

Ad.2. MOH, characterized by anatomical dissection and minimal resections, was found to be feasible and safe.
Ad.3. MOH and THD both showed reduction in symptoms and improvement of quality of life. However, more patients operated with THD reported symptoms of prolapse and needed treatment for recurrence one year after surgery. Moreover, MOH had higher patient satisfaction and lower hospital treatment costs. MOH had a similar postoperative pain pattern, analgesic consumption and recovery compared with THD.
Ad.4. Haemorrhoidal symptoms had a negative impact on quality of life, which improved when haemorrhoidal disease was treated with an operation. There was no association between quality of life and the severity of haemorrhoidal pathology graded by the surgeon.

Conclusion: The Haemorrhoidal Disease Symptom Score and Short Health Scale$_{HD}$ questionnaires give a good overview of symptoms and patient wellbeing. Patient-reported quality of life improves after surgical treatment of haemorrhoidal disease. Haemorrhoidectomy should still be considered the gold standard when operating for haemorrhoidal disease and MOH may be a valuable option.

Summary in Danish - Dansk resumé

Baggrund: Symptomatiske hæmorider (hæmoridesygdom) er udbredt i den voksne befolkning, og operative indgreb mod hæmoridesygdom foretages hyppigt. Hæmoridesygdom er en benign sygdom, og det primære formål med behandlingen er derfor, at afhjælpe symptomerne og forbedre af patientens velbefindende. Hidtil har vurderingen af disse to effektmål vært vanskeliggjort af manglen på validerede måleinstrumenter. Operationer for hæmoridesygdom kan være ablative (hæmoridektomi) eller ikke-ablative (f.eks. staplet hæmoridopeksi eller transanal ligatur af hæmoridearterierne (THD)). Tidligere undersøgelser har vist, at ablativ operation giver bedre resultater på længere sigt mht. tilbagefald, men at de er forbundet med flere smerter efter operation end de ikke-ablative indgreb.

Formålet med denne PhD afhandlingen var:

1. At udvikle spørgeskemaer for evaluering af symptomer og livskvalitet ved hæmoridesygdom.
2. At beskrive en minimal invasiv, ablativ operationsmetode for hæmoridesygdom (minimal åben hæmoridektomi, MOH).
3. At gennemføre et randomiseret kontrolleret studie som sammenligner effekten af MOH med en ikke-ablativ operation (THD) på postoperative symptomer og livskvalitet.
4. At undersøge livskvaliteten hos patienter med hæmoridesygdom og effekten af kirurgisk behandling på patientrapporteret livskvalitet.

Resultater:

Ad. 1. Patientrapporterede spørgeskemaer for henholdsvis symptomer og livskvalitet blev konstrueret og måleegenskaberne vurderet. Et mål for symptomer, Haemorrhoidal Disease Symptom Score, baseret på frekvensen af de fem hovedsymptomer (smerter, kløe, blødning, soiling og prolaps) fandtes at være valid, reliabelt og responsivt (evne til at fange op ændring). Short Health Scale, et forenklet målinstrument for livskvalitet med bare ét spørgsmål for hver af dets fire dimensioner, fandtes at være valid, reliabelt og responsivt, når det blev tilpasset til brug ved hæmoridesygdom (Short Health Scale$_{HD}$).

Ad. 2. MOH, som er karakteriseret ved anatomisk dissektion og minimal resektion, fandtes at være en anvendelig og sikker operationsmetode.
Ad.3. MOH og THD viste begge en reduktion av symptomerne og en forbedring af livskvaliteten, men flere patienter rapporterede symptomer på prolaps, og blev behandlet for recidiv et år efter THD. MOH viste desuden højere patienttilfredshed og kunne gennemføres til lavere omkostninger. MOH havde et tilsvarende post-operativt smertebillede, forbrug af smertestillende midler og rekonvalescens som THD.
Ad.4. Symptomer på hæmorider fandtes at have en negativ indvirkning på livskvaliteten, hvilket blev forbedret når hæmoridesygdommen blev behandlet med operation. Der blev ikke fundet sammenhæng mellem livskvaliteten og kirurgens vurdering af graden af hæmoridepatologi.

Konklusion: Spørgeskemaerne Haemorrhoidal Disease Symptom Score og Short Health Scale$_{HD}$ giver et godt overblik over symptomerne og patientens velbefindende. Kirurgisk behandling af hæmoridesygdom forbedrer patienternes livskvalitet. Hæmoridektomi bør stadig betragtes som guldstandarden ved operationer for hæmoridesygdom, og MOH kan være et værdifuldt alternativ.

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ORIGINAL CONTRIBUTION

Hemorrhoidal Disease Symptom Score and Short Health Scale$_{HD}$: New Tools to Evaluate Symptoms and Health-Related Quality of Life in Hemorrhoidal Disease

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BACKGROUND: There are no adequately validated tools to evaluate symptoms or disease-specific health-related quality of life in hemorrhoidal disease.

OBJECTIVE: The purpose of this study was to assess validity, reliability, and responsiveness of a symptom score of patient-reported pain, itching, bleeding, soiling, and prolapse (Hemorrhoidal Disease Symptom Score). In addition, the study set out to assess reliability and responsiveness of an instrument to measure health-related quality of life in patients with hemorrhoids (Short Health Scale$_{HD}$), with 1 item in its 4 dimensions: symptom load, functional status, disease-specific worries, and general well-being.

DESIGN: This was a cross-sectional (validity and reliability) and longitudinal (responsiveness) study.

SETTINGS: The study was conducted at a single center.

PATIENTS: Cohort 1 included 295 patients with hemorrhoids to study validity and 60 patients with test–retest scores to study reliability. Cohort 2 included 128 and 121 patients operated for hemorrhoids to study responsiveness of the Hemorrhoidal Disease Symptom Score and the Short Health Scale$_{HD}$.

MAIN OUTCOME MEASURES: The study evaluated validity, reliability, and responsiveness. Patient-reported symptom load on a 7-point Likert scale was used as comparator, and receiver operating characteristics curve assessed discriminative validity. Interclass correlation assessed reliability. Receiver operating characteristics curve assessed responsiveness, meaning the ability to discriminate between patients with and without improvement after surgery.

RESULTS: The Hemorrhoidal Disease Symptom Score demonstrated the ability to discriminate between patients reporting high or low symptom load (area under the curve = 0.786 (95% CI, 0.725–0.848)). The Hemorrhoidal Disease Symptom Score and the Short Health Scale$_{HD}$ demonstrated adequate reliability and responsiveness, with interclass correlation of 0.822 (95% CI, 0.715–0.891) and 0.763 (95% CI, 0.634–0.851) and area under the curve of 0.843 (95% CI, 0.756–0.929) and 0.840 (95% CI, 0.752–0.929).

LIMITATIONS: We had no gold standard comparator to assess validity and responsiveness.

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CONCLUSIONS: The findings suggest that the Hemorrhoidal Disease Symptom Score is valid, reliable, and responsive and that the Short Health Scale$_{HD}$ is reliable and responsive. Used together, these tools provide a good overview of symptoms and their impact on patient well-being. See **Video Abstract** at http://links.lww.com/DCR/A770.

KEY WORDS: Health-related quality of life; Hemorrhoids; Measurement properties; Patient-reported outcomes; Symptom score; Validation.

Hemorrhoidal disease (HD) is the most common proctologic condition in adults.[1] A prevalence of ≈4.4% is estimated in the United States, with a peak at 45 to 65 years of age.[2] Various treatment options are available, ranging from conservative treatments to several surgical procedures. Over the last decades, new surgical techniques have been introduced, such as LigaSure hemorrhoidectomy, stapled hemorrhoidopexy, and hemorrhoidal artery ligation.[3–5] The number of treatment options may reflect differing preferences among surgeons and patients, as well as a lack of evidence regarding the best choice in a given situation. Several clinical trials have compared treatment options, but standardized outcome measures are lacking, making comparisons difficult.[6]

The Consensus-Based Standards for the Selection of Health Measurement Instruments (COSMIN) initiative has proposed quality criteria to evaluate the measurement properties of patient-reported outcomes.[7,8] Before introducing any new instrument, researchers should examine its validity, reliability, and ability to detect change (responsiveness).[9] To date, none of the available instruments for symptom measurement in HD have been evaluated according to the COSMIN guidelines.[10–12] Nyström et al[10] proposed a symptom score (HDSS (HD Symptom Score)) based on the 5 cardinal symptoms (pain, itching, bleeding, soiling, and prolapse), which has been used in a few clinical trials, but its measurement properties have never been tested.[13,14] No disease-specific measure of health-related quality of life (HRQoL) in HD exists. The Short Health Scale (SHS) is a patient-reported measurement instrument of subjective health originally developed for patients with IBD.[15,16] SHS is proposed as a simplified HRQoL instrument with just 1 question in each of its 4 dimensions, including symptom burden, functional status, disease-specific worries, and general well-being.[15] SHS has not been used previously in patients with HD. The purpose of this study was to examine the validity, reliability, and responsiveness of the HDSS and the reliability and responsiveness of the SHS adapted for HD (SHS$_{HD}$) in accordance with the COSMIN guidelines.

PATIENTS AND METHODS

Patients

This study was a cross-sectional (cohort 1) and longitudinal (cohort 2) study conducted on 2 patient cohorts. Patients referred for HD to the proctologic outpatient clinic at Holbaek Hospital were assessed for eligibility. All of the patients diagnosed with HD who were treated conservatively or surgically between January 15, 2015, and August 30, 2017, were included in cohort 1. Data were used in validity and reliability analyses. To study responsiveness, we used a cohort of patients operated for HD at our department between November 6, 2013, and October 3, 2016 (cohort 2). Patients in cohort 1 operated within this period were included in both cohorts.

The attending surgeon set the diagnosis and grading of HD based on patient history, physical examination, and anoscopy. According to local guidelines, sigmoidoscopy or colonoscopy was performed in all of the patients aged ≥40 years and in patients <40 years if found to be indicated by the surgeon. Excluded were pediatric patients (16 years or younger), patients with acute HD (bleeding requiring admission, strangulated internal hemorrhoids, and thrombosed external hemorrhoids), and patients with concomitant anal fistula or fissure, anal or rectal prolapse, IBD, or colorectal or anal cancer. Internal hemorrhoids were graded using Goligher's classification.[17] The study did not interfere with patient treatment. The only intervention introduced was the completion of the questionnaires used in the study. Patients were asked to participate in a letter sent to them that included the questionnaires and consented by completing the questionnaires. Patients with cognitive and language inabilities were therefore excluded. The study was approved by the Regional Committee on Health Research Ethics (SJ-430) and the Danish Data Protection Agency (REG-71–2013).

Measurements

Symptoms

Symptoms were assessed using patient-reported frequency of the 5 symptoms, including pain, itching, bleeding, soiling, and prolapse, as proposed by Nyström et al (Table 1).[10] Patients were instructed to answer based on their experience during the previous 3 months. Each symptom was graded on a 5-point scale (0 = never, 1 = less than once a month, 2 = less than once a week, 3 = 1–6 days per week, 4 = every day or always), giving a total score ranging from 0 to 20. In the original score presented by Nyström et al,[10] the presence of prolapse was reported as the frequency of manual reduction. Instead, we asked the patients how often they experienced prolapse, reflecting HD grade II, III, and IV (Goligher's classification[17]). To investigate whether these questions were exhaustive for patient symptoms, we

TABLE 1. HDSS and SHS_{HD}

Hemorrhoidal Disease Symptom Score

The following questions deal with symptoms caused by hemorrhoids. Your answers should reflect your symptoms during the last 3 months (1 answer per question).

1. How often do you feel pain from your hemorrhoids?
   □ Never □ Less than once a month □ Less than once a week □ 1–6 days per week □ Every day (always)
2. How often do you feel itching or discomfort of the anus?
   □ Never □ Less than once a month □ Less than once a week □ 1–6 days per week □ Every day (always)
3. How often do you bleed when passing stool?
   □ Never □ Less than once a month □ Less than once a week □ 1–6 days per week □ Every day (always)
4. How often do you soil your underwear (soiling from the anus)?
   □ Never □ Less than once a month □ Less than once a week □ 1–6 days per week □ Every day (always)
5. How often do you feel a swelling or a prolapsing hemorrhoid?
   □ Never □ Less than once a month □ Less than once a week □ 1–6 days per week □ Every day (always)

Short Health $Scale_{HD}$

The following questions deal with how your symptoms caused by hemorrhoids affect your daily life (one answer per question).

1. In your view, how severe are your symptoms caused by hemorrhoids? Please grade your symptoms on a 7-point scale, where 1 is "no symptoms" and 7 is "severe symptoms."

No symptoms						Severe symptoms
1 □	2 □	3 □	4 □	5 □	6 □	7 □

2. Do your symptoms interfere with your daily activities? Please grade your answer on a 7-point scale, where 1 is "not at all" and 7 is "interfere to a very high degree."

Not at all						Interfere to a very high degree
1 □	2 □	3 □	4 □	5 □	6 □	7 □

3. Do your symptoms cause much concern? Please grade your answer on a 7-point scale, where 1 is "no concerns" and 7 is "constant concerns.".

No concerns						Constant concerns
1 □	2 □	3 □	4 □	5 □	6 □	7 □

4. How is your general feeling of well-being? Please grade your answer on a 7-point scale, where 1 is "very good" and 7 is "very bad."

Very good						Very bad
1 □	2 □	3 □	4 □	5 □	6 □	7 □

HDSS = Hemorrhoidal Disease Symptom Score; SHS_{HD} = Short Health Scale adapted for hemorrhoidal disease.

asked 50 patients to report any other symptoms experienced related to HD. Additional symptoms were reported in only a few cases (3 different symptoms in 3 different patients). Based on these findings, we found no reason to include additional symptoms in the score. We called this modification of the Nyström score the HDSS.

Health-Related Quality of Life

HRQoL was assessed using SHS_{HD} (Table 1). Patients were asked to report overall symptom load, interference with daily activities, and worries caused by HD. The fourth question regarded general well-being. We used a 7-point Likert scale, giving a total score ranging from 4 to 28.[18]

Patient Global Impression of Change and Satisfaction With the Operation

Patient global impression of change (PGIC) was assessed on a 7-point Likert scale. On this scale, scores >4 indicate improvement, and scores ≤4 indicate no change or worsening. PGIC can be used as an external criterion to measure clinically important change when no gold standard is available.[9] In this study, PGIC reported change in symptom load at postoperative follow-up. Patients were also asked to grade their satisfaction with the operation on a 7-point Likert scale (1 = very dissatisfied, 7 = very satisfied).

Procedure

Data were collected prospectively and registered in a local database. The patients completed the HDSS and SHS_{HD} questionnaires twice at inclusion. Patients operated for HD (cohort 2) also completed the questionnaires at planned follow-up 12 months postoperatively. All of the questionnaires were in Danish and distributed on paper. The questionnaires were sent to the patients by postal mail, stating the scheduled meeting time at the outpatient clinic. Patients were asked to complete the questionnaires at home and return them by mail. When the patients attended the outpatient clinic, they were asked to complete the same questionnaires a second time. Patients who had completed the questionnaires twice at inclusion were eligible for test–retest analysis. At postoperative follow-up, patients were asked to bring with them or finalize the questionnaires in the outpatient clinic.

Statistical Analyses

Patients

Descriptive statistics described demographic data. Missing data for the HDSS and the SHS_{HD} were handled as follows: if 2 questionnaires (test and retest) were available, missing answers in the first questionnaire were completed with data from the second. In cases with only 1 questionnaire available, the series median was used. Patients with missing data were excluded in test–retest and responsiveness analyses.

Validity

Lacking a gold standard to measure symptoms in HD, we used the first question of the SHS_{HD} on severity of symptom load (symptom load (SHS_{HD})) to assess validity of the HDSS. Receiver operating characteristics curve analysis assessed discriminative validity: the ability to discriminate between patients reporting low (<4 points) and high symptom load (>4 points). A minimum criterion for discriminative validity was set as an area under the curve (AUC) of 0.70.[19] To examine the contribution of each symptom, we used binary logistic regression and the correlation coefficient of each symptom with symptom load (SHS_{HD}). The association with grade of hemorrhoids (Goligher's classification[17]) was assessed by the Spearman ρ, and we compared the scores of patients treated conservatively versus surgically using the Mann–Whitney *U* test. The proportion of patients with the highest and lowest possible HDSS and SHS_{HD} scores was used to assess floor and ceiling effects, which are considered to be present if >15% of patients get the lowest or highest possible score.[20]

Reliability

We assessed the internal consistency of the SHS_{HD} but not of the HDSS, because we considered the HDSS to be based on a formative model, where items are not necessarily highly correlated.[21] The dimensionality of the SHS_{HD} was tested before the assessment of internal consistency using explorative factor analysis (EFA), with an eigenvalue of >1.0 as the criterion for factor extraction. EFA tests to which degree items in a questionnaire are measures of ≥1 underlying phenomena (factors).[9] Internal consistency was assessed using a Cronbach α. A value of 0.70 to 0.95 was considered as acceptable.[20] Relative and absolute reliability were assessed in test–retest analysis. We chose an interval of 10 to 25 days as an adequate interval between test and retest. Interclass correlation coefficient using 2-way random absolute agreement assessed relative reliability. An interclass correlation coefficient of 0.70 is recommended as the minimum for relative reliability.[20] The $SEM_{AGREEMENT}$ was calculated by taking the square root of the within-subject variance consisting of the variance between the measures plus the residual variance. $SEM_{AGREEMENT}$ was used to estimate smallest detectable change (SDC): $2.77 \times SEM_{AGREEMENT}$. SDC is the test value that a patient must exceed to demonstrate change above measurement error with 95% certainty.[22] Bland–Altman plots were constructed to visualize test–retest reliability.[23]

Responsiveness

Responsiveness was assessed using receiver operating characteristic curve analysis. PGIC was used as an external criterion for change. Changes in the HDSS and SHS_{HD} were calculated. PGIC was dichotomized and used as an anchor to contrast patients with (>4) and without improvement (≤4) after treatment. AUC was used as a measure of responsiveness and should be >0.70.[20] The cutoff value with the best combination of sensitivity and specificity (highest sum of sensitivity plus specificity) was used to determine minimal important change (MIC). The Spearman ρ assessed an expected linear trend of increasing improvement of HDSS and SHS_{HD} scores in line with more improvement reported on PIGC.

Sample Sizes

No sample size calculations were performed. We relied on the COSMIN guidelines, which rate a number >100 as excellent, >50 as good, and >40 as fair sample sizes for the assessment of measurement properties.[24] IBM SPSS 24 (IBM Corp, Armonk, NY) was used for analysis.

RESULTS

Patients

In cohort 1, 295 patients were included for the assessment of validity and internal consistency (Fig. 1). Sixty patients had completed the test and retest questionnaires with an interval of 10 to 25 days and were included in absolute and relative reliability analyses. Cohort 2 included 143 patients. At 12-month follow-up, complete data were obtained from 128 (89.5%) of 143 patients and 121 (84.6%) of 143 patients for the HDSS and SHS_{HD}. Patient characteristics are presented in Table 2.

Validity

The HDSS demonstrated ability to discriminate between patients reporting a low (<4) or high symptom load (>4) in the SHS_{HD}, with an AUC of 0.786 (95% CI, 0.725–0.848; n = 227). The correlation coefficient between HDSS and symptom load (SHS_{HD}) was 0.483 (95% CI, 0.382–0.578; n = 295; $p < 0.001$, Spearman ρ; Fig. 2). Logistic regression showed that only pain and itching had a significant contribution (Table 3). Similarly, pain and itching had the highest correlation with symptom load (SHS_{HD}). However, only 4 (1.4%) of 295 patients reported symptoms exclusively in these 2 items. A symptom score with only 2 items, pain

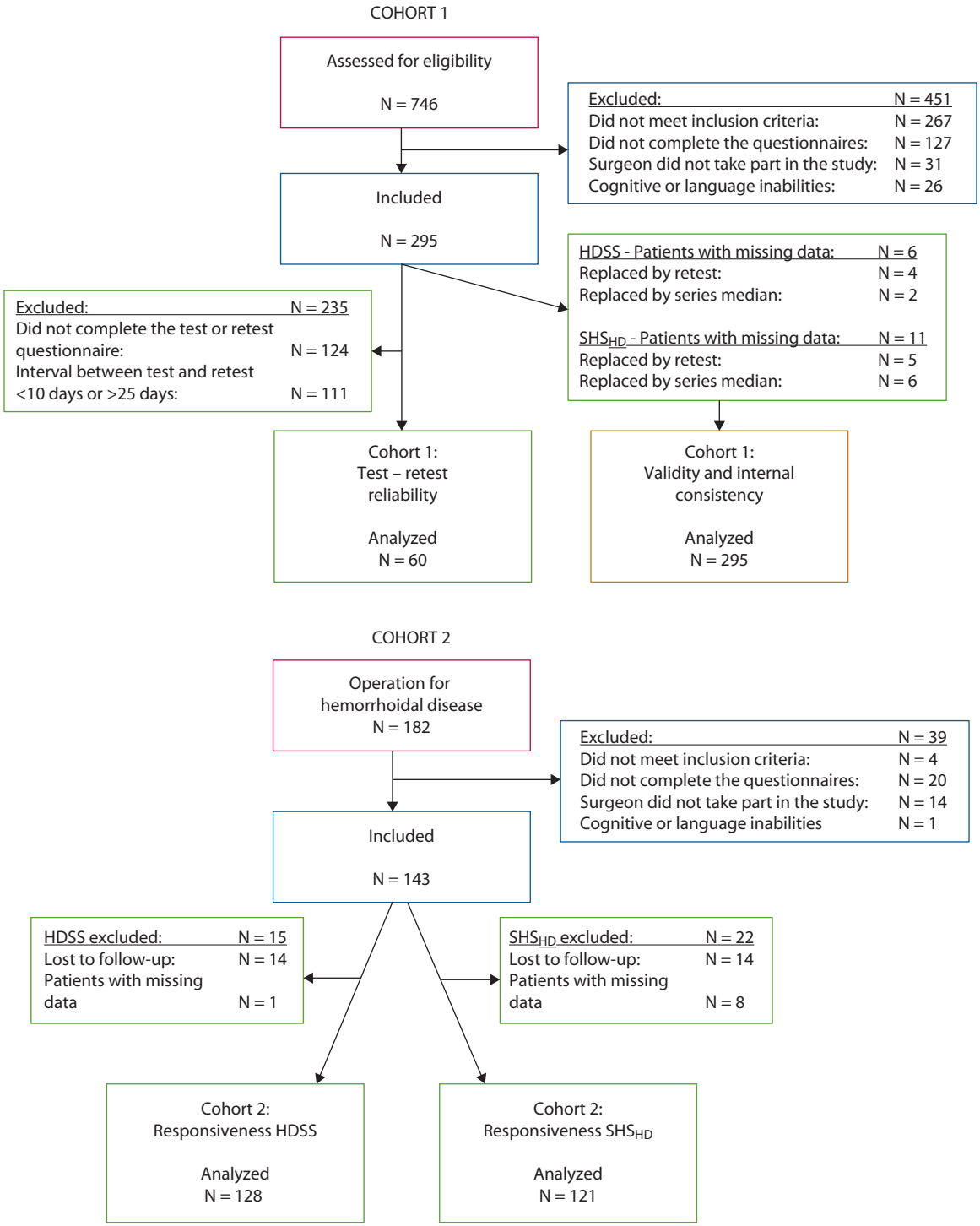

FIGURE 1. Flow chart: inclusion of patients in cohort 1 for the analysis of validity and reliability and cohort 2 for the analysis of responsiveness. HDSS = Hemorrhoidal Disease Symptom Score; SHS_{HD} = Short Health Scale adapted for hemorrhoidal disease.

and itching, would not be useful in a clinical setting. Bleeding, soiling, and prolapse all showed a significant, positive correlation with symptom load (SHS_{HD}). Therefore, all 5 items were kept in the symptom score. Post hoc analysis of patients in cohort 2 showed stronger correlation with symptom load (SHS_{HD}) for all of the items at 12-month follow-up, and in logistic regression prolapse changed from nonsignificant at baseline to significant contribution at follow-up. The correlation coefficient between the HDSS and symptom load (SHS_{HD}) at follow-up was 0.728 (95% CI, 0.628–0.802; $p < 0.001$, Spearman ρ; n = 128). The correlation coefficient between the HDSS and grade of

TABLE 2. Patient characteristics

Variable	*Cohort 1 (N = 295)*	*Test–retest (N = 60)*		*Cohort 2 (N = 143)*	
Sex, n (%)					
Women	144 (48.8)	28 (46.7)		86 (60.1)	
Men	151 (51.2)	32 (53.3)		57 (39.9)	
Age, mean (SD), y	52.9 (15.4)	52.6 (15.8)		54.4 (14.3)	
Goligher's classification, n (%)					
Grade I	77 (26.1)	26 (43.3)		1 (0.7)	
Grade II	63 (21.4)	13 (21.7)		6 (4.2)	
Grade III	71 (24.1)	7 (11.7)		55 (38.5)	
Grade IV	84 (28.5)	14 (23.3)		81 (56.6)	
		Test	Retest	Baseline	Follow-up
HDSS, median (range)	11 (1–20)	11 (1–18)	10 (1–17)	12 (3–20)	4.0 (0–17)
Missing, n (%)	–	2 (3.3)	–	1 (0.7)	14 (9.8)
SHS_{HD}, median (range)	14 (4–27)	15 (4–24)	13 (4–25)	16 (6–25)	6 (4–19)
Missing, n (%)	–	–	–	8 (5.6)	15 (10.5)
PGIC, n (%)					
Improved					109 (76.2)
Not improved					20 (14.0)
Missing					14 (9.8)
Treatment, n (%)					
Conservative treatment	186 (63.1)	46 (76.7)		–	
Open hemorrhoidectomy	47 (15.9)	6 (10.0)		73 (51.0)	
Transanal hemorrhoidal dearterialization	37 (12.5)	5 (8.3)		69 (48.3)	
LigaSure hemorrhoidectomy	25 (8.5)	3 (5.0)		1 (0.7)	

Cohort 1 included 295 patients for the study of validity and internal consistency and 60 patients for the study of reliability. Cohort 2 included 143 patients operated for hemorrhoidal disease for the study of responsiveness.
HDSS = Hemorrhoidal Disease Symptom Score; SHS_{HD} = Short Health Scale adapted for hemorrhoidal disease; PGIC = patient global impression of change.

hemorrhoids was 0.317 (95% CI, 0.207–0.422; n = 295; $p < 0.001$, Spearman ρ; Table 4). We found no signs of floor or ceiling effects (≤2% of the patients had the lowest or highest possible score).

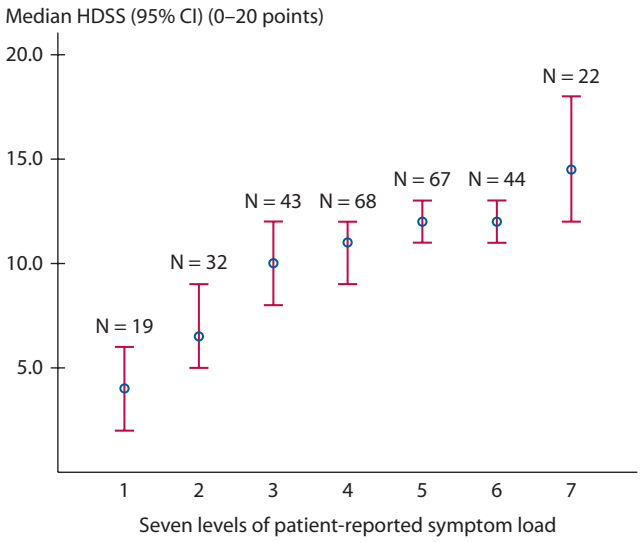

FIGURE 2. Distribution of Hemorrhoidal Disease Symptom Scores (HDSS) for 7 levels of patient-reported symptom load (1 = no symptoms; 7 = severe symptoms). Spearman ρ = 0.483 (95% CI, 0.382–0.578; n = 295; $p < 0.001$).

Reliability

EFA revealed that the SHS_{HD} was unidimensional (1 factor extracted), with a Cronbach α of 0.773 (95% CI, 0.728–0.813). The interclass correlations of the HDSS and SHS_{HD} were 0.822 (95% CI, 0.715–0.891; n = 58) and 0.763 (95% CI, 0.634–0.851; n = 60). $SEM_{AGREEMENT}$ was 1.81 (95% CI, 1.53–2.21; 9.0% of total score) for the HDSS and 2.51 (95% CI, 2.13–3.06; 10.5% of total score) for the SHS_{HD}, giving SDC values of 5.0 and 7.0. Figure 3 presents the Bland–Altman plots.

Responsiveness

The HDSS and SHS_{HD} demonstrated ability to discriminate between patients with (PGIC >4) and without (PGIC ≤4) improvement after treatment, with an AUC of 0.843 (95% CI, 0.756–0.929) for the HDSS and 0.840 (95% CI, 0.752–0.929) for the SHS_{HD} (Fig. 4). The MIC was estimated to 6.5 points for the HDSS, with sensitivity and specificity of 72.2% and 90.0%. At a sensitivity of 78.6% and specificity of 83.3%, the MIC (SHS_{HD}) was estimated to 4.5. The correlation coefficient between change in HDSS and PGIC was 0.521 (95% CI, 0.370–0.650; n = 128; $p < 0.001$; Spearman ρ) and between change in SHS_{HD} and PGIC was 0.581 (95% CI, 0.440–0.697; n = 121; $p < 0.001$, Spearman ρ; Table 5). A linear relationship existed between changes in HDSS and SHS_{HD} scores postoperatively

TABLE 3. Validity

	Baseline (cohort 1)		*Follow-up (cohort 2)*	
Variable	*CC (95% CI)*[a]	*OR (95% CI)*[b]	*CC (95% CI)*[a]	*OR (95% CI)*[b]
Item	N = 295	N = 227	N = 128	N = 117
1: Pain	0.467***	1.523**	0.617***	1.656
	(0.364–0.565)	(1.180–1.725)	(0.474–0.736)	(0.774–3.540)
2: Itching	0.468***	1.767***	0.565***	2.671*
	(0.367–0.562)	(1.317–2.371)	(0.423–0.691)	(1.091–6.540)
3: Bleeding	0.211***	1.180	0.407***	1.352
	(0.099–0.316)	(0.910–1.530)	(0.240–0.560)	(0.587–3.111)
4: Soiling	0.167***	1.180	0.321***	1.029
	(0.057–0.274)	(0.864–1.405)	(0.138–0.485)	(0.463–2.287)
5: Prolapse	0.246***	1.046	0.604***	2.556*
	(0.126–0.363)	(0.832–1.315)	(0.459–0.728)	(1.158–5.641)
HDSS	0.483***	1.305***	0.728***	1.692***
	(0.382–0.578)	(1.206–1.412)	(0.628–0.802)	(1.326–2.159)

Data show the relationship between the items of the Hemorrhoidal Disease Symptom Score (HDSS) and patient-reported symptom load (7-point Likert scale, 1 = no symptoms; 7 = severe symptoms).
[a]Data include correlation coefficient (Spearman ρ) with 95% bootstrapping CI (bias corrected and accelerated, 5000 iterations).
[b]Data include OR, binary logistic regression with dependent variable: high (>4) versus low (<4) patient-reported symptom load.
*$p < 0.05$;
**$p < 0.01$;
*** $p < 0.001$.

and baseline scores. A stronger correlation was found in post hoc analysis of the relation between relative improvement in HDSS and SHS_{HD} scores and PGIC. Low HDSS and SHS_{HD} scores at 12-month follow-up showed a high correlation with a high degree of improvement reported on PGIC and patient satisfaction with the operation.

DISCUSSION

The present findings suggest that the HDSS is a valid, reliable, and responsive measure for symptoms in HD and that the SHS_{HD} is a reliable and responsive measure for HRQoL. HDSS and SHS_{HD} together ask 9 questions. When used in combination, they provide the surgeon with a good overview of symptoms experienced by the patient and their impact on daily life and well-being.

The lack of properly validated outcome measures in HD is recognized in the literature, and to our knowledge this is the first study to examine validity, reliability, and responsiveness of a symptom score in patients with HD. No disease-specific HRQoL measurement instruments have been investigated previously. The major strengths of this study are the large sample sizes and complete evaluation of measurement properties. Without a gold standard, we used the overall assessment of symptom load to assess validity. We found a moderate correlation and discriminative validity. The correlation was weak for bleeding, soiling, and prolapse, indicating that these symptoms were less important to the patients' overall experience of symptom load. Prolapse was an important symptom at postoperative follow-up. The HDSS assesses the frequency rather than the intensity of symptoms, which might explain why stronger

TABLE 4. Distribution of the HDSS and SHS_{HD} in cohort 1 (N = 295) according to grade of hemorrhoids and treatment

Goligher's classification	*HDSS median (range)*	*p*[a]	*SHS_{HD} median (range)*	*p*[a]
Grade I (n = 77)	9.0 (1–19)		12.0 (4–24)	
Grade II (n = 63)	10.0 (2–19)		13.0 (4–26)	
Grade III (n = 71)	11.0 (1–19)		15.0 (4–27)	
Grade IV (n = 84)	12.5 (2–20)		14.0 (6–25)	
CC (95% CI)[a]	0.317 (0.207–0.422)	<0.001	0.174 (0.059–0.287)	0.003
Treatment	HDSS median (range)	*p*[c]	SHS_{HD} median (range)	*p*[c]
Conservative (n = 186)	9.0 (1–20)		13.0 (4–27)	
Operation (n = 109)	12.0 (3–20)		15.0 (6–25)	
Median difference (95% CI)[b]	3.0 (2.0–4.0)	<0.001	2.0 (1.0–4.0)	<0.001

HDSS = Hemorrhoidal Disease Symptom Score; SHS_{HD} = Short Health Scale adapted to hemorrhoidal disease.
[a]Data show the correlation coefficient (Spearman ρ) with 95% bootstrapping CI (bias corrected and accelerated, 5000 iterations).
[b]Data include the Hodges–Lehman estimate of median difference.
[c]Data were calculated by Mann-Whitney *U*.

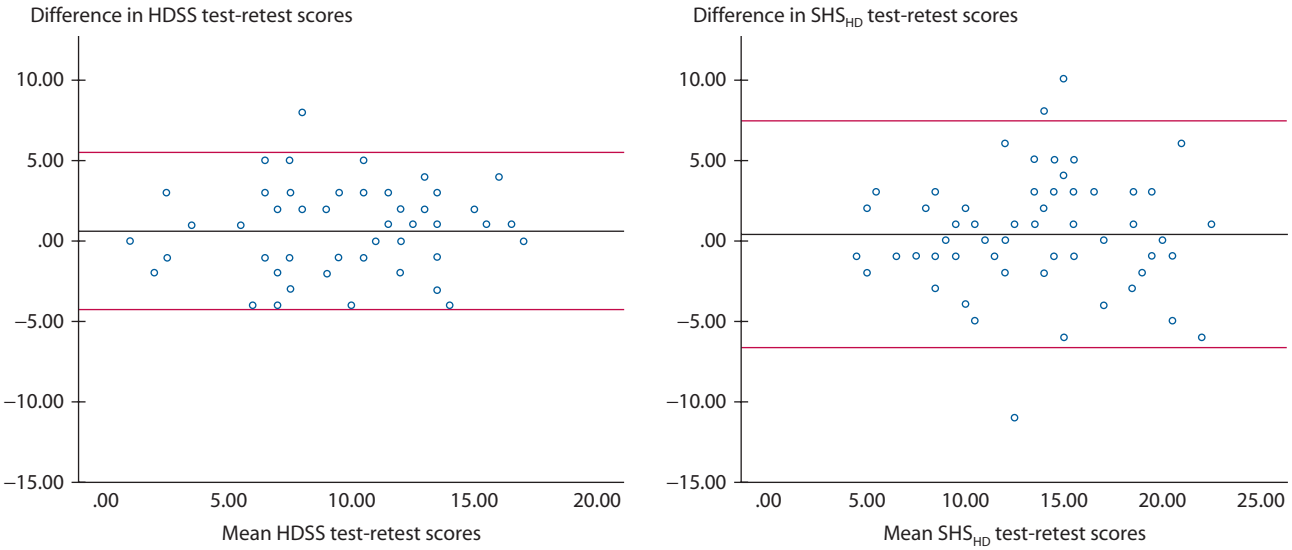

FIGURE 3. Reliability: Bland–Altman plots constructed from test–retest analysis. No drift in scores was found (HDSS: $p = 0.61$; SHS_{HD}: $p = 0.86$, linear regression). HDSS = Hemorrhoidal Disease Symptom Score; SHS_{HD} = Short Health Scale adapted for hemorrhoidal disease.

associations were not found. The SHS_{HD} could therefore complement the HDSS, measuring the impact of less frequent but severe symptoms on daily life and well-being. Whether symptoms should be measured by their frequency or intensity is debated. Frequency and intensity measures are often highly correlated, and frequency measures have shown beneficial psychometric properties compared with intensity measures.[25–27]

Our results are in agreement with those of Pucher et al,[12] who have presented a symptom score for HD: the Södergren score. In this score, items were selected based on their impact on quality of life and after regression analysis the symptoms bleeding and soiling were excluded. The final score showed ability to discriminate between patients allocated to surgical versus conservative treatment. However, the Södergren score was developed on a relatively small

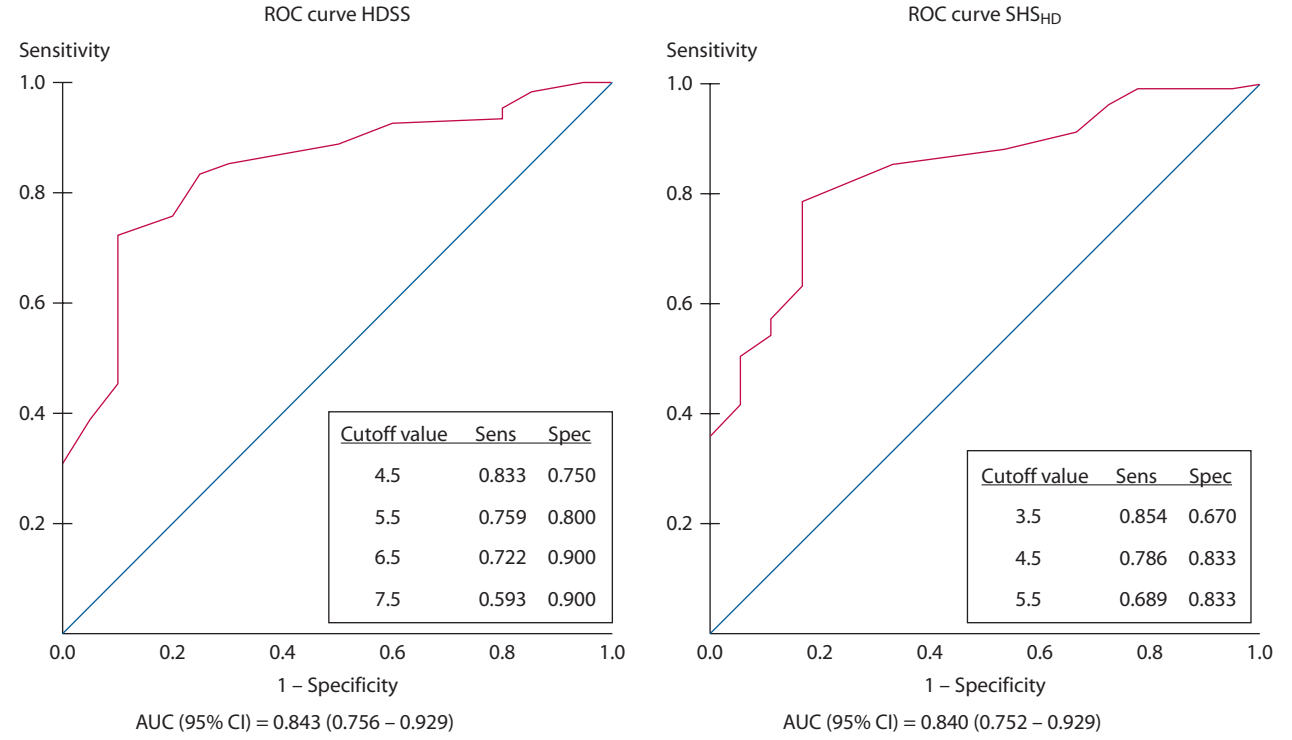

FIGURE 4. Responsiveness: Receiver operating characteristic (ROC) curve and cutoff values used as estimates for minimally important change (MIC). HDSS = Hemorrhoidal Disease Symptom Score; SHS_{HD} = Short Health Scale adapted for hemorrhoidal disease; AUC = area under the curve; Sens = sensitivity; Spec = specificity.

TABLE 5. Responsiveness assessed 12 months postoperatively

Measurement	*PGIC CC (95% CI)*[a]	*PS CC (95% CI)*[a]
Change in HDSS (absolute)	0.521* (0.370 to 0.650)	–
Change in SHS_{HD} (absolute)	0.581* (0.440 to 0.697)	–
Change in HDSS (relative)	0.658* (0.551 to 0.747)	–
Change in SHS_{HD} (relative)	0.656* (0.529 to 0.753)	–
HDSS at follow-up	–0.680* (–0.769 to –0.569)	–0.660* (–0.754 to –0.541)
SHS_{HD} at follow-up	–0.654* (–0.752 to –0.527)	–0.622* (–0.731 to –0.487)

This table shows the Hemorrhoidal Disease Symptom Score (HDSS; n = 128) and Short Health Scale adapted for hemorrhoidal disease (SHS_{HD}; n = 121) versus patient global impression of change (PGIC) and patient satisfaction with the operation (PS).
[a]Data include the correlation coefficient (Spearman ρ) with 95% bootstrapping CI (bias corrected and accelerated, 5000 iterations).
*$p < 0.001$.

sample size (n = 45), and the results need to be confirmed in a larger population. Moreover, no analyses of reliability and responsiveness were presented. These properties would need to be assessed before the Södergren scores could be adequately interpreted in clinical practice or clinical trials.

The association with Goligher's anatomic classification[17] was weak. This is in line with previous findings in which grade of prolapse and symptoms were poorly correlated.[28] We did, however, find a difference in scores between patients treated conservatively versus surgically. HDSS and SHS_{HD} also responded to change, which is essential when used in longitudinal studies of treatment effects. HDSS and SHS_{HD} scores at postoperative follow-up were highly correlated with symptom load and patient satisfaction, supporting their validity as outcome measures after treatment. We used PGIC to measure change in symptoms postoperatively. Global rating scales have been criticized for being influenced by current disease status but are still considered appropriate external criteria of change when no gold standard is available.[29–31]

HDSS and SHS_{HD} showed sufficient relative reliability, but absolute reliability (measurement error) was somewhat high. MIC was lower than SDC for SHS_{HD}, which implicates that small but potentially clinically relevant changes cannot be securely distinguished from measurement error. The time interval used in test–retest analyses might influence reliability estimates.[32] Limited evidence of the optimal time interval exists, but an interval of ≈2 weeks is often recommended.[9] We cannot exclude some selection bias of patients who did and did not follow the instructions by completing the questionnaire twice. However, apart from lower grade of hemorrhoids, the test–retest population had similar characteristics compared with the patients in cohort 1.

The validity of a measurement instrument should always be viewed in the context of the purpose of the instrument and the population in which it has been validated.[33] The HDSS and SHS_{HD} have been developed to assess symptoms but are not diagnostic or prognostic instruments. They should neither be used to diagnose HD nor to determine treatment alone. Moreover, validation is a continuously ongoing process of accumulating evidence.[31,33,34] Recently, several attempts to develop new outcome measures in HD have been initiated.[35–37] In future research the measurement properties of these new instruments can be compared with those of the HDSS, and attempts to improve the assessment of bleeding and soiling in the HDSS can be explored. The validity of the SHS_{HD} needs to be tested against other more extensive HRQoL measures.

CONCLUSION

The HDSS and SHS_{HD} questionnaires are easy and rapid to use. When used in combination, they give a good overview of the patient's symptoms, how these symptoms are experienced, and their impact on daily life and well-being. Our results suggest that HDSS is a valid, reliable, and responsive measurement instrument of symptoms in HD and that SHS_{HD} is a reliable and responsive measurement instrument of HRQoL.

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TRICK OF THE TRADE

Minimal open hemorrhoidectomy

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Introduction

The original operation for open hemorrhoidectomy as described by Milligan–Morgan is no longer used. There is a great variation in how the operation is described in clinical trials. A number of modifications have been proposed attempting to reduce postoperative pain. An anatomical plane for the dissection was first described by Loder and Phillips [1]. They encountered small fibers passing from the internal sphincter to the anal cushions and emphasized the importance of dividing these fibers close to the cushions leaving an intact surface over the internal sphincter. Gerjy et al. described a subdermal fascia continuing into a membrane covering the internal sphincter, which was easily identified after incision of the skin of the pedicle [2]. In addition, Loder and Phillips were the first to suggest diathermy dissection and coagulation [1]. A better knowledge of hemorrhoidal vascular anatomy, demonstrating, how the arterial supply to the hemorrhoids crosses the rectal wall, has reduced the need for pedicle ligation. Seow-Chonen et al. demonstrated in a randomized study that diathermy dissection, when compared to scissor dissection, resulted in less postoperative pain and Bessa et al. showed how diathermy coagulation of the pedicle was superior to ligation in reducing postoperative pain [3, 4]. We adapted these principles and also minimized excision of the skin and the hemorrhoid. In addition, we left a part of the hemorrhoid intra-anally to reduce any impact on anal continence. We called this modification "minimal open hemorrhoidectomy" (MOH).

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Materials and methods

Patients who underwent MOH, THD or OH were evaluated from a prospectively maintained hemorrhoidal disease database. The type of operation was chosen based on the surgeon's and patients' preferences. Patients were examined before operation and 3 months postoperatively in the outpatient clinic. Patients assessed their symptoms using the Hemorrhoidal Disease Symptom Score (HDSS) [5]. Goligher's classification was used to grade the hemorrhoids, the surgeon also reported an overall assessment of hemorrhoidal pathology on a seven-point Likert scale (1 = "no pathology" to 7 = "severe pathology"). The Wexner fecal incontinence score was used to assess anal continence (10). After 3 months, patients also reported their satisfaction with the operation on a seven-point Likert scale (1 = very unsatisfied, 7 = very satisfied).

The patients kept a diary for 14 days postoperatively to register average pain over the day, peak pain and their use of analgesics. Pain was scored on a daily basis as, 0 = "no pain" to 10 = "worst pain imaginable". Pain scores were summarized for the 14 days. Patients also registered recovery, as being normal wellbeing, slightly decreased, or decreased (feeling ill).

MOH patients had a preoperative enema. Antibiotic prophylaxis was not given, and anesthesia was general or spinal, supplemented by a perianal block of 40 ml ropivacaine 5 mg/ml. Operations were performed with the patients in the lithotomy position (Fig. 1).

MOH: A retractor is not used. The external components are grasped by clamps using gentle traction. Diathermy is used for dissection and hemostasis. The skin is incised midway to one-third of the distance from the top of the pedicle, thus, minimizing the skin excision. The subdermal fascia continuing into a submucosal fascia covering the internal anal sphincter is identified as are fibers passing between the hemorrhoid and this fascia. The hemorrhoid is dissected free from the underlying internal sphincter in this plane, leaving the sphincter unharmed. THD and LH are performed as standard procedures, previously prescribed.

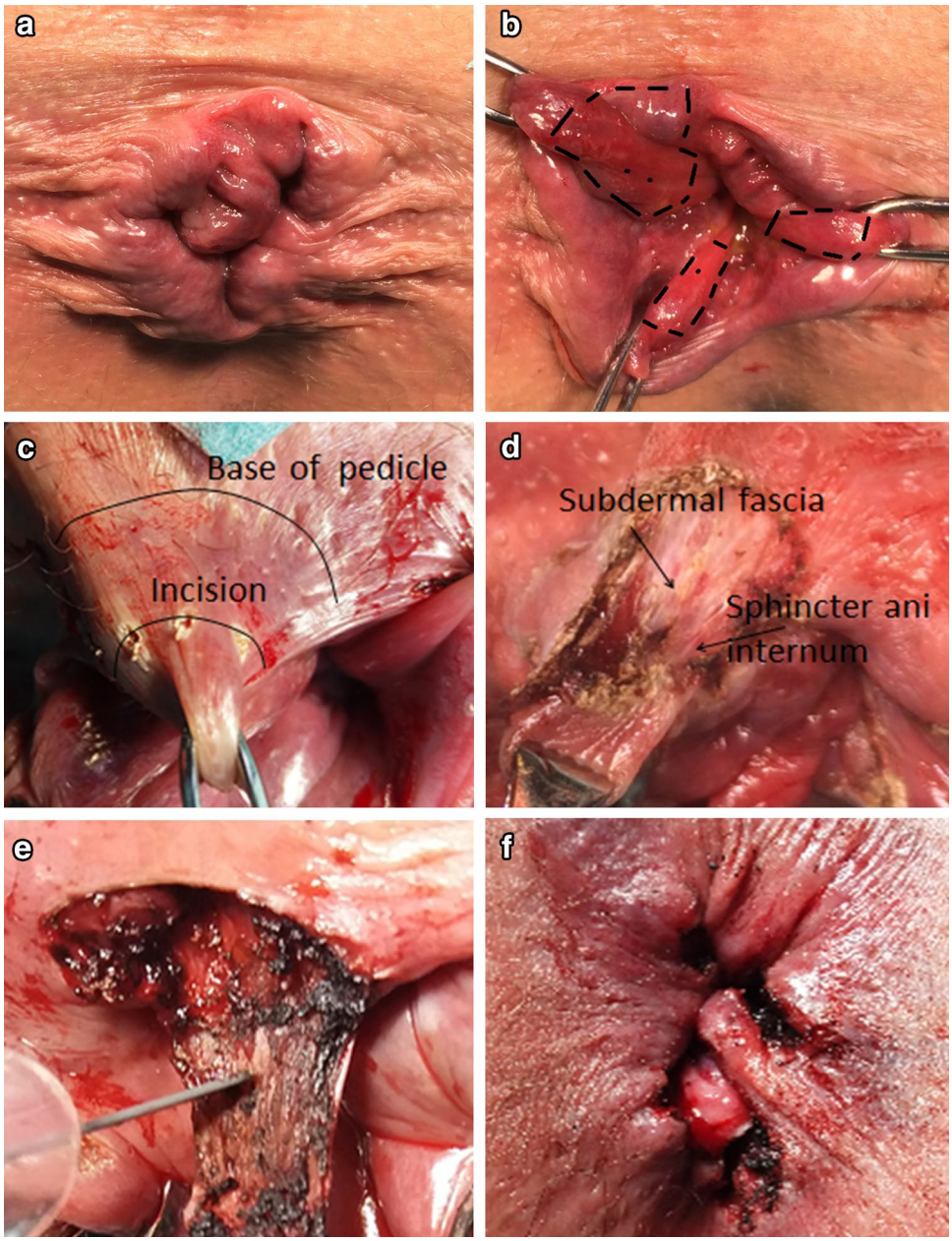

Fig. 1 **a** Three hemorrhoids Goligher grade IV. **b** Planning the excision. The hemorrhoids are exposed after gentle traction with a clamp. The incision of hemorrhoidal mucosa is marked, in real with diathermy. Excision ends at the anal orifice. **c** Hemorrhoidal pedicle is incised one-third of the distance from top to base. Skin excision is thus minimized. **d** The subdermal fascia which continues in a membrane covering the internal sphincter is identified. Dissection is performed in front of this fascia/membrane. The internal sphincter is left unharmed. Dissection ends at the anal orifice. **e** The hemorrhoid held with gentle traction and divided at the orifice of the anus. This leaves a residual part of the hemorrhoid, that when traction is released, will have its lower end 1–2 cm orally from the anal orifice. **f** Anus after the hemorrhoidal excisions

The anal mucosa is incised at the transition from anal mucosa to hemorrhoidal mucosa and only anal mucosa overlying the hemorrhoid is excised. Only the caudal part of the hemorrhoid is excised. With the hemorrhoid held with gentle traction it is divided at the anal orifice. There will thus be a residual part of the hemorrhoid intra-anally with its caudal end 1–2 cm proximal to the anal orifice.

The number of excisions is individualized. The procedure is repeated for each hemorrhoid leaving adequate skin and mucosal bridges.

The postoperative regimen was similar for all three treatment groups. Treatment for pain was Paracetamol 1 g four times daily, Ibuprofen 400 mg three times daily and a local anesthetic gel (lidocaine) for the first 7 days, with reduction as needed. Patients also were given eight tablets of morphine 10 mg or Tramadol 50 mg, to use as needed. They were prescribed a laxative, magnesium oxide 1 g two times daily for the first 7 days.

Demographic data were described with descriptive statistics. Fisher's exact analyzed frequencies. Kruskal–Wallis test by ranks was used for ordinal and continuous data. Significance level was 0.05 (two-sided). IBM SPSS 24 (IBM Corp, Armonk, NY, USA) was used for statistical analyses.

Results

Seventeen patients had MOH, 12 THD and 13 LH. There were no differences between the groups as regards age, sex ratio, preoperative anatomical pathology or symptoms ($p > 0.05$) (Table 1). One patient who had MOH 7 years earlier had sclerotherapy for hemorrhoids and then TDH later that year. None of the other patients had previously had an operation for hemorrhoids, treatment with rubber band ligation or sclerotherapy.

THD had a longer operation time compared to MOH and LH. Estimated bleeding was less than 50 ml for all operations.

No difference was found between the groups in summed pain scores, or for average or for peak pain. There was no difference in use of postoperative pain medication or

Table 1 Baseline characteristics, perioperative data, postoperative pain and recovery, data at 3 months follow-up for patients operated on for hemorrhoids with MOH, THD or LH

	MOH *n* = 17	THD *n* = 12	LH *n* = 13	*p*
Sex				
Female/male	11 (65)/6 (35)	9 (75)/3 (25)	4 (31)/9 (69)	0.07
Age (years)	64 (35–81)	56.5 (30–77)	64 (36–79)	0.53
Preoperative				
Goligher's classification anatomy				
Grade II	2 (12)	0 (0)	1 (8)	0.35
Grade III	4 (23)	4 (33)	7 (54)	
Grade IV	11 (65)	8 (67)	5 (38)	
Surgeon's Global Assessment of Pathology (1–7)	4.0 (3–6)	3.5 (3–5)	4.0 (3–6)	0.09
Hemorrhoidal Disease Symptom Score (0–20)	11.0 (5–20)	11.0 (5–16)	13.0 (5–20)	0.46
Wexner fecal incontinence score (0–20)	4.0 (0–12)	6.0 (0–15)	3.0 (0–13)	0.41
Perioperative				
Operative time (min)	30.0 (10–67)	51.5 (32–84)	27.0 (10–41)	**0.001**
Postoperative pain				
Postoperative average pain, summed pain scores day 1–14	35.0 (7–90)	28.5 (6–59)	39.0 (0–83)	0.34
Postoperative peak pain, summed pain scores day 1–14	57.0 (8–104)	38.0 (9–73)	66.0 (0–106)	0.24
Analgesic consumption				
Paracetamol day 1–14 (tablets à 500 mg)	64.5 (0–112)	44.0 (0–126)	75 (30–104)	0.21
Ibuprofen day 1–14 (tablets à 400 mg)	25.5 (13–43)	22 (1–36)	20 (0–47)	0.24
Morphine day 1–14 (tablets à 10 mg)	0.0 (0–6.5)	1.0 (0–12)	0 (0–10)	0.55
Recovery				
Wellbeing day 7				
Normal or slightly decreased/feeling ill	14 (82)/3 (18)	11 (92)/1 (8)	9 (69)/3 (23)	0.53
Wellbeing day 14				
Normal or slightly decreased/feeling ill	15 (88)/0 (0)	11 (92)/0 (0)	11 (85)/1 (8)	0.61
Postoperative follow-up 3 months				
Goligher's classification anatomy				
Grade I	13 (76)	7 (58)	10 (77)	0.34
Grade II	3 (18)	3 (25)	2 (15)	
Grade III	0 (0)	0 (0)	0 (0)	
Grade IV	0 (0)	2 (17)	0 (0)	
Surgeon's Global Assessment of Pathology (1–7)	1.5 (1–3)	2.0 (1–3)	1.5 (1–3)	0.08
Hemorrhoidal Disease Symptom Score (0–20)	2.0 (0–17)	4.0 (0–15)	3.0 (0–13)	0.73
Wexner Fecal Incontinence Score (0–20)	3.0 (0–12)	3.5 (1–13)	3.0 (0–16)	0.71
Patient satisfaction (1–7)	6.0 (1–7)	6.0 (1–7)	6.0 (2–7)	0.32

Values are given as median (range) or nominal (%)

MOH minimal open hemorrhoidectomy, *THD* transanal hemorrhoidal dearterialization, *LH* LigaSure hemorrhoidectomy

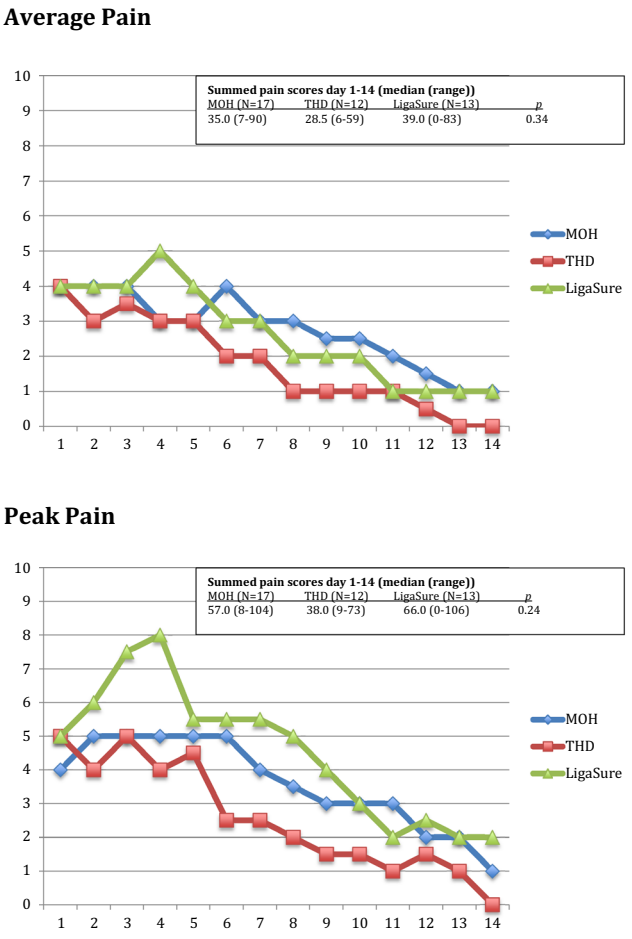

Fig. 2 Average pain and peak pain postoperatively, registered on days 1–14, in patients operated on with minimal open hemorrhoidectomy (MOH) $n=17$, transanal hemorrhoidal dearterialization (THD) $n=12$ and LigaSure hemorrhoidectomy (LH) $n=13$, values are median. Inserted are the sum of pain scores over the 14 days, values are median, range

recovery between the three groups of operated patients (Fig. 2; Table 1).

MOH patients had four perioperative adverse events (Clavien–Dindo grade 1): two were observed for postoperative bleeding with spontaneous resolution without need for intervention or transfusion; one patient had an anal fissure, conservatively treated. One patient had occasional incontinence to loose stools when using laxatives postoperatively. Among THD patients there was one case of postoperative bleeding with spontaneous resolution and no need for transfusion (Clavien–Dindo grade 1). LH patients had four adverse events (3 Clavien–Dindo grade 3B and 1 grade 1): two cases of postoperative bleeding that needed transfusions and reoperation, two patients with anal fissure, conservatively treated of whom one also had a submucosal fistula that was managed surgically.

Hemorrhoidal symptoms as evaluated by HDSS improved in all three groups with no differences. Patient satisfaction was similar. There were two grade 4 prolapses after THD. A tendency for worse "Surgeons global assessment of pathology" were noted after THD operations (Table 1).

The Wexner anal continence score improved similarly in all three groups without any difference between the groups. This improvement was mainly due to decreased soiling (Table 1).

Discussion

This study is an initial evaluation of a modified technique for open hemorrhoidectomy, MOH. The rationale for our modification was a combination of experience of hemorrhoidectomy as the operation with best long-term results, and a series of previous modifications proven to reduce postoperative pain. In addition, we postulated that the hemorrhoidal and concomitant skin excision could be smaller without inferior results. This would leave smaller wounds and a part of the hemorrhoid intra-anally, potentially lessen pain postoperatively and impact on anal continence.

When MOH was compared to THD and LH no differences in postoperative pain, need of pain medication or recovery were found. The results suggest that open hemorrhoidectomy may be performed with a postoperative pain pattern and recovery similar to non-ablative techniques like THD and a closed technique like LH. This may be due to factors such as dissection in an anatomical cleavage leaving the internal sphincter unharmed, the use of diathermy for dissection and hemostasis and a minimal extent of hemorrhoidal excision.

To our knowledge, our non-radical hemorrhoidectomy is a new concept, not previously described. Whether this poses an increased risk for recurrence can be clarified only after long-term follow-up. After a short-term follow-up, we did not note any disadvantages to using this technique. The Wexner anal continence score improved in all three patient groups. This has been observed previously after hemorrhoidal operations and is usually attributed to decreased soiling. Whether our approach to hemorrhoidal resection has a positive influence on anal continence needs further evaluation.

Conclusions

Minimal open hemorrhoidectomy is a promising option and should be evaluated in larger controlled studies with long-term follow-up.

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Compliance with ethical standards

Conflict of interest Gunnar Olaison received in 2013 grants from SacoMed (the Danish distributor of THD) to attend a course on the operative technique in Transanal Haemorrhoidal Dearterialization (THD). The other authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study, formal consent is not required.

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Title pages:

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Minimal Open Hemorrhoidectomy versus Transanal Hemorrhoidal Dearterialization: the effect on symptoms. An open-label randomized controlled trial.

2. Running title: MOH vs. THD: an open-label RCT.

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An abstract and poster presentation of the study was presented at:

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Haavard Dragesund Roervik: a, b and c.

André Heiner Campos: a, b and c.

Karl Styr: a, b and c.

Lars Ilum: a, b and c.

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11. Category:

d. Anorectal disease

Abstract:

BACKGROUND: There is limited evidence on the long-term efficacy of Transanal Hemorrhoidal Dearterialization compared with hemorrhoidectomy. Most studies investigated short-term effects with postoperative pain as the primary outcome. Being a benign disease the long-term goal of treatment for hemorrhoids is the resolution of symptoms and improvement of quality of life.

OBJECTIVE: To compare the effect of Minimal Open Hemorrhoidectomy versus Transanal Hemorrhoidal Dearterialization on patient-reported symptoms.

DESIGN: Open-label randomized controlled trial.

SETTINGS: Single-center study.

PATIENTS: Patients with symptomatic hemorrhoids grade II-IV (Goligher's classification).

INTERVENTIONS: Patients were randomly allocated to Minimal Open Hemorrhoidectomy or Transanal Hemorrhoidal Dearterialization.

MAIN OUTCOME MEASURES: Primary outcome was symptoms assessed by the Hemorrhoidal Disease Symptom Score one year postoperatively. Secondary outcomes included health-related quality of life, patient satisfaction, postoperative pain and recovery, adverse events, recurrence and hospital costs.

RESULTS: Forty-eight patients received Minimal Open Hemorrhoidectomy and fifty patients received Transanal Hemorrhoidal Dearterialization. No difference in symptom score at one-year follow-up was found. Median (range) symptom score was 3 (0-17) after Minimal Open Hemorrhoidectomy and 5 (0-17) after Transanal Hemorrhoidal Dearterialization (median difference [CI95%]: -1.0 [-3.0-0.0], p=0.15). Residual hemorrhoidal prolapse was reported more frequently (p=0.008) and more patients had treatment for recurrence after Transanal Hemorrhoidal Dearterialization (7 vs. 0 patients, p=0.013). Patient satisfaction was higher after Minimal Open Hemorrhoidectomy (p=0.049). No differences were found in the impact on health-related quality of life, average and peak postoperative pain, recovery, or adverse events (p>0.05). Transanal Hemorrhoidal Dearterialization was more expensive (Median difference [CI95%]: € 555 [472-693], p<0.001).

LIMITATIONS: No blinding.

CONCLUSION: No difference was found in symptom score one year postoperatively. Minimal Open Hemorrhoidectomy had better effect on the hemorrhoidal prolapse and higher patient satisfaction. More patients needed treatment for recurrence after Transanal Hemorrhoidal Dearterialization. Minimal Open Hemorrhoidectomy has an immediate postoperative course similar to Transanal Hemorrhoidal Dearterialization.

Key words: 'hemorrhoids', 'hemorrhoidectomy', 'Minimal Open Hemorrhoidectomy', 'Transanal Hemorrhoidal Dearterialization', 'Hemorrhoidal Disease Symptom Score', 'Randomized Controlled Trial'.

Trial registration: clinicaltrials.gov (NCT02061176).

Introduction:

Hemorrhoidectomy is the operation for hemorrhoidal disease (HD) that has demonstrated the lowest recurrence rates.[1] The operation has, however, been associated with postoperative pain and some studies point to the risk of impaired anal continence.[2,3] New non-ablative methods have been introduced that are aimed at reducing postoperative pain and the risk of complications.[4,5] Transanal hemorrhoidal dearterialization (THD) was described in the mid-nineties.[4] This operation involves no excision: the hemorrhoidal arteries are ligated and the haemorrhoidal prolapse is treated by a suture mucopexi. THD has gained increased popularity. It is regarded as a safe, efficient and less painful operation for HD according to initial studies.[6] However, the evidence on long-term efficacy of THD compared with hemorrhoidectomy is limited.[7] Only a few randomized controlled trials (RCTs) have been published. The majority have been designed to study short-term outcomes with postoperative pain as the primary outcome.[8–13] Although postoperative pain might influence a patient's preference for a specific operation, the risk of symptom recurrence or complications seems to be of greater importance.[14]

The original operation for open hemorrhoidectomy as described by Milligan and Morgan is no longer used. Several modifications have been proposed in order to reduce postoperative pain and the operation is not currently standardized. Some studies have reported reduced postoperative pain when using diathermy for dissection and coagulation of blood vessels instead of ligature and trans-fixation of the hemorrhoid pedicle.[15,16] Other authors have emphasized the importance of

dissection in the anatomical plane to reduce the risk of injury to the internal anal sphincter.[17,18] We adapted these principles and additionally minimized the excision to reduce postoperative pain and the risk of influencing anal continence. We called this modification Minimal Open Hemorrhoidectomy (MOH)[19].

The aim of this trial was to compare the long-term effect of MOH versus THD on patient-reported symptoms at one and five years postoperatively. The results after one-year follow-up are reported here.

Materials and Methods

Study design and participants

This study was a single-center, open-labeled, parallel group RCT carried out at the Department of Surgery at Holbaek Hospital, Denmark. The study protocol is available at clinicaltrials.gov (NCT02061176).

Patients referred to the proctologic outpatient clinic for anal symptoms were assessed for eligibility. The attending surgeon identified potential participants and graded hemorrhoids using Goligher's classification.[20,21] Eligible were adult patients (age 18-85 years) with a Hemorrhoidal Disease Symptom Score > 4 and grade III-IV hemorrhoids or grade II hemorrhoids if bleeding was present despite previous rubber band ligation or sclerotherapy. All patients had an endoscopic examination before inclusion. We excluded patients with acute strangulated hemorrhoids, previous operation for hemorrhoids within two years before inclusion, active anal fissure or fistula, anal stenosis, anal incontinence to solid stool, previous operation for anal incontinence, previous pelvic radiation, colorectal malignancy, inflammatory bowel disease, cognitive or language inabilities, or ASA score > II. Patients were included after giving oral and written consent. The study was approved by the Regional Committee on Health Research Ethics (SJ-348) and The Danish Data Protection Agency (REG-71-2013).

Randomization and blinding

Participants were randomly allocated (in a 1:1 ratio) to either MOH or THD. The randomization sequence was computer-generated and stratified by gender using blocks of ten. The randomization list was kept in a locker accessible to the study secretary, but not to any of the investigators. The allocations were kept in sealed, opaque, consecutively numbered envelopes. The day before the operation, the study secretary opened the envelope and wrote the allocated procedure in the electronic patient record. The study was open-labeled without blinding of participants, surgeons, hospital, or research staff.

Operations:

Five surgeons (GO, KS, HDR, GKM and LI) examined the patients pre- and postoperatively and performed both operations. All surgeons had performed at least ten supervised MOH and THD operations before operating independently. The operations were planned as outpatient surgeries except for patients living alone or who for other reasons could not be discharged without any home surveillance. A preoperative enema was used to evacuate the rectum. No antibiotic prophylaxis was given, and anesthesia was either general or spinal supplemented by a perianal block of 40 mL ropivacaine 5 milligrams per milliliter.[22] The patients were placed in the lithotomy position. MOH was performed without using a retractor.[19] Diathermy was used for both dissection and hemostasis. The external components were grasped by forceps and the skin was incised midway to one third of the distance from the top of the pedicle, thereby minimizing skin excision. The subdermal fascia, which continues in a membrane covering the internal anal sphincter, was identified. The hemorrhoid

was dissected off the internal sphincter in this plane leaving the internal sphincter unharmed. The anal mucosa was incised at the transition of the hemorrhoid. Only part of the hemorrhoid and overlying mucosa was excised. The hemorrhoid was divided leaving a residual part intra-anally. Only prolapsing hemorrhoids (grade II-IV) were excised. The THD-procedure has previously been described.[8] We used the THD proctoscope (G.F Medical Division, Correggio, Italy) for Doppler-guided localization of the hemorrhoidal arteries at the 1,3,5,7,9 and 11 o'clock position (anterior midline representing 12 o'clock). The hemorrhoidal arteries were suture ligated using absorbable suture. The suture was not cut but used to perform a mucopexy reducing prolapsing hemorrhoids. The mucopexy was performed as a running suture ending at least five millimeters above the dentate line. Mucopexy was performed in all patients. Median number of mucopexies was 6 (range 3-8). Additional excision of skin tags was optional in both procedures. The postoperative regimen was equal in the two groups. Patients were discharged when pain relief was adequate and they were able to eat, drink and pass urine. Pain treatment was paracetamol 1 gram 4 times daily, ibuprofen 400 mg 3 times daily, and a local anesthetic gel (xylocaine) for the first 7 days, with reduction as needed. Eight tablets of morphine 10 mg or tramadol 50 mg were given to be used if needed. A laxative (magnesium oxide 1 gram 2 times daily) was prescribed for the first 7 days. Patients were encouraged to return to work and daily activities as soon as possible.

Procedure:

Participants were assessed in the outpatient clinic at inclusion and at planned 3- and 12- month postoperative follow-up. The attending surgeon assessed pre-

and postoperative anal anatomy. Patient questionnaires were distributed on printed-paper. In cases of non-compliance, the patient was contacted by telephone and mail first by the study secretary and secondly by one of the surgeons. If a patient refused to come to the outpatient clinic for follow-up, the patient was asked to complete the questionnaires and mail them to the study secretary.

Primary outcome:

The primary outcome was symptoms one year after surgery assessed by the Hemorrhoidal Disease Symptom Score (HDSS)(Appendix 1).[23] The HDSS consists of five items measuring patient-reported frequency of pain, itching, bleeding, soiling, and prolapse. Results from a recent study suggest that HDSS is a valid, reliable and responsive measure of symptoms in patients with HD.[23]

Secondary outcomes:

Secondary outcomes were health-related quality of life (HRQoL), patient satisfaction with the operation, perioperative blood loss, operative time, time spent in the operating room, length of hospital stay, postoperative pain and recovery, postoperative anatomical assessment, anal continence, adverse events, re-interventions for recurrence, and health-costs.

The surgeon and the hospital staff recorded perioperative data. The patients registered in a diary information on average pain, peak pain, pain when passing stool, use of analgesics and recovery the first 14 days postoperatively. Pain was scored using a numeric rating scale (0= "no pain" to 10= "worst pain imaginable"). Pain scores were summarized to assess the overall experience of

pain. Recovery was assessed with a single question, whether wellbeing was normal, slightly decreased, or decreased (feeling ill).

Recurrent hemorrhoids were graded using Goligher's classification. Grade I haemorrhoids was considered a normal finding. The surgeon also reported his/her global assessment of pathology (1= "no pathology" to 7= "severe pathology"). Anal continence was assessed by the Wexner fecal incontinence score (Wexner score) and the Revised Fecal Incontinence Scale (RFIS).[24,25]

All adverse events and re-operations were registered. In addition, the hospital patient records were screened 12 months postoperatively to identify missing data. Adverse events were graded using the Clavien-Dindo classification[26]. At follow-up, patients graded their satisfaction with the operation (1= "very unsatisfied" to 7= "very satisfied"), and HRQoL was assessed by the Short Health Scale adapted to hemorrhoidal disease (SHS_{HD})(Appendix 1),[23] EuroQoL 5-dimensions 5-levels (EQ-5D-5L),[27] and Short-Form 36 version 2 (SF36v2).[28]

Quality-adjusted life years (QALY) was calculated from EQ-5D-5L scores, using the Danish Time Trade-Off (TTO) value set.[29] Cost-utility analysis was planned from the healthcare giver perspective (i.e. hospital costs per QALY gained). Procedural costs were calculated based on the costs of equipment (cost per unit) and staff (average costs per time unit). Costs of adverse events and re-interventions were estimated based on the Danish DRG (disease-related group) rates obtained from the Danish National Patient Registry.[30]

Statistical analyses

We calculated that a sample of 80 patients, 40 in each group, was needed to detect a difference of 1.5 points on the HDSS score with a 0.05 significance level

and power of 0.80. Based on this, we initially planned to include 90 patients, but the number of patients lost to follow-up was higher than expected. We therefore increased the sample size to 102 patients.

Descriptive statistics described demographic data. Data were assessed for normality and if present, Chi-square test analyzed frequencies and *t*-test continuous data. In cases of non-normality, Fisher's exact test analyzed frequencies and the Mann-Whitney U test continuous data. Ordinal data were analyzed using Goodman and Kruskal's gamma. Significance level was 0.05 (two-sided). Median differences and confidence intervals for non-parametric analyses were reported using the Hodges-Lehmann estimate (Mdiff). The primary outcome, adverse events and health-cost analysis were analyzed according to a *modified* intention to treat (*m*ITT) principle: patients that underwent surgery for hemorrhoids were analyzed. Missing HDSS values from patients lost to follow-up were replaced by the group's median and sensitivity analysis was performed with best and worst outcomes for both groups. Other outcomes were analyzed per-protocol excluding missing data.

IBM SPSS 24 (IBM Corp, Armonk, New York, USA) was used for statistical analyses. SF36v2 scores were obtained using the QualityMetric™ scoring software (5.1).

Results:

Participants

Between November 24, 2013 and October 3, 2016 102 patients were randomly assigned to receive MOH or THD (51 vs. 51) (Figure 1). Follow-up was completed on November 22, 2017. Of 48 (MOH) and 50 (THD) patients who received the allocated treatment, primary outcome data was obtained in 45 (MOH) and 46 (THD) patients at one-year follow-up (complete cases). In one patient operated with THD, the surgeon could not reduce the hemorrhoidal prolapse with mucopexies and added hemorrhoidal excision. Another patient in the THD-group received hemorrhoidectomy for recurrence during the follow-up period. These patients were included in the *m*ITT analyses, but the first patient was excluded in the analysis of postoperative pain and recovery and both patients were excluded in the per-protocol analysis of patient-reported outcomes and anatomical assessment at 12 months follow-up. One patient in the THD-group had a missing item (itching) in the baseline HDSS, which was replaced by zero. Baseline data were similar in the two groups (Table 1).

Primary outcome

We found no difference in symptom score one year postoperatively. In complete cases HDSS (median (range)) after MOH was 3 (0-17) and after THD 5 (0-17)(Mdiff [CI95%]=-1.0 [-3.0 to 0.0], p=0.15). The *m*ITT and sensitivity analyses showed a significant difference in HDSS only in case of the worst outcomes of THD versus the best and median outcomes of MOH (Appendix 2).

Per-protocol analyses: Patient-reported outcomes and anatomical assessment

Table 2 presents the results of the per-protocol analyses. Higher patient satisfaction and a non-significant trend towards greater improvement of symptoms after MOH were seen. More patients reported symptoms of prolapse after THD, while no difference was found for pain, bleeding, itching or soiling. Postoperative anatomical assessment by the surgeon showed that more patients in the THD-group had residual hemorrhoidal prolapse at one-year follow-up. Postoperative incontinence scores were without differences between the two groups.

We found no difference in the impact on HRQoL. The SHS_{HD} had improved after both operations, but without any difference in improvement between the groups. Similarly, no differences in the improvement of SF36v2 scores were seen (Figure 2).

Postoperative pain and recovery

Figure 3 presents the postoperative pain scores. Summed average and peak pain scores for postoperative days 1-14 were similar after MOH and THD. The MOH-group reported pain a few days longer than the THD-group. Summed scores for pain when passing stool were higher in the MOH-group. Use of analgesics and recovery were similar in the two groups (Table 3). When we excluded patients in the THD-group who had concomitant skin excision from the analysis, results remained the same.

Adverse events and re-intervention for recurrence

Table 4 presents adverse events and re-interventions. No difference in the number of patients with adverse events was seen. Anal stenosis was reported in 3 patients after MOH. In one patient the stenosis subsided after dilatation under general anesthesia. In another patient the stenosis subsided after self-dilatations. The third patient was still using self-dilatations at one-year follow-up. Anal incontinence was reported in 2 patients after MOH. One patient responded to conservative treatment. The second patient had preoperative compromised anal continence and reported deterioration. This patient did not respond satisfactorily to conservative treatment and was referred to a specialist clinic. Seven patients had a re-intervention for recurrence in the THD-group (7 vs. 0 patients, p=0.013)(Table 5). Of the 7 patients with a re-intervention for recurrence 3 patients had preoperative grade III hemorrhoids and 4 patients had preoperative grade IV hemorrhoids.

Health-cost analysis

Figure 4 presents the health-cost analysis. THD had higher hospital costs than MOH, without a difference in QALYs during the first 12 months postoperatively. The difference in costs was mainly due to the costs of the THD-instruments and longer operative time in the THD-group. We performed a sensitivity analysis reducing operative time in the THD-group to 30 minutes and excluding patients not planned for outpatient surgery. Nevertheless, the difference in hospital costs was significant (Mdiff [CI95%] = € -429 [-525 to -368], p<0.001).

Discussion

This RCT compared the effect of Minimal Open Hemorrhoidectomy (MOH) and Transanal Hemorrhoidal Dearterialization (THD) on symptoms in patients with grade II-IV hemorrhoids. We found no difference in symptom score one year postoperatively, although higher patient satisfaction and a tendency towards greater improvement of symptoms after MOH were noted. More patients reported symptoms of prolapse and needed a re-intervention for recurrence after THD. HRQoL improved postoperatively, but without any differences between the two operations. THD had higher hospital costs. Postoperative pain pattern and recovery was in the same range for the two groups.

To our knowledge this study is the first RCT designed to compare THD with hemorrhoidectomy in terms of effect on symptoms. Comparing our results with those of other studies is challenging because different outcome measures for symptoms have been used. Most studies have reported equal control of symptoms after hemorrhoidectomy and THD.[9,11,12,31] This study is the first to report a difference in the effect on hemorrhoidal prolapse. A likely explanation is that our study included a relatively high proportion of patients with grade IV hemorrhoids. Only two of the previous RCTs included patients with grade IV hemorrhoids.[10,11] Our results are in line previous findings that a high grade of prolapse preoperatively will negatively effect outcome and patient satisfaction after THD, and that restored anal anatomy postoperatively predicts symptom control.[32–35]

Postoperative pain is reported to be higher after open hemorrhoidectomy compared with THD.[7] Interestingly, we found no difference in average and peak pain during the first 14 days postoperatively. The median pain scores for these variables were low, not exceeding 3 for average pain and 5 for peak pain in both groups. This is in line with our preliminary observations of similar postoperative pain pattern after MOH, THD and LigaSure Haemorrhoidectomy.[19] Dissection in a defined anatomical plane without harming the internal sphincter and minimized resection of hemorrhoid and skin make open hemorrhoidectomy less painful. The old notion of open hemorrhoidectomy as a very painful operation might need to be revised. Pain at defecation was still higher after MOH. The clinical importance of this difference could be questioned as no difference in recovery or the use of analgesics was seen.

The optimal operation for hemorrhoids should resolve symptoms with a minimal risk of recurrence and complications. We found that treatment for recurrence was more frequent after THD and that patient satisfaction was higher after hemorrhoidectomy. In MOH we left a part of the hemorrhoid intra-anally. This may increase the risk of recurrence, but this was not seen within a one-year follow-up. THD is a less invasive procedure and serious complications are rare.[1,34] In this study most complications after MOH and THD were mild and transient. However, the impact on anal continence after hemorrhoidectomy may still be a concern. Non-ablative techniques could be a better choice for patients with preoperative compromised anal continence.[3]

The present study has strengths and limitations. The strengths are that symptoms were assessed using a validated symptom score and the operations were performed by a small group of trained surgeons that performed both operations. A learning curve for the hemorrhoidal operations has not been determined, but poorer results in initial cases have been reported.[36] Our criteria for surgeon participation were comparable to those of other studies.[9,37] The postoperative treatment was standardized and the assessment of postoperative pain was thorough. This study is the first trial to compare the costs of THD and hemorrhoidectomy. However, the single-center design reduces generalizability. The cost-utility analysis did not include costs of sick leave or consultations with the general practitioner, but our results did not indicate a difference in postoperative recovery. This study was open-labeled. We did not consider blinding of patients or surgeons a realistic option when comparing an ablative with a non-ablative method. However, a neutral observer could have limited potential bias in the postoperative assessment of pathology and anatomical recurrence. Goligher's classification was used to grade haemorrhoids. The classification is the most widely used and facilitates comparison with other studies. However, the inter-rater reliability is unknown and the risk of misclassifications has been highlighted.[35,38] A follow-up period of 12 months might be too short and follow-up after 5 years is planned.

Conclusion:

This RCT compared the effect on symptoms of MOH and THD in patients with grade II-IV hemorrhoids. We found no difference in symptom score one year after surgery. MOH had a better effect on the hemorrhoidal prolapse and higher patient satisfaction. More patients needed treatment for recurrence after THD. MOH has an immediate postoperative course similar to that of THD.

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Legends:

Figure 1: CONSORT flow diagram for inclusion of patients.

Figure 2: Health-related quality of life. Changes in Short Form 36 version 2 scores from baseline to one-year follow-up. A positive change indicates improvement. No differences were found between the groups. MOH = Minimal Open Hemorrhoidectomy; THD = Transanal Hemorrhoidal Dearterialization.

Figure 3: Postoperative pain the first 14 days. The patients reported pain on a numeric rating scale (NRS 0-10). MOH = Minimal Open Hemorrhoidectomy; THD = Transanal Hemorrhoidal Dearterialization; Mdiff = Hodges-Lehmann estimate of median difference; IQR = Interquartile range.

Figure 4: Cost-utility analysis. Utility index, Quality adjusted life years (QALYs) and hospital costs during the first year postoperatively. Missing data for utility indexes were replaced by linear interpolation. In one patient (MOH-group) missing data for operative time and time the operative theatre were replaced by the group's mean. MOH = Minimal Open Hemorrhoidectomy; THD = Transanal Hemorrhoidal Dearterialization; TTO = Time Trade-Off; $\bar{x}$ diff = mean difference; Mdiff = Hodges-Lehmann estimate of median difference; IQR = Interquartile range.

TABLE 1. Baseline characteristics

Variable		MOH N = 48	THD N = 50
Sex, N (%)	Female	27 (56)	30 (60)
Age in years, mean (SD)		53.5 (15.1)	54.0 (14.1)
ASA score, N (%)	ASA I/ASAII	25 (52) / 23 (48)	22 (44) / 28 (56)
BMI (kg/m²), mean (SD)		26.8 (4.3)	27.1 (4.7)
Goligher's classification, N (%)	Grade II	2 (4)	1 (2)
	Grade III	23 (48)	18 (36)
	Grade IV	23 (48)	31 (62)
Surgeon's global assessment of pathology (1-7), median (range)		4.0 (2-7)	5.0 (3-6)
	Missing, N (%)	1 (2)	2 (4)
Hemorrhoidal Disease Symptom Score (0-20), median (range) (IQR)		13.0 (3-18) (4.0)	12.0 (3-19) (6.0)
Wexner fecal incontinence score (0-20), median (range) (IQR)		4.0 (0-15) (5.3)	4.0 (0-14) (5.0)
	Missing, N (%)	2 (4)	4 (8)
Revised Fecal Incontinence Score (0-20), median (range) (IQR)		1.0 (0-13) (4.0)	1.0 (0-18) (3.0)
	Missing, N (%)	2 (4)	5 (10)
Short Health Scale$_{HD}$ (4-28), median (range) (IQR)		14.0 (6-24) (6.0)	17.0 (6-23) (7.0)
	Missing, N (%)	3 (6)	3 (6)
SF36v2, median (range) (IQR)	**MCS**	54.3 (22.0-63.4) (11.7)	56.3 (14.6-66.1) (12.7)
	Missing N (%)	0 (0)	4 (8)
	PCS	53.3 (28.2-66.5) (10.9)	51.1 (28.3-60.5) (10.9)
	Missing N (%)	0 (0)	4 (8)
Previous RBL or sclerotherapy N (%)	Yes	15 (31)	13 (26)
	No	29 (60)	31 (62)
	Unknown	4 (8)	6 (12)
Previous operation for hemorrhoids, N (%)	Yes	4 (8)	12 (24)
	No	40 (83)	35 (70)
	Unknown	4 (8)	3 (6)

MOH = Minimal Open Hemorrhoidectomy; THD = Transanal Hemorrhoidal Dearterialization; IQR = Interquartile range; RBL = Rubber band ligation; SF36v2 = Short Form 36 version 2; MCS = Mental Component Summary; PCS = Physical Component Summary. SF36v2 scores are standardized based on the United States (US) general population norm (A score of 50 represents the US 2009 population mean). Higher scores indicate better quality of life.

TABLE 2: Per protocol analysis of outcomes at one-year follow-up

Outcome		**MOH N = 45**	**THD N = 44**	**Effect size**	***P***
SYMPTOMS					
Hemorrhoidal Disease Symptom Score, median (range) (IQR)		3.0 (0-17) (5.0)	5.0 (0-17) (9.0)	Mdiff [CI95%] = -1.0 [-3.0 to 0.0]	0.18
Improvement in Hemorrhoidal Disease Symptom Score, mean (SD)		8.40 (4.65)	6.36 (5.34)	$\bar{x}$ diff [CI95%] = 2.04 [-0.07 to 4.14]	0.058
Patients reporting symptoms of					
Pain, N(%)	Yes	15 (33)	20 (45)	OR [CI95%] = 0.73 [0.43 to 1.24]	0.24
Itching, N(%)	Yes	28 (62)	26 (59)	OR [CI95%] = 1.14 [0.49 to 2.67]	0.76
Bleeding, (N%)	Yes	16 (36)	15 (34)	OR [CI95%] = 1.07 [0.45 to 2.55]	0.89
Soiling, N(%)	Yes	22 (49)	20 (45)	OR [CI95%] = 1.15 [0.50 to 2.64]	0.75
Prolapse, (N%)	Yes	14 (31)	26 (59)	OR [CI95%] = 0.31 [0.13 to 0.75]	**0.008**
ANAL CONTINENCE					
Wexner score, median (range) (IQR)		2.0 (0-12) (4.8)	3.0 (0-13) (4.0)	Mdiff [CI95%] = -1.0 [-2.0 to 0.0]	0.11
	Missing, N(%)	1 (2)	1 (2)		
Revised Fecal Incontinence Score, median (range) (IQR)		0.0 (0-7) (2.5)	0.0 (0-11) (2.0)	Mdiff [CI95%] = 0.0 [0.0 to 0.0]	0.43
	Missing, N(%)	0 (0)	3 (7)		
PATIENT SATISFACTION AND QUALITY OF LIFE					
Patient satisfaction,					
1= very dissatisfied to	1	1 (2)	2 (4)		
7= very satisfied, N%	2	1 (2)	6 (14)		
	3	2 (4)	3 (7)		
	4	3 (7)	2 (4)	γ = -0.32	**0.049**
	5	1 (2)	4 (9)		
	6	13 (29)	10 (23)		
	7	24 (53)	17 (39)		
Short Health Scale$_{HD}$, median (range) (IQR)		6.0 (4-19) (5.0)	7.0 (4-19) (6.0)	Mdiff [CI95%] = -1.0 [-2.0 to 0.0]	0.08
	Missing, N(%)	1 (2)	0 (0)		
POSTOPERATIVE ANATOMICAL ASSESSMENT					
Goligher's classification, N(%)	Grade I / Normal	38 (84)	20 (46)		
	Grade II	3 (7)	8 (18)		
	Grade III	1 (2)	2 (5)	γ = 0.79	**<0.001**
	Grade IV	0 (0)	9 (21)		
	Missing	3 (7)	5 (11)		
Surgeon's overall assessment of pathology (1-7), median (range) (IQR)		2.0 (1-6) (1.0)	2.0 (1-5) (2.0)	γ = 0.62	**<0.001**
	Missing	3 (7)	6 (14)		

OR = odds ratio; Mdiff = Hodges-Lehmann estimate of median difference; $\bar{x}$ diff = mean difference; γ = Goodman and Kruskal's gamma; IQR = Interquartile range; MOH = Minimal Open Hemorrhoidectomy; THD = Transanal Hemorrhoidal Dearterialization.

TABLE 3: Perioperative data and recovery

Variable		**MOH** N = 48	**THD** N = 50	**Mean diff** [CI95%]	**OR** [CI95%]	***p***
Anaesthesia, N (%)	General / Spinal	45 (94) / 3 (6)	45 (90) / 5 (10)			NT
Local Anaesthesia, N (%)		48 (100)	49 (98)			NT
Hemorrhoids excised, N (%)	None	0 (0)	49 (98.0)			NT
	One	4 (8)	0 (0)			
	Two	9 (19)	1 (2)			
	Three	35 (73)	0 (0)			
Mucopexies, median (range) (IQR)		-	6.0 (3-8) (0.0)			NT
Excision of skin tags, N (%)	Yes	18 (37)	7 (14)			NT
Estimated blood loss, N (%)	<50mL / 50-100mL	43 (90) / 3 (6)	46 (92) / 2 (4)		0.62 [0.10 to 3.91]	0.67
	Missing	2 (4)	2 (4)			
Operative time (min), mean (SD)		29.0 (14.2)	57.6 (13.2)	-28.6 [-34.1 to -23.1]		**<0.001**
	Missing, N(%)	1 (2)	0 (0)			
Time in operating room (min), mean (SD)		75.0 (19.6)	106.6 (18.6)	-31.6 [-39.3 to -23.9]		**<0.001**
	Missing, N(%)	1 (2)	0 (0)			
Hospital stay (days), mean (SD)		0.40 (0.24)	0.56 (0.36)	-0.15 [-0.28 to -0.03]		**0.015**
Discharged the same day*, N (%)	Yes	45 (96)	41 (87)		0.30 [0.06 to 1.59]	0.27
ANALGESIC CONSUMPTION**		N = 43	N = 41			
Paracetamol day 1-14 (tablets à 500 mg), mean (SD)		54.0 (27.0)	54.6 (29.0)	-0.6 [-12.7 to 11.5]		0.92
Ibuprofen day 1-14 (tablet à 400 mg), mean (SD)		17.6 (9.2)	18.8 (11.9)	-1.3 [-5.9 to 3.4]		0.60
Opioids day 1-14 (tablets à 10 mg), median (range) (IQR)		1.0 (0-52) (3.5)	1.0 (0-64) (4.8)	0.0*** [-0.5 to 0.0]		0.84
RECOVERY		N = 43	N = 41			
Wellbeing day 7, N (%)	Normal/slightly decreased	35 (81)	27 (66)		2.41 [0.85 to 6.86]	0.10
	Feeling ill	7 (16)	13 (32)			
	Missing	1 (2)	1 (2)			
Wellbeing day 14, N (%)	Normal/slightly decreased	37 (86)	36 (88)		0.26 [0.03 to 2.41]	0.36
	Feeling ill	4 (9)	1 (2)			
	Missing	2 (5)	4 (10)			

*Of patients scheduled for day surgery. **Summed analgesic consumption day 1-14. ***Hodges-Lehmann estimate of median difference [CI95%]

MOH = Minimal Open Hemorrhoidectomy; THD = Transanal Hemorrhoidal Dearterialization; OR = Odds ratio; Mean diff = Mean difference; IQR = Interquartile range; NT = not tested.

TABLE 4: Patients with Adverse Events (AEs) classified according to the Clavien-Dindo Grading System during the first year after surgery.

ADVERSE EVENTS (AEs)		MOH N = 48	THD N = 50	OR [CI95%]	*P*
		N (%)	N (%)		
GRADE I	Reevaluation (outpatient clinic) without intervention (pain, bleeding or other concerns)	5 (10)	2 (4)		
	Local anal complication (fissure, eczema, anal spasm)	6 (12)	3 (6)		
	Fever without identification of source	-	1 (2)		
	PATIENTS WITH AEs GRADE I	11 (23)	6 (12)	0.46 [0.16 to 1.36]	0.15
GRADE II	Prolonged hospital stay or readmission due to pain, nausea or bleeding.	2 (4)	6 (12)		
	Bleeding (readmission and observation)	1 (2)			
	Urinary retention	-	3 (6)		
	Infection (pneumonia, urinary tract)	-	2 (4)		
	Anal incontinence (conservative treatment)[1]	1 (2)	-		
	Anal incontinence (referred to specialist center)	1 (2)	-		
	PATIENTS WITH AEs GRADE II	5 (10)	11 (22)	2.43 [0.77 to 7.60]	0.12
GRADE IIIa	Stomach ulcer (diagnostic endoscopy)	1 (2)	-		
	Anal stenosis (responding to conservative treatment)[2]	2 (4)	-		
GRADE IIIb	Bleeding (reoperation)	1 (2)	1 (2)		
	Perianal abscess	-	2 (4)		
	Anal stenosis (reoperation)	1 (2)	-		
	PATIENTS WITH AEs GRADE III	5 (10)	3 (6)	0.45 [0.11 to 1.90]	0.48

No AEs grade IV (severe organ failure/intensive care required) or V (death) were registered. [1]Conservative treatment with fiber supplements and pelvic floor exercises. [2]Conservative treatment with laxatives and self-dilatations.

MOH = Minimal Open Hemorrhoidectomy; THD = Transanal Hemorrhoidal Dearterialization; OR = Odds ratio.

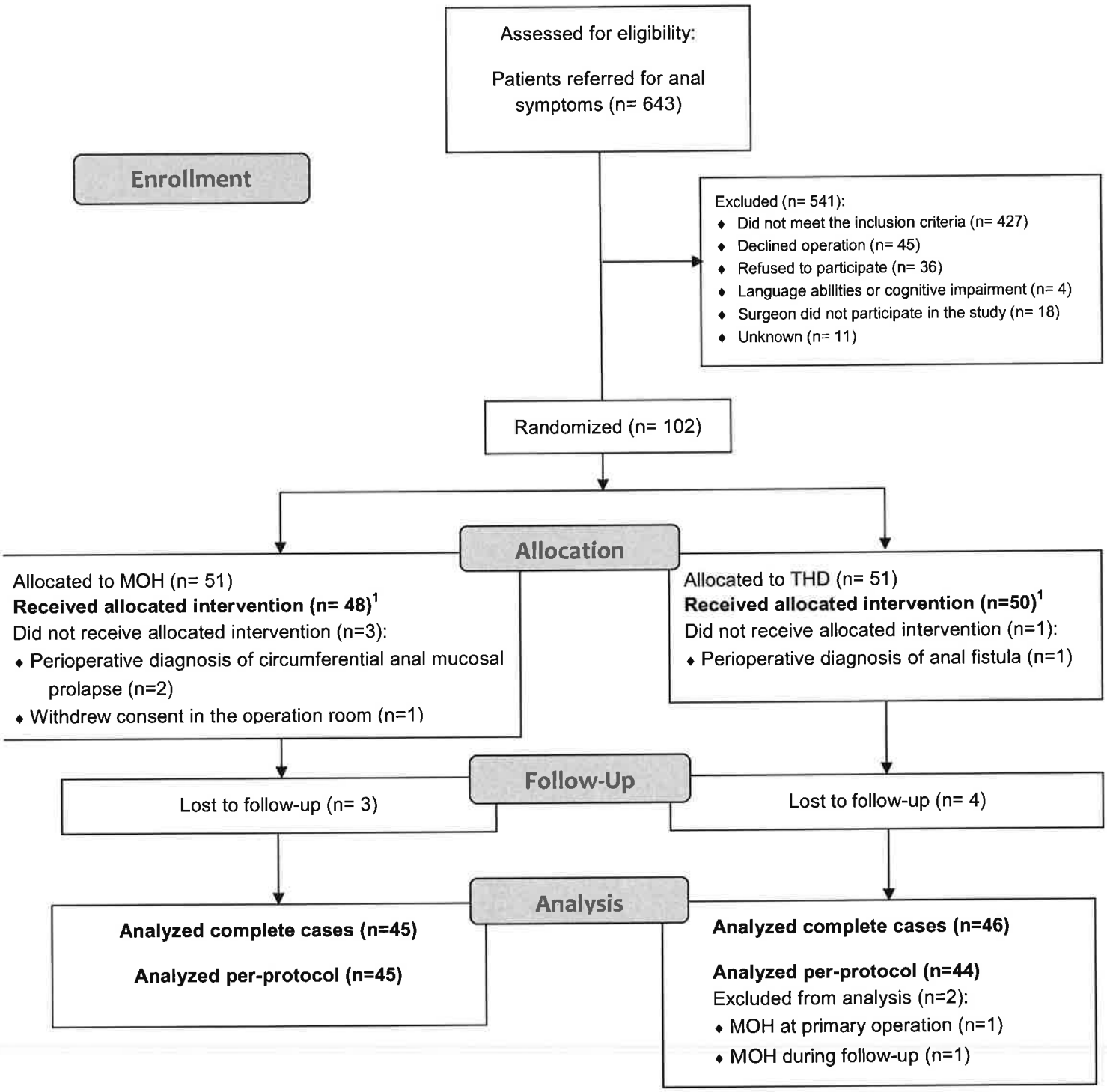
TABLE 5: Patients with re-interventions after the primary operation.

RE-INTERVENTIONS (RIs)	MOH N = 48	THD N = 50	OR [CI95%]	*P*
	N (%)	N (%)		
Excision of skin tags[1]	3 (6)	6 (12)		
Rubber band ligation	-	4 (8)		
Reoperation	-	4 (8)[2]		
PATIENTS WITH RIs FOR RECURRENCE[1]	-	7 (14)[3]	undeterminable	**0.013**

[1]Excision of skin tags was not considered recurrence. [2]One patient operated during follow-up period and three patients scheduled for operation at one-year postoperative follow-up. [3]One patient had new recurrence after rubber band ligation and was scheduled for operation.

MOH = Minimal Open Hemorrhoidectomy; THD = Transanal Hemorrhoidal Dearterialization; OR = Odds ratio.

Figure 1: Flow chart. Patients randomly allocated to minimal open hemorrhoidectomy (MOH) or transanal hemorrhoidal dearterialization (THD).



[1] Patients analyzed in *modified* intention-to-treat analyses (*m*ITT).

Figure 2

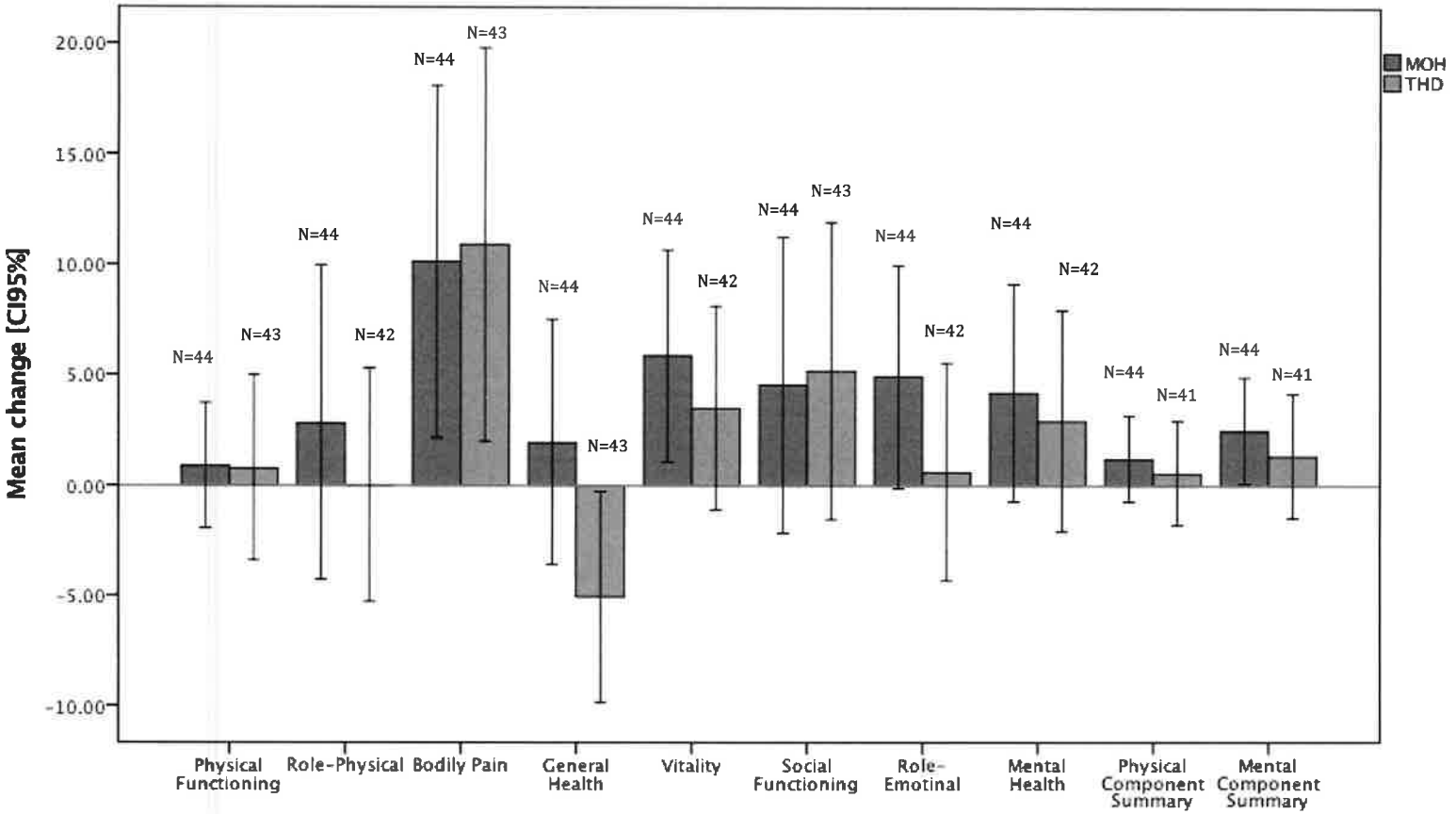

Mean change [CI95%]
20.00
15.00
10.00
5.00
0.00
-5.00
-10.00
MOH
THD
N=44
N=43
N=44
N=42
N=44
N=43
N=44
N=43
N=44
N=42
N=44
N=43
N=44
N=42
N=44
N=42
N=44
N=41
N=44
N=41
Physical Functioning
Role-Physical
Bodily Pain
General Health
Vitality
Social Functioning
Role-Emotinal
Mental Health
Physical Component Summary
Mental Component Summary

FIGURE 3

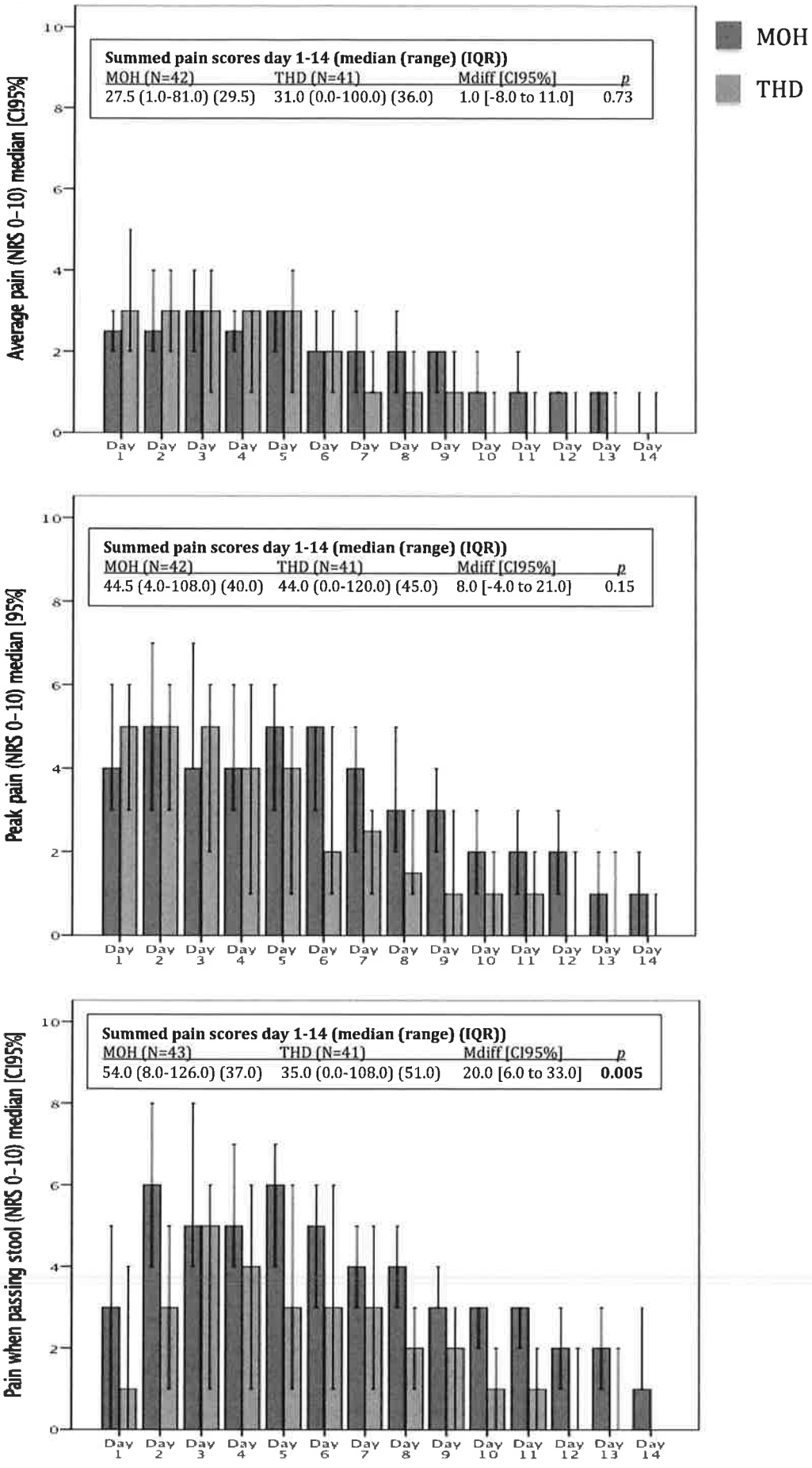
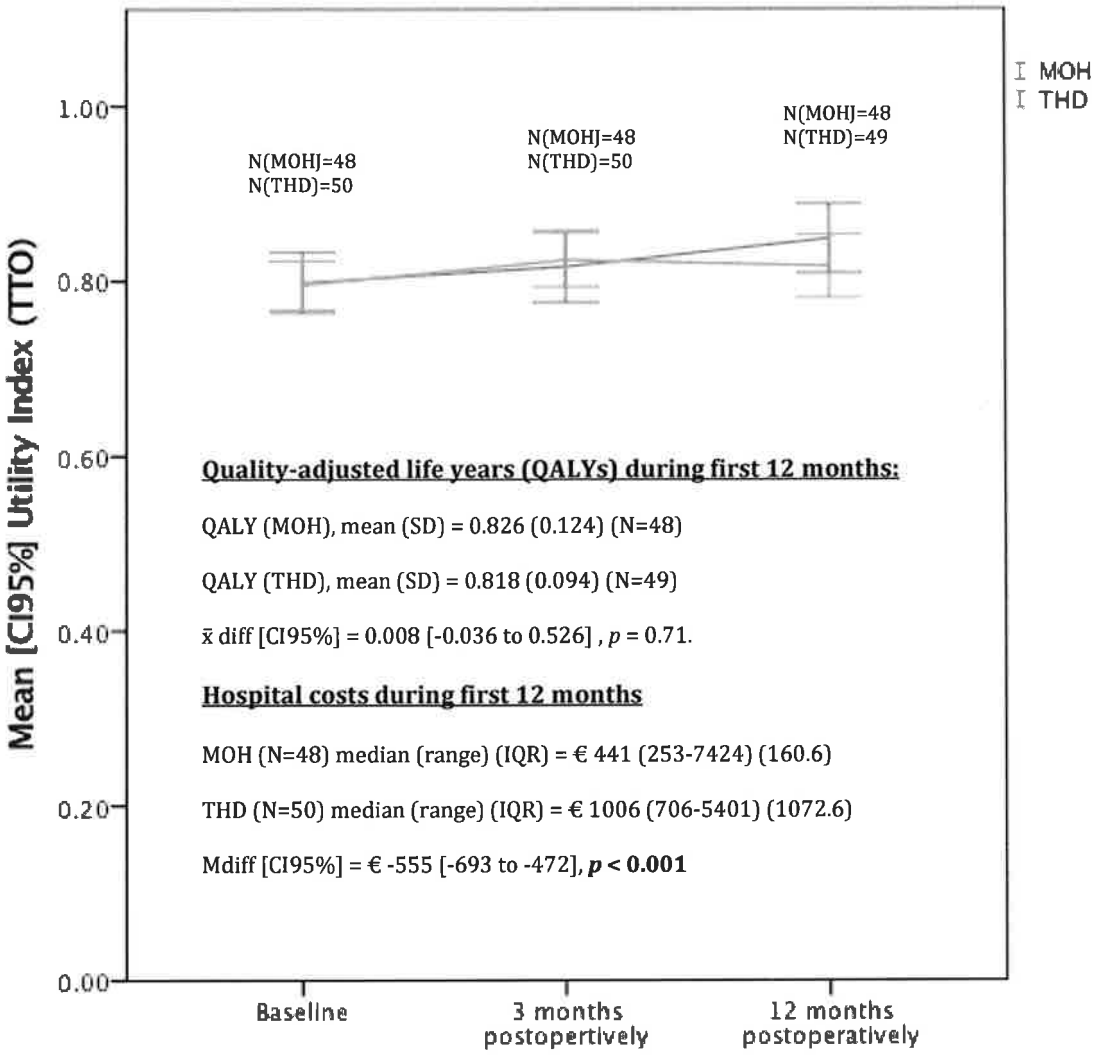

MOH
THD
Average pain (NRS 0-10) median [CI95%]
Summed pain scores day 1-14 (median (range) (IQR))
MOH (N=42) THD (N=41) Mdiff [CI95%] p
27.5 (1.0-81.0) (29.5) 31.0 (0.0-100.0) (36.0) 1.0 [-8.0 to 11.0] 0.73
Peak pain (NRS 0-10) median [95%]
Summed pain scores day 1-14 (median (range) (IQR))
MOH (N=42) THD (N=41) Mdiff [CI95%] p
44.5 (4.0-108.0) (40.0) 44.0 (0.0-120.0) (45.0) 8.0 [-4.0 to 21.0] 0.15
Pain when passing stool (NRS 0-10) median [CI95%]
Summed pain scores day 1-14 (median (range) (IQR))
MOH (N=43) THD (N=41) Mdiff [CI95%] p
54.0 (8.0-126.0) (37.0) 35.0 (0.0-108.0) (51.0) 20.0 [6.0 to 33.0] 0.005
0
2
4
6
8
10
Day 1
Day 2
Day 3
Day 4
Day 5
Day 6
Day 7
Day 8
Day 9
Day 10
Day 11
Day 12
Day 13
Day 14

FIGURE 4 Cost-utility analysis.



1. Title:

Quality of Life in patients with Haemorrhoidal Disease

2. Short title: Haemorrhoids and QoL

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The authors declare no conflicts of interest.

Abstract:

Background and Aims:

The impact of haemorrhoidal disease on health-related quality of life (HRQoL) in the Scandinavian population is unknown. In this study we compared HRQoL in patients with symptomatic haemorrhoids with a background population and evaluated the impact of clinical characteristics and surgical treatment.

Material and Methods:

This was a single-center cross-sectional and cohort study. HRQoL was assessed using the Short Form 12 and 36 (SF12 and SF36), EuroQoL 5-dimensions 5-levels (EQ-5D), and a disease specific questionnaire; Short Health Scale$_{HD}$ (SHS$_{HD}$). SF12 and EQ-5D scores in 257 patients with symptomatic haemorrhoids referred to our proctologic outpatient clinic were compared to a Danish background population adjusting for age, gender, body mass index and educational status. Symptoms were assessed using the Haemorrhoidal Disease Symptom Score. The anatomical pathology was graded using Goligher's classification. The associations between clinical characteristics and HRQoL were tested. The impact of surgical treatment was assessed in 111 patients followed one year postoperatively.

Results:

Patients reporting a high symptom load had lower SF12 physical health scores compared with the background population. The EQ-5D indexes indicated

impaired HRQoL in men, women <50 years and patients with higher education. Improvements in all three HRQoL measures were seen after surgery. Symptom burden had a negative association with HRQoL measures, whereas the surgeon's grading of anatomical pathology had no association.

Conclusion:

Haemorrhoidal disease had a negative impact on HRQoL. The influence of haemorrhoidal disease is related to symptoms and HRQoL improves after surgical treatment.

Key words:

Haemorrhoids; Haemorrhoidal disease; Quality of life; Health-related quality of life.

Introduction:

Haemorrhoids are enlargement of the anal cushions. The anal cushions are mucosa covered protrusions located just above the dentate line in the anal canal contributing to anal continence (1,2). Haemorrhoids localized intra-anally are considered a normal finding in adults and the term haemorrhoidal disease (HD) is used when the haemorrhoids cause symptoms (3). HD is the most common proctologic pathology in adults. Estimates from Western European countries suggest that 17% of adults suffer from symptomatic haemorrhoids (4), and approximately 50 per 100,000 adults undergo an operation for HD each year (5–7).

Health-related quality of life (HRQoL) is the impact of health on quality of life and can be defined as "how well a person functions in their life and his or her perceived wellbeing in physical, mental, and social domains of health" (8,9). As HD is a benign disease, the primary aim of its treatment is to resolve symptoms and improve patient wellbeing. HRQoL measures are frequently included as outcomes in clinical trials of HD treatments, and the impact on HRQoL can be used to evaluate the cost-effectiveness of an intervention (7). We have limited knowledge on HRQoL in patients with HD compared to the background population. A few studies have been published but the results are inconsistent (10–13). No previous studies have addressed HRQoL in patients with HD in a Scandinavian population. The impact on HRQoL of clinical characteristics such as degree of symptoms and anatomical grading of disease severity is scarcely investigated.

The aim of this study was to compare HRQoL in patients with haemorrhoidal disease with HRQoL in the general population. Secondly, we investigated the impact of clinical characteristics and surgical treatment on HRQoL.

Material and Methods:

Patients:

This was a cross-sectional (Cohort I) and longitudinal study (Cohort II) carried out at the Department of Surgery at Holbaek Hospital (Denmark). Patients referred to the proctologic outpatient clinic for anorectal complaints were assessed for eligibility. All patients (aged >16 years) diagnosed with HD including those treated either conservatively or surgically were eligible for inclusion in Cohort I. The HRQoL measured in Cohort I was compared with the HRQoL in a background population and the impact of clinical characteristics were also examined. To study the impact of surgical treatment we used data from patients operated for HD (Cohort II). Patients in Cohort I that received an operation could be included in both cohorts.

The attending surgeon in the outpatient clinic identified potential participants. Haemorrhoidal disease was diagnosed based on patient history, clinical examination, and anoscopy. Sigmoidoscopy or colonoscopy was performed according to Danish guidelines: For patients ≥40 years endoscopy was mandatory, while in patients <40 years the decision to perform endoscopy was left to the surgeon's discretion. We excluded patients with acute HD (bleeding requiring admission, strangulated internal haemorrhoids and thrombosed external haemorrhoids), and patients with concomitant anal fistula or fissure, anal or rectal prolapse, inflammatory bowel disease, or colorectal or anal cancer.

The study had no influence on patient treatment. Patients received a letter informing them about the study, and they consented to participate by completing

the questionnaires. The study was approved by the Regional Committee on Health Research Ethics (SJ-430/SJ348) and The Danish Data Protection Agency (REG-71-2013).

Measurements:

HRQoL was assessed using the Optum™ Short Form 36 version 2® (SF36v2), EuroQoL 5-dimensions 5-levels (EQ-5D-5L), and the Short Health Scale adapted to haemorrhoidal disease (SHS_{HD})(14–16). SF36v2 and EQ-5D-5L are two of the most widely used generic HRQoL questionnaires. The SF36v2 questionnaire consists of 36 questions (items) that are used to calculate eight health domain scales: physical functioning (PF), role participation with physical health problems (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role participation with emotional health problems (RE), and mental health (MH)(Appendix 1). The health domain scales can be evaluated separately or used to calculate the mental and physical component summary measures (MCS and PCS). The EQ-5D-5L questionnaire has five dimensions (mobility, self-care, daily activities, pain/discomfort and anxiety/depression). The patients grade their problems or impairments in each dimension on a five-level scale, giving 5^5 (3,125) possible health states. In addition, the patients report their self-rated health on a 0-100 visual analogue scale (EQ-VAS). The EQ-5D-5L health states were transformed to an index value (EQ-5D utility index) using the Danish Time-Trade-Off (TTO) value set (17). In both the SF36v2 and EQ-5D-5L higher scores indicate better HRQoL The SHS_{HD} is a disease-specific HRQoL instrument in patients with HD. The questionnaire has four items measuring overall symptom load, interference of symptoms with daily activities,

disease-specific worries, and general wellbeing. Each item is graded on a seven-point Likert scale. Higher scores indicate a higher impact of HD on patients' daily life and wellbeing.

Symptoms were assessed using the Haemorrhoidal Disease Symptom Score (HDSS)(16). HDSS measures the patient-reported frequency of pain, itching, bleeding, soiling and prolapse. Each symptom is graded 0-4 (0= never, 1= less than once a month, 2= less than once a week, 3= 1-6 days per week, 4= every day-/-always) giving a total score from 0-20.

The attending surgeon graded the anatomical pathology based on patient history and clinical examination using Goligher's classification (18). The surgeon also reported his or her global assessment of pathology on a seven-point Likert scale and registered data on symptom duration and previous treatments for HD.

Procedure

All questionnaires were written in Danish and administered on printed-paper. A letter describing the study was sent to all patients referred to the proctologic outpatient clinic. The letter stated the scheduled meeting time and included the questionnaires used in the study. The patients were asked to complete the questionnaires at home and return them to the outpatient clinic. In the event of non-compliance patients were asked to complete the questionnaires when attending the outpatient clinic. Patients operated for HD (Cohort II) completed the same questionnaires at planned follow-up one year after surgery. Any patient who did not want to attend the outpatient clinic at follow-up, was contacted by us and asked to send the questionnaires by mail.

Background population

Danish population norms for the EQ-5D utility index were published in 2009 (19). Danish population norms for the SF36v2 are not available. To establish a comparison group we used data from the Danish Health Interview Survey 2017 (SUSY 2017), performed by the Danish National Institute of Public Health, University of Southern Denmark (20). The survey was performed on a region-stratified, random sample of 25,000 Danish citizens (≥16 years). The questionnaires used in the SUSY 2017 were sent by electronic or paper mail and 14,022 citizens responded (response rate 56.1%). The survey included the Optum™ Short Form 12 version 2® (SF12v2) questionnaire. SF12v2 is a simplified version of the SF36v2 questionnaire with 12 items used to calculate the physical and mental component measures.

Primary outcome:

The primary outcome was the SF12v2 Physical Component and Mental Component Summary (Cohort I) compared with the background population (SUSY 2017). The SF12v2 scores of patients with HD (Cohort I) were extracted from the SF36v2 questionnaire.

Secondary outcomes:

The secondary outcomes were the EQ-5D utility index (Cohort I) compared with the background population, the associations between clinical characteristics and HRQoL (Cohort I), and changes in HRQoL measures one year after an operation for HD (Cohort II). The clinical characteristics assessed were duration of symptoms, previous operation for HD, patient-reported symptoms, grade of

prolapse (Goligher's classification), surgeon's global assessment of pathology, and allocated treatment (conservative vs. operation). The impact of surgical treatment was investigated comparing SHS_{HD}, SF36v2, and EQ-5D-5L scores before and one year after surgery.

Statistical analyses

Descriptive statistics described demographic data. Continuous data were tested for normality, and parametric (*t*-test) or non-parametric tests (Mann-Withney U-test (two samples) or Wilcoxon signed rank test (one sample)) were used depending on the distribution. Multiple linear regression analysis was performed to adjust for the confounding variables age, sex, and body mass index (BMI). When comparing with the general population we also adjusted for educational status, excluding patients aged <30 years. We excluded missing data in all analyses. Significance level was 0.05 (two-sided). Statistical analyses were performed in IBM SPSS 24 (IBM Corp, Armonk, New York, USA) and SAS 9.4 (SAS institute, Cary, North Carolina, USA). SF36v2 scores were obtained using the QualityMetric™ scoring software (5.1).

Sample size estimates were obtained from the SF36v2 User's Manual (21). According to this manual a difference of 2 points for the PCS and 3 points for the MCS are considered clinically relevant. To detect a difference in PCS and MCS of 2 points with significance level of 5% and statistical power of 80% required a sample size of 208-212 patients.

Results:

Patients

From 15 January 2015 to 29 August 2017, 257 patients were included in Cohort I for a comparison with the background population (Figure 1). In Cohort II, 123 patients operated for HD were included between 13 November 2013 and 24 August 2016. At one-year follow up, HRQoL data were obtained in 111 patients (90%). Table 1 presents baseline characteristics.

Comparison with background population

The SF12v2 Physical Component Score was lower in patients with HD but after adjustment for confounding variables (age, sex, BMI and educational status) no difference was found (Table 2). The Mental Component Score in patients with HD was higher compared with the background population. Patients reporting a high symptom load (HDSS >14) had lower SF12 v2 Physical Component Score compared with the background population (Table 3). Measured with the EQ-5D utility index HRQoL was lower in patients with HD compared with the background population and after adjustment for sex, age and educational status it stayed lower in men, women <50 years, and individuals with higher education (Table 4).

Impact of clinical characteristics

The patient-reported frequency of symptoms (HDSS) showed an association with HRQoL (Table 5). The HDSS was associated with the EQ-5D utility index, five of the eight health domain scales (BP, GH, VT, SF, and MH) and both component summary measures (PCS and MCS) of the SF36v2. The SHS_{HD} was associated with all health domains scales, both component summary measures and the EQ-5D utility index. No association was found between HRQoL measures and grade of prolapse (Goligher's classification), surgeon's global assessment of pathology, or allocated treatment (conservative vs. operation).

Impact of surgical treatment

Symptoms improved after surgery (Table 1). The HDSS showed a mean improvement [CI95%] of -7.19 [-8.16 to -6.23] (p<0.001). Four health domain scales and the mental component summary score of the SF36v2 improved one year after surgery (Figure 2). The greatest improvement was seen in Bodily Pain (mean difference [CI95%]: 4.05 [2.05 to 6.05], p<0.001). An improvement above minimal important difference (MID) of the physical component summary (MID: 2 points) was seen in 47% of the patients and of the MCS (MID: 3 points) in 32% of the patients. The EQ-VAS showed a mean improvement [CI95%] of 2.59 [-0.16 to 5.34](p=0.064), while the EQ-5D utility index showed a mean improvement [CI95%] of 0.042 [0.012 to 0.072](p=0.006). The SHS_{HD} had a mean improvement [CI95%] of -7.86 [-8.91 to -6.81] (p<0.001).

Discussion

In the present study we compared health-related quality of life (HRQoL) in patients diagnosed with haemorrhoidal disease (HD) with the background population. HRQoL was assessed using two widely used generic self-reported questionnaires (SF12v2 and EQ-5D-5L). We found that HD was associated with a decrease in HRQoL. Although HRQoL measured by SF12v2 was not lower in patients with HD, the SF12v2 physical health scores were below the population average in patients with a high symptom burden. Moreover, the EQ-5D utility index was lower in patients with HD compared with the background population, except for women ≥50 years and patients without higher education. Improvements in most HRQoL measures were seen when HD was surgically treated.

Only a few studies have compared HRQoL in patients with HD with healthy controls. In general our results are in agreement with reports from other countries. In a Turkish study the bodily pain and vitality domain scores (Short Form 36) were lower in patients with haemorrhoids compared with healthy controls (13). No differences were found for the physical and mental component summary measures. A national health survey in South Korea reported an association between HD and lower EQ-5D scores (12). This study is limited by the fact that a self-reported questionnaire set the diagnosis of HD. No association was found when the analysis was restricted to patients with HD diagnosed by a physician. Another study assessed HRQoL (using the Short Form 12) in patients attending the colorectal cancer-screening program in Austria (11). No difference

in HRQoL was found between patients with and without haemorrhoids. In contrast to our findings, the authors could not demonstrate a negative impact of haemorrhoidal symptoms. The patient population was, however, different from our study where patients were referred to a proctologic clinic for anal complaints. The majority of the patients included in the Austrian study (>90%) had low grade of disease (Grade I and II). Moreover, symptoms were categorized as present or not present, while in the present study symptoms were assessed using a validated symptom score (16).

Interestingly, we did not find an association between HRQoL measures and the anatomical pathology graded by the surgeon (Goligher's classification and global assessment of pathology) or allocated treatment (conservative vs. operation). These findings emphasize the importance of including patient-reported outcome measures in the evaluation of HD and are in line with previous findings, which showed that grade of prolapse and symptoms are poorly correlated (22). The Short Health Scale$_{HD}$ showed significant association with all domains of the SF36v2 and the EQ-5D utility index, supporting its validity as a simplified HRQoL tool for patients with haemorrhoidal disease.

Interventions for HD are primarily aimed at treating symptoms and improving HRQoL. We found that after surgery patient-reported symptoms improved largely and improvements in HRQoL measures were also seen. The health domain scale bodily pain (level of pain and interference with normal activities) showed the greatest improvement. Several clinical trials on treatments for HD have reported changes in SF-36 or SF-12 scores postoperatively, and

improvement in bodily pain is a consistent finding (23–27). The changes found in the other health domain scales and the EQ-5D utility index were relatively small. Our results indicate that changes in HRQoL are better demonstrated by a disease-specific rather than a generic HRQoL instrument. Surgeons and researchers should be aware of this when choosing outcome measures for clinical trials or clinical practice. A disease-specific HRQoL instrument such as the SHS_{HD} will most likely serve as a useful outcome measure. Recently, other HRQoL measures intended for proctologic diseases have also been presented (28,29).

The strength of the present study is that the patients were included consecutively and examined by surgeons experienced in the treatment of proctologic diseases. HRQoL was assessed by both a disease-specific HRQoL instrument (SHS_{HD}) and two of the most widely used generic questionnaires (SF36 and EQ-5D). Generic HRQoL instruments might be less sensitive to changes in HRQoL caused by a specific condition. However, generic HRQoL instruments enable comparison with healthy subjects and the wide use of SF36 and EQ-5D allows comparison with other studies. The limitations are our relatively high rate of non-responders, even though we asked the patients twice to participate. The rate of non-responders was even higher in the background population sample (43.9%). The finding of higher MCS in the patients with HD might be caused by selection bias. The patients included were a selection referred to a proctologic outpatient clinic. Studies have shown that many patients with proctologic symptoms conceal their complaints and fail to seek medical advice (30). A difference in characteristics may exist in patients that do

and do not seek medical advice for their complaints. The population in the present study should reflect the population seen by most Scandinavian colorectal or general surgeons, but the results can not necessarily be extrapolated to all patients with haemorrhoids.

Conclusion:

Haemorrhoidal disease has a negative impact on quality of life, which is related to the degree of symptoms. Quality of life is improved after surgical treatment. The surgeon's grading of anal pathology had no association with quality of life.

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Authors' contributions:

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3. Gierløff MC: 1,2,3,4
4. Brandstrup B: 1,2,3,4
5. Olaison G: 1,2,3,4

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The authors declare no conflicts of interest.

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Legends:

Figure 1: Flow chart for inclusion of patients in Cohort I and Cohort II.

Figure 2: The impact of surgery on HRQoL. Mean difference [CI95%] in Short Form 36 version 2 scores preoperatively and one year after surgery. A positive difference indicates improvement of HRQoL.

TABLE 1. Patient characteristics:

		Cohort I (N=257)	Control Group (SUSY 2017) (N=14,022)	Cohort II (N=123)	
Sex (M/F), N(%)		132 (51) / 125 (49)	6,417 (49) / 7,605 (51)	74 (60) / 49 (40)	
Age (years), mean (SD)		52.7 (15.6)	48.1 (19.3)	54.0 (14.1)	
BMI (kg/m²), mean (SD) [Missing, N(%)]		26.8 (4.8) [17 (7)]	25.7 (4.9) [1,273 (9)]	26.6 (4.4) [0 (0)]	
Educational status[1], N(%)	None	44 (17)	1,634 (13)	17 (14)	
	Short (1-4 years)	163 (63)	7,515 (48)	82 (67)	
	Long (>4 years)	23 (9)	1,346 (9)	5 (4)	
	Missing / <30 years old	10 (4) / 17 (7)	1,047 (9) / 2,480 (22)	13 (11) / 6 (5)	
Symptom duration (months), median (range) [Missing, N(%)]		61.0 (1-726) [60 (23)]	-	64 (2-726) [50 (41)]	
Previous operation for HD, N(%)	Yes	32 (13)	-	18 (15)	
	No	211 (82)	-	95 (77)	
	Missing	14 (5)	-	10 (8)	
				Preoperative	**1 year postoperatively**
Goligher's classification, N(%)	Grade I	66 (26)	-	1 (1)	71 (58)
	Grade II	54 (21)	-	5 (4)	14 (11)
	Grade III	64 (24)	-	47 (38)	7 (6)
	Grade IV	73 (28)	-	70 (57)	11 (9)
	Missing	0 (0)		0 (0)	20 (16)
Surgeon's global assessment of pathology (1-7), median (range) [Missing, N(%)]		3.0 (1-7) [8 (3)]	-	4.0 (2-7) [4 (3)]	2.0 (1-6) [22 (18)]
Haemorrhoidal Disease Symptom Score (0-20), mean (SD) [Missing, N(%)]		10.5 (4.3) [4 (2)]	-	12.1 (3.7) [1 (1)]	4.6 (4.3) [12 (10)]
Short Health Scale$_{HD}$ (4-28), mean (SD) [Missing, N(%)]		13.9 (5.2) [6 (2)]	-	15.5 (4.6) [7 (6)]	7.6 (4.1) [14 (11)]
Treatment, N(%)	Conservative	157 (61)	-	0 (0)	
	Operation	100 (39)	-	123 (100)	
	MOH	44 (17)		60 (49)	
	LigaSure	21 (8)		0 (0.0)	
	THD	35 (14)		63 (51)	

[1]Level of higher education. Patients <30 years old excluded. SUSY 2017 = Danish Health Interview Survey 2017; MOH = Minimal Open Haemorrhoidectomy; LigaSure = LigaSure Haemorrhoidectomy; THD = Transanal Haemorrhoidal Dearterialization.

TABLE 2. Comparison of HRQoL (SF12v2) between patients with haemorrhoidal disease (Cohort I) and the general population (SUSY 2017).

	Haemrrhoidal Disease (Cohort I) Mean [CI95%]	**General population (SUSY 2017)** Mean [CI95%]	**Calculated difference[1] [CI95%]**	***p***
UNADJUSTED	N = 257	N = 12,217		
Mental Component Summary	51.05 [49.71 to 52.40]	48.40 [48.20 to 48.59]	2.65 [1.31 to 4.00]	**<0.001**
Physical Component Summary	47.79 [46.53 to 49.04]	50.40 [50.22 to 50.58]	-2.61 [-3.87 to -1.36]	**<0.001**
ADJUSTED FOR AGE, SEX AND BMI	N = 238	N = 11,406		
Mental Component Summary			2.16 [0.81 to 3.51]	**0.0017**
Physical Component Summary			-1.17 [-2.37 to 0.02]	0.054
ADJUSTED FOR AGE, SEX, BMI and EDUCATIONAL STATUS[2]	N = 230	N = 11,135		
Mental Component Summary			2.01 [0.66 to 3.36]	**0.0034**
Physical Component Summary			-1.14 [-2.40 to 0.12]	0.076

[1]Negative difference indicates decreased HRQoL. [2]Individuals <30 years excluded.
HRQoL = Health-Related Quality of Life; SF12v2 = Short Form 12 version 2; SUSY 2017 = Danish Health Interview Survey 2017.

TABLE 3. HRQoL (SF12v2) related to the severity of symptoms (HDSS) in patients with haemorrhoidal disease (Cohort I) compared with a general population (SUSY 2017).

		Calculated difference[2] [CI95%]	*p*
Mental Component Summary (SF12v2)			
COHORT I[1]	HDSS 1-7	4.82 [2.10 to 7.54]	**0.001**
	HDSS 8-11	1.14 [-1.35 to 3.63]	0.6
	HDSS 12-14	1.35 [-1.09 to 4.21]	0.2
	HDSS 15-20	1.21 [-1.82 to 4.25]	0.4
SUSY 2017		Reference	
Physical Component Summary (SF12v2)			
COHORT I[1]	HDSS 1-7	-0.12 [-2.52 to 2.29]	0.9
	HDSS 8-11	0.17 [-2.03 to 2.37]	0.9
	HDSS 12-14	-2.03 [-4.37 to 0.32]	0.09
	HDSS 15-20	-4.37 [-7.05 to -1.69]	**0.001**
SUSY 2017		reference	

[1]Patients in Cohort I divided in quartiles based on HDSS. [2]Adjusted for age, sex, BMI and educational status excluding individuals <30 years. Negative difference indicates decreased HRQoL.

HRQoL = Health-Related Quality of Life; SF12v2 = Short Form 12 version 2; HDSS = Haemorrhoidal Disease Symptom Score; SUSY 2017 = Danish Health Interview Survey 2017

TABLE 4. Comparison of HRQoL (EQ-5D utility index) between patients with haemorrhoidal disease (Cohort I) and a general population.

		Haemorrhoidal Disease (Cohort I)		General population[1]		Calculated difference[2] [CI95%]	*p*
TOTAL		N	Mean (SD)	N	Mean (SD)		
EQ-5D Utility Score (0-1)		250	0.793 (0.148)	15,700	0.887 (<0.001)	-0.094 [-0.112 to -0.076]	**<0.001**
MEN		N	Mean (SD)	N	Mean (SD)		
Age <50 years	EQ-5D Utility Score (0-1)	42	0.780 (0.172)	1,562	0.908 (0.134)	-0.128 [-0.182 to -0.074]	**<0.001**
Age 50-69 years	EQ-5D Utility Score (0-1)	56	0.805 (0.109)	1,012	0.883 (0.153)	-0.078 [-0.119 to -0.037]	**<0.001**
Age ≥70 years	EQ-5D Utility Score (0-1)	30	0.777 (0.131)	667	0.847 (0.183)	-0.070 [-0.121 to -0.019]	**0.008**
WOMEN		N	Mean (SD)	N	Mean (SD)		
Age <50 years	EQ-5D Utility Score (0-1)	64	0.789 (0.180)	1,702	0.881 (0.159)	-0.092 [-0.138 to -0.046]	**<0.001**
Age 50-69 years	EQ-5D Utility Score (0-1)	42	0.804 (0.136)	1,109	0.839 (0.177)	-0.035 [-0.079 to 0.009]	0.11
Age ≥70 years	EQ-5D Utility Score (0-1)	16	0.810 (0.127)	741	0.818 (0.198)	-0.008 [-0.077 to 0.061]	0.81
HIGHER EDUCATION[3]		N	Mean (SD)	N	Mean (SD)		
None	EQ-5D Utility Score (0-1)	40	0.805 (0.129)	2,879	0.842 (0.189)	-0.037 [-0.079 to 0.005]	0.08
Short	EQ-5D Utility Score (0-1)	161	0.792 (0.148)	6,642	0.885 (0,150)	-0.093 [-0.116 to 0.070]	**<0.001**
Long	EQ-5D Utility Score (0-1)	22	0.805 (0.147)	2,858	0,912 (0,130)	-0.107 [-0.172 to -0.042]	**0.003**

[1]Sørensen J, Davidsen M et al. Danish EQ-5D population norms. *Scand J Public Health*. 2009 Jul 17;37(5):467–74.
[2]Negative difference indicates decreased HRQoL.
[3]Length of higher education. Individuals <30 years excluded.

HRQoL = Health-Related Quality of Life; EQ-5D = EuroQoL 5-dimensions.

Table 5. The impact of clinical characteristics on HRQoL measured by SF36 version 2 and Danish EQ-5D utility index (Time Trade Off).

CLINICAL CHARACTERISTICS		Physical Functioning	Role-Physical	Bodily Pain	General Health	Vitality	Social Functioning	Role-Emotional	Mental Health	Mental Component Summary	Physical Component Summary	EQ-5D Utility Index[1]
Symptom duration (months)		0.06 [-0.18 to 0.30]	**0.34* [0.03 to 0.65]**	-0.10 [-0.44 to 0.24]	0.12 [-0.21 to 0.45]	0.07 [-0.27 to 0.41]	0.05 [-0.23 to 0.32]	0.26 [-0.05 to 0.56]	0.11 [-0.17 to 0.40]	0.17 [-013 to 0.48]	0.03 [-0.27 to 0.33]	0.00 [-0.02 to 0.02]
Previous operation (no or yes)		-1.08 [-4.12 to 1.96]	-0.25 [-4.07 to 3.56]	-3.47 [-7.39 to 0.44]	-1.73 [-5.59 to 2.12]	-2.59 [-6.65 to 1.46]	1.51 [-1.94 to 4.97]	1.93 [-1.70 to 5.57]	-0.01 [-3.45 to 3.42]	1.18 [-2.57 to 4.92]	-3.25 [-6.99 to 0.50]	-0.004 [-0.01 to 0.01]
HDSS (0-20 points)		-0.18 [-0.40 to 0.04]	-0.21 [-0.50 to 0.07]	**-0.81*** [-1.09 to -0.53]**	**-0.40** [-0.68 to -0.12]**	**-0.44** [-0.74 to -0.15]**	**-0.41** [-0.66 to -0.16]**	-0.12 [-0.39 to 0.14]	**-0.32* [-0.57 to -0.07]**	**-0.35* [-0.62 to -0.08]**	**-0.38** [-0.65 to -0.11]**	**-0.88*** [-1.31 to 0.45]**
Symptom load (1-7 points)		**-1.35*** [-1.95 to -0.75]**	**-1.68*** [-2.45 to -0.92]**	**-2.74*** [-3.48 to -2.00]**	**-1.51*** [-2.29 to -0.74]**	**-1.77*** [-2.57 to -0.97]**	**-1.84*** [-2.52 to -1.17]**	**-0.99** [-1.74 to -0.25]**	**-1.62*** [-2.29 to -0.94]**	**-1.30*** [-2.05 to -0.56]**	**-2.02*** [-2.75 to -1.29]**	**-2.99*** [-4.14 to -1.84]**
SHS_{HD} (4-28 points)		**-0.55*** [-0.73 to -0.37]**	**-0.72*** [-0.94 to -0.49]**	**-0.95*** [-1.17 to -0.73]**	**-0.63*** [-0.85 to -0.40]**	**-0.68*** [-0.92 to -0.44]**	**-0.74*** [-0.94 to -0.54]**	**-0.47*** [-0.68 to -0.25]**	**-0.64*** [-0.83 to -0.45]**	**-0.58*** [-0.79 to -0.36]**	**-0.76*** [-0.98 to -0.55]**	**-1.24*** [-1.57 to -0.91]**
Goligher's classification	Grade I	1.22 [-1.50 to 3.94]	0.17 [-3.27 to 3.60]	1.81 [-1.73 to 5.36]	1.57 [-1.90 to 5.04]	2.04 [-1.57 to 5.64]	0.34 [-2.77 to 3.46]	0.56 [-2.68 to 3.81]	-0.03 [-3.12 to 3.06]	-0.39 [-3.71 to 2.93]	1.65 [-1.69 to 4.98]	1.27 [-4.04 to 6.59]
	Grade II	-0.60 [-3.41 to 2.20]	-2.92 [-6.47 to 0.64]	-1.44 [-5.10 to 2.23]	-1.16 [-4.74 to 2.41]	-0.85 [-4.57 to 2.86]	-1.22 [-4.42 to 1.99]	-1.76 [-5.14 to 1.63]	-0.34 [-3.52 to 2.84]	-0.91 [-4.39 to 2.57]	-2.64 [-6.13 to 0.86]	-2.74 [-8.30 to 2.82]
	Grade III	-1.54 [-4.23 to 1.15]	-1.62 [-5.03 to 1.79]	0.17 [-3.34 to 3.69]	-1.21 [-4.64 to 2.23]	0.07 [-3.50 to 3.65]	-0.86 [-3.95 to 2.23]	-1.53 [-4.75 to 1.69]	-0.001 [-3.06 to 3.06]	-0.62 [-3.9 to 2.66]	-2.06 [-5.35 to 1.24]	-4.30 [-9.53 to 0.92]
	Grade IV	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
Surgeon's global assessment of pathology (1-7 points)		-0.43 [-1.20 to 0.35]	0.06 0.91 to 1.04]	-0.06 [-1.07 to 0.94]	-0.17 [-1.16 to 0.82]	0.12 [-0.89 to 1.13]	0.04 [-0.84 to 0.92]	-0.04 [-0.96 to 0.88]	0.56 [-0.31 to 1.42]	0.62 [-0.31 to 1.55]	-0.43 [-1.39 to 0.52]	0.36 [-1.09 to 1.80]
Operative treatment (no or yes)		-0.22 [-2.25 to 1.81]	-0.06 [-2.63 to 2.51]	-0.42 [-3.07 to 2.22]	-1.78 [-4.35 to 0.80]	-1.49 [-4.17 to 1.19]	0.18 [-2.14 to 2.49]	0.43 [-2.00 to 2.85]	0.39 [-1.90 to 2.68]	0.65 [-1.82 to 3.12]	-0.91 [-3.42 to 1.60]	-0.269 [-4.25 to 3.71]

Calculated impact [CI95%] per unit increase in linear regression model adjusting for sex, age and body mass index. *p<0.05 **p<0.01 ***p<0.001. [1]EQ-5D utility index was multiplied by 100.

HRQoL = Health-Related Quality of Life; HDSS = Haemorrhoidal Disease Symptom Score; Symptom load = Overall symptom load on 7-point Likert scale; SHS_{HD} = Short Health Scale adapted for haemorrhoidal disease.

Figure 1: Flow chart

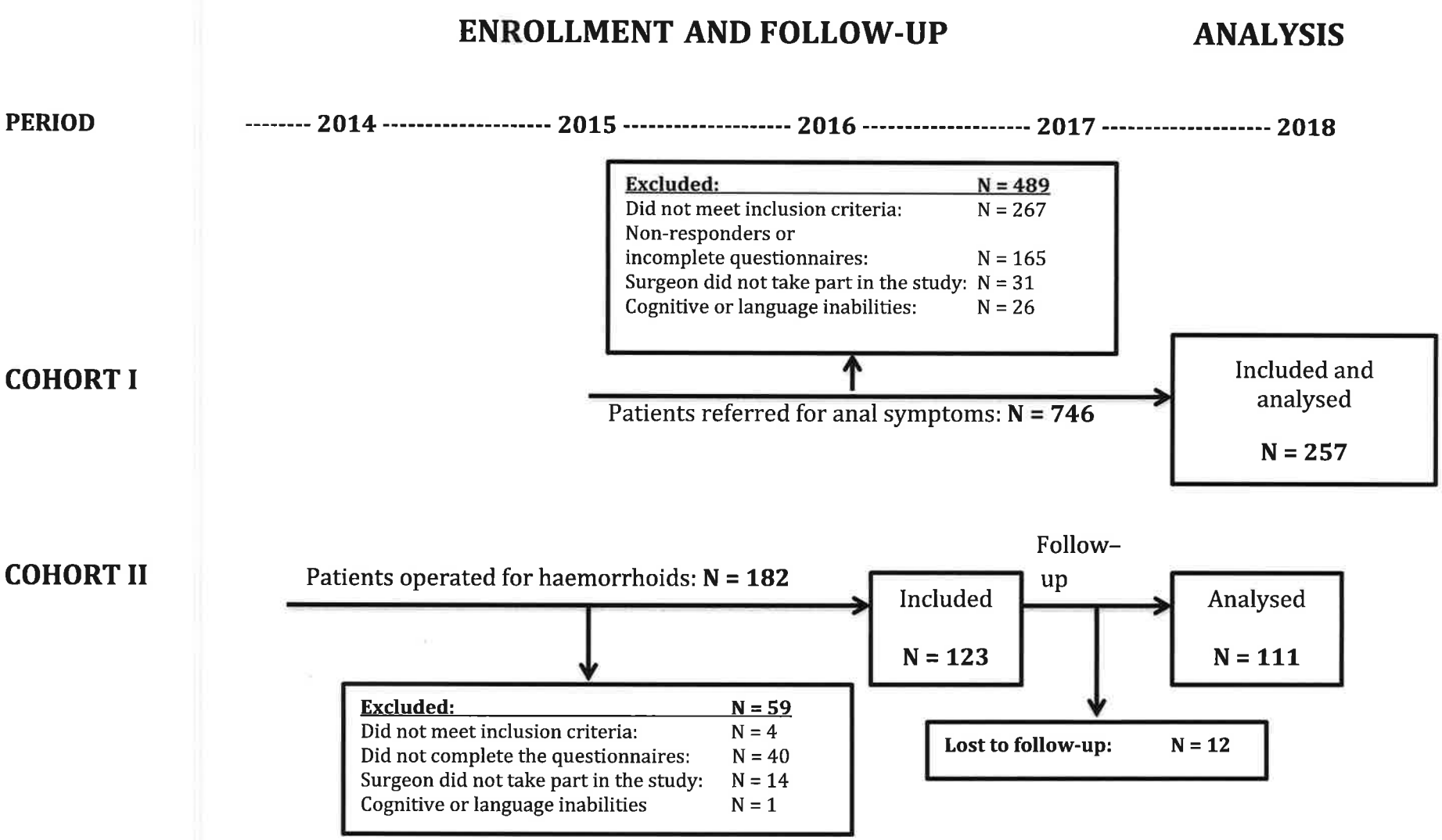
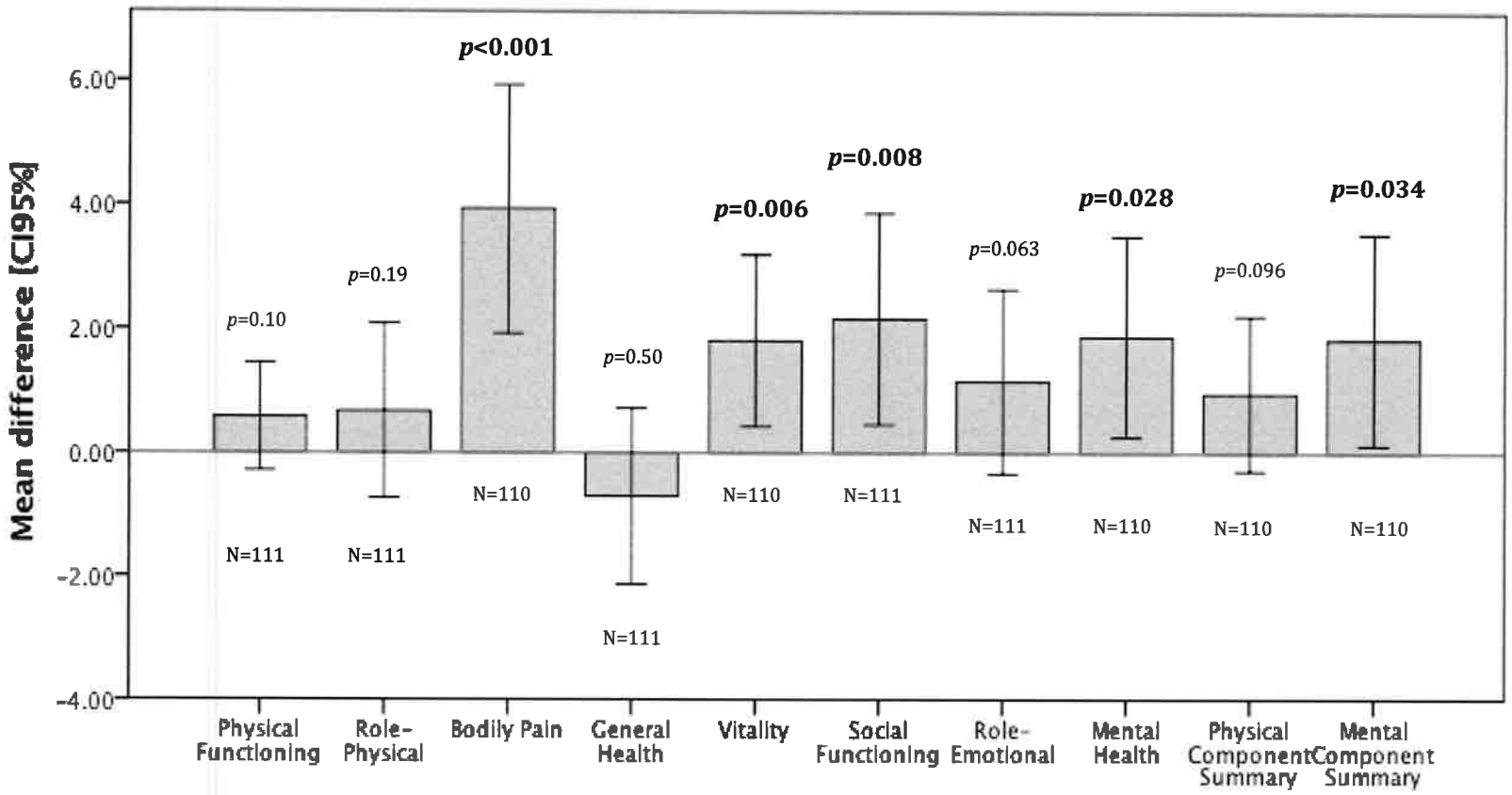


Figure 2. The impact of surgery on HRQoL



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Article status	
Published ☒ Date: March 2019	Accepted for publication ☐ Date:
Manuscript submitted ☐ Date:	Manuscript not submitted ☐
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2. The declaration applies to the following article	
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If the article is published or accepted for publication, please state the name of journal, year, volume, page and DOI (if you have the information).	Tech Coloproctol. 2019;23(1):73-77. doi:10.1007/s10151-018-1915-x

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5. Conducting the analysis of data	A
6. Interpretation of the results	A
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The declaration is for PhD students and must be completed for each conjointly authored article. Please note that if a manuscript or published paper has ten or less co-authors, all co-authors must sign the declaration of co-authorship. If it has more than ten co-authors, declarations of co-authorship from the corresponding author(s), the senior author and the principal supervisor (if relevant) are a minimum requirement.

1. Declaration by	
Name of PhD student	Håvard Dragesund Rørvik
E-mail	havardrorvik@hotmail.com
Name of principal supervisor	Birgitte Brandstrup
Title of the PhD thesis	Haemorrhoidal Disease: Minimal Open Haemorrhoidectomy, Symptoms and Health-related quality of life

2. The declaration applies to the following article	
Title of article	Minimal Open Haemorrhoidectomy versus Transanal Haemorrhoidal Dearterialization: the effect on symptoms. An open-label randomized controlled trial.
Article status	
Published ☐ Date:	Accepted for publication ☒ Date: 26.11.2019
Manuscript submitted ☐ Date:	Manuscript not submitted ☐
If the article is published or accepted for publication, please state the name of journal, year, volume, page and DOI (if you have the information).	Dis Colon Rectum

3. The PhD student's contribution to the article *(please use the scale A-F as benchmark)* Benchmark scale of the PhD-student's contribution to the article **A.** Has essentially done all the work (> 90 %) **B.** Has done most of the work (60-90 %) **C.** Has contributed considerably (30-60 %) **D.** Has contributed (10-30 %) **E.** No or little contribution (<10 %) **F.** Not relevant	**A, B, C, D, E, F**
1. Formulation/identification of the scientific problem	B
2. Development of the key methods	A
3. Planning of the experiments and methodology design and development	A
4. Conducting the experimental work/clinical studies/data collection/obtaining access to data	A
5. Conducting the analysis of data	A
6. Interpretation of the results	A
7. Writing of the first draft of the manuscript	A
8. Finalisation of the manuscript and submission	A

Provide a short description of the PhD student´s specific contribution to the article.'
The PhD student has designed the study in collaboration with the supervisors. He has participated in data collection and conducted the data analysis and interpretation of the result. The PhD student has written the manuscript and in collabration with the co-authors finilized the paper . The PhD student submitted the paper to the journal and was the corresponding author in the review process.

4. Material from another thesis / dissertation[II]	
Does the article contain work which has also formed part of another thesis, e.g. master's thesis, PhD thesis or doctoral dissertation (the PhD student's or another person's)?	Yes: ☐ No: ☒
If yes, please state name of the author and title of thesis / dissertation.	
If the article is part of another author's academic degree, please describe the PhD student's and the author's contributions to the article so that the individual contributions are clearly distinguishable from one another.	

5. Signatures of the co-authors[III]

	Date	Name	Title	Signature
1.	12/12	Birgitte Brandstrup	[illegible]	[signature]
2.	19/1-2020	Gunnar Olaison	MD, PhD	[signature]
3.	12/12/19	Andre Campos	MD	[signature]
4.	12/12 19	Karl Styr	MD	[signature]
5.	040120	Grant McKinstry	MD	[signature]
6.	20/12/2019	LARS ILLUM	MD	[signature]
7.				
8.				
9.				
10.				

6. Signature of the principal supervisor

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.

Date: 12/12 -19

Principal supervisor: [signature]

7. Signature of the PhD student

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.

Date: 24/1-20

PhD student: [signature]

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GRADUATE SCHOOL OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

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1. Declaration by	
Name of PhD student	Håvard Dragesund Rørvik
E-mail	havardrorvik@hotmail.com
Name of principal supervisor	Birgitte Brandstrup
Title of the PhD thesis	Haemorrhoidal Disease: Minimal Open Haemorrhoidectomy, Symptoms and Health-related quality of life

2. The declaration applies to the following article	
Title of article	Quality of life in patients with Haemorrhoidal Disease.
Article status	
Published ☐ Date:	Accepted for publication ☐ Date:
Manuscript submitted ☐ Date:	Manuscript not submitted ☒
If the article is published or accepted for publication, please state the name of journal, year, volume, page and DOI (if you have the information).	

3. The PhD student's contribution to the article *(please use the scale A-F as benchmark)* Benchmark scale of the PhD-student's contribution to the article **A.** Has essentially done all the work (> 90 %) **B.** Has done most of the work (60-90 %) **C.** Has contributed considerably (30-60 %) **D.** Has contributed (10-30 %) **E.** No or little contribution (<10 %) **F.** Not relevant	**A, B, C, D, E, F**
1. Formulation/identification of the scientific problem	A
2. Development of the key methods	A
3. Planning of the experiments and methodology design and development	A
4. Conducting the experimental work/clinical studies/data collection/obtaining access to data	A
5. Conducting the analysis of data	C
6. Interpretation of the results	A
7. Writing of the first draft of the manuscript	A
8. Finalisation of the manuscript and submission	A
Provide a short description of the PhD student's specific contribution to the article.[1] The PhD student has designed the study in collaboration with the supervisors. He has participated in data collection and conducted som of the data analysis. The PhD student has contributed in the interpreation of the results, has written the manuscript and in collabration with the co-authors finilized the paper.	

Latest update of the declaration: December 2018

4. Material from another thesis / dissertation[ii]	
Does the article contain work which has also formed part of another thesis, e.g. master's thesis, PhD thesis or doctoral dissertation (the PhD student's or another person's)?	Yes: ☐ No: ☒
If yes, please state name of the author and title of thesis / dissertation.	
If the article is part of another author's academic degree, please describe the PhD student's and the author's contributions to the article so that the individual contributions are clearly distinguishable from one another.	

5. Signatures of the co-authors[iii]

	Date	Name	Title	Signature
1.	12/12-19	Birgitte Brandstrup	MD, PhD	B Brandstrup
2.	10/1-20	Gunnar Olaison	M.D., Ph.D.	
3.	14/12-19	Matthias Gierløff	M.D.	
4.	16/12-19	Michael Davidsen	Senior researcher	
5.				
6.				
7.				
8.				
9.				
10.				

6. Signature of the principal supervisor

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.
Date: 12/12-19
Principal supervisor: B Brandstrup

7. Signature of the PhD student

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.
Date: 24/1-20
PhD student:

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