Thesis for doctoral degree (Ph.D.)
2022

Inguinal Hernia Surgery - Aspects on Chronic Pain and Contralateral Repair

Anders Olsson

Karolinska Institutet

Department of Clinical Science and Education, Södersjukhuset
Karolinska Institutet, Stockholm, Sweden

INGUINAL HERNIA SURGERY
ASPECTS ON CHRONIC PAIN AND CONTRALATERAL REPAIR

Anders Olsson

Karolinska Institutet

Stockholm 2022

All previously published papers were reproduced with permission from the publisher.
Published by Karolinska Institutet.
Printed by Universitetsservice US-AB, 2022

ISBN 978-91-8016-721-5
Cover illustration: Licensed from Getty Images, 101 Bayham Street, London NW1 0AG, UK

INGUINAL HERNIA SURGERY – ASPECTS ON CHRONIC GROIN PAIN AND CONTRALATERAL REPAIR

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Anders Olsson

The thesis will be defended in public in Ihresalen at Södersjukhuset, Stockholm, on Wednesday the 9th of November 2022.

Principal Supervisor:
Ursula Dahlstrand, M.D. Ph.D.,
Karolinska Institutet
Department of Clinical Science, Intervention and Technology

Co-supervisor(s):
Gabriel Sandblom, Associate professor,
Karolinska Institutet
Department of Clinical Science and Education, Södersjukhuset

Ulf Fränneby, M.D. Ph.D.,
Karolinska Institutet
Department of Clinical Science, Intervention and Technology

Ulf Gunnarsson, Professor
Umeå University
Department of Surgical and perioperative sciences

Anders Sondén, Associate professor
Karolinska Institutet
Department of Clinical Science and Education, Södersjukhuset

Opponent:
Jan Dalenbäck, Associate professor,
Sahlgrenska Academy, University of Gothenburg
Department of Surgery

Examination Board:
Jacob Freedman, Associate professor,
Karolinska Institutet
Department of Clinical Sciences, Danderyd Hospital

Lovisa Strömmer, Associate professor,
Karolinska Institutet
Department of Clinical Science, Intervention and Technology

Jakob Hedberg, Associate professor,
Uppsala University
Department of Surgical Sciences

To my family

ABSTRACT

Inguinal hernia is common, and the only permanent treatment is surgical repair. Approximately 16,000 hernia repairs are performed annually in Sweden. Optimized surgical technique including mesh prosthesis decreases the prevalence of recurrences and the main outcome measurement is today chronic postoperative inguinal pain (CPIP). CPIP prevalence is often reported as 10-30%.

The wider use of endo-laparoscopic surgical technique has slightly decreased the prevalence of CPIP and has also offered the opportunity to perform a bilateral inguinal hernia repair, as well as exploration for occult hernias in the contralateral groin, during one procedure without additional incisions. Considering the large number of patients with CPIP it is vital to better understand the etiology and causes for the development of CPIP. It is also of interest to evaluate the benefits and risks to an extended laparoscopic procedure such as a bilateral prophylactic hernia repair.

In **Paper I**, the aim was to explore if surgical postoperative complications increased the risk for CPIP in a long-term cohort study. Participants responded to the Inguinal Pain Questionnaire (IPQ) regarding postoperative groin pain 8 years after inguinal hernia repair. Responses to the questionnaire were matched with data regarding self-reported postoperative complications after open inguinal hernia repair. A total of 170 patients (17.9%) reported persistent groin pain and 29 patients (3.0%) reported severe persistent groin pain. Severe pain in the preoperative or immediate postoperative period was a significant risk factor while increasing age was negatively correlated to the risk for chronic groin pain.

In **Paper II**, the aim was to develop and evaluate a condensed version of the IPQ. The IPQ is a standardized and validated instrument for assessing CPIP after groin hernia surgery. The Short-Form Inguinal Pain Questionnaire (sf-IPQ) comprises two main items extracted from the IPQ.

Four hundred patients with groin hernia repairs were recruited from the Swedish Hernia Register (SHR) and were sent the IPQ, sf-IPQ and the Short-Form McGill Pain Questionnaire (SF-MPQ) three years after hernia repair. Correlation, consistency, and agreement were seen between the IPQ and sf-IPQ despite a systematic difference in level of pain score. The forms appeared to provide similar responses for parameters assessed by both instruments, though the sf-IPQ may be a more sensitive instrument.

In **Paper III**, the aim was to analyze if specific postoperative complications constitute predictors for the risk of developing CPIP using a population-based prospective cohort of 30,659 patients operated for groin hernia 2015–2017 included in the SHR. Registered post-operative complications were categorized into hematomas, surgical site infections (SSI), seromas, urinary tract complications, and acute post-operative pain. A questionnaire enquiring about groin pain was distributed to all patients 1 year after surgery. Acute postoperative pain was a strong predictor for CPIP following both open anterior and endo-laparoscopic hernia repair. SSI and hematoma were predictors for CPIP following open anterior hernia repair.

In **Paper IV**, the aim was to investigate the incidence as well as the factors predictive for a subsequent hernia repair on the contralateral side following a primary unilateral hernia repair. Participants were recruited from the SHR. 151,297 patients operated with a unilateral groin hernia repair using open and endo-laparoscopic technique, during 2007-2019, were studied.

There were 7.4% registered contralateral hernia repairs with a median time to contralateral repair of 2.7 years. Significant predictors for a subsequent contralateral hernia were, male sex, high age, medial inguinal hernia, combined inguinal hernia, hernia defect size $\geq$1.5 cm, and a repair on the left side. Endo-laparoscopic repairs and obesity were associated with a lower incidence of a later contralateral repair.

In conclusion, patient reported CPIP is a significant negative outcome following groin hernia repair that needs to be evaluated continuously. The sf-IPQ can be recommended as an evaluation tool in daily clinical practice. The postoperative complications: postoperative severe pain, hematomas, and SSI were associated with CPIP. These predictors may be related to surgical technique. Considering the relatively low incidence of subsequent contralateral hernia repairs, a routine extended exposure of the contralateral groin or a prophylactic contralateral repair cannot be recommended considering the risk for surgical complications and associated CPIP.

LIST OF SCIENTIFIC PAPERS

The thesis is based on the following papers, which will be referred to by their roman numerals.

I. **Impact of postoperative complications on the risk for chronic groin pain after open inguinal hernia repair** A. Olsson, G. Sandblom, U. Fränneby, A. Sondén, U. Gunnarsson and U. Dahlstrand *Surgery 2017 Vol. 161 Issue 2 Pages 509-516*

II. **The Short-Form Inguinal Pain Questionnaire (sf-IPQ): An Instrument for Rating Groin Pain After Inguinal Hernia Surgery in Daily Clinical Practice** A. Olsson, G. Sandblom, U. Fränneby, A. Sondén, U. Gunnarsson and U. Dahlstrand *World J Surg 2019 Vol. 43 Issue 3 Pages 806-811*

III. **Do postoperative complications correlate to chronic pain following inguinal hernia repair? A prospective cohort study from the Swedish Hernia Register** A. Olsson, G. Sandblom, U. Franneby, A. Sondén, U. Gunnarsson and U. Dahlstrand *Hernia 2021 Online ahead of print. PMID: 34894341 DOI: 10.1007/s10029-021-02545-y*

IV. Manuscript **Risk for contralateral inguinal hernia repair following primary unilateral hernia repair – a register-based study** A. Olsson, G. Sandblom, U. Franneby, A. Sondén, U. Gunnarsson, J. Österberg, U. Dahlstrand *Manuscript*

CONTENTS

ABBREVIATIONS

- APIP Acute Postoperative Inguinal Pain
- ASA American Society of Anesthesiologists classification
- BMI Body mass index
- CI Confidence interval
- CPIP Chronic Postoperative Inguinal Pain
- EHS European Hernia Society
- HR Hazard ratio
- IPQ Inguinal Pain Questionnaire
- OR Odds ratio
- PROM Patient-Reported Outcome Measure
- SHR Swedish Hernia Register
- SSI Surgical site infection
- TAPP Trans-abdominal pre-peritoneal repair
- TEP Totally extra-peritoneal repair

1 INTRODUCTION

"A surgeon can do more for the community by operating on hernia cases and seeing the recurrence rates low than operating on malignant diseases" Dr. Cecil Wakely

Inguinal hernia is a common condition. The lifetime risk for an inguinal hernia repair in Western countries is estimated to be 27% in men and 3% in women (1). Approximately 16,000 hernia repairs are performed annually in Sweden and 20 million worldwide (2). Improved surgical technique, and using mesh prosthesis for reinforcement, has reduced the incidence of recurrences. However, as the risk for hernia recurrence gradually diminishes, focus has changed to other adverse postoperative outcomes such as chronic postoperative inguinal pain (CPIP) (3).

The prevalence of persistent postoperative pain after groin hernia repair is reported to be 20-30% while severe pain affecting daily activities is reported to 6-10%, (4, 5). Even though the natural course is a gradual decrease over time, pain persists in 14%, resulting in suffering for many operated patients (6). With regards to the large number of patients with CPIP it is of great importance to better understand the etiology and causes for the development of CPIP.

The increasing use of laparoscopic surgical technique has slightly decreased the prevalence of CPIP. The endo-laparoscopic technique provides advantages such as an easy access to bilateral repairs during one procedure and within the same incisions. It also enables exploration for occult hernias in the contralateral groin in cases of unilateral repair, though this practice needs to be evaluated regarding benefits and risks.

1.1 DEFINITION OF THE INGUINAL HERNIA

A hernia is a protrusion of the interior contents through a defect of the surrounding tissues. The development of a groin hernia is a consequence of a weakening, or a rupture of the transverse fascia combined with an increased intraabdominal pressure (7), and the definition is: a protrusion of a hernia sac consisting of peritoneum where intraabdominal contents may protrude (8).

The integrity of the abdominal wall in the groin area relies on the oblique orientation and the sphincter function of the inguinal canal. Other conditions presenting with similar complaints, such as a spermatic cord lipoma, cystocele or varicose veins may cause similar clinical manifestations but need a different management than a true inguinal hernia.

1.1.1 Anatomy

One theory on the origin of inguinal hernias is the hypothesis that the development of bipedalism resulted in a stretching and secondary weakness of the anatomy in the groin area.

The myopectineal orifice (MPO) is a well-defined weak area in the lower anterior abdominal wall which is the site of all groin hernias, both inguinal and femoral (9). The inguinal ligament divides the MPO in a cranial and a caudal part. Anatomic boundaries of the inguinal canal are the inguinal ligament caudally, the internal oblique aponeurosis cranially, the transversalis fascia posteriorly and the external oblique aponeurosis anteriorly. The inguinal canal surrounds the spermatic cord, consisting of vas deferens, vessels, testicular nerves and the cremaster muscle in men; and the round ligament of the uterus in women (10). Figure 1.

During childhood, the internal and external apertures of the canal are sited upon each other and forms a direct orifice for the spermatic cord or the round ligament running from the intraabdominal cavity through the abdominal wall. During the transition from child to adult anatomy, the external orifice moves medially, and the slanted inguinal canal is formed (11).

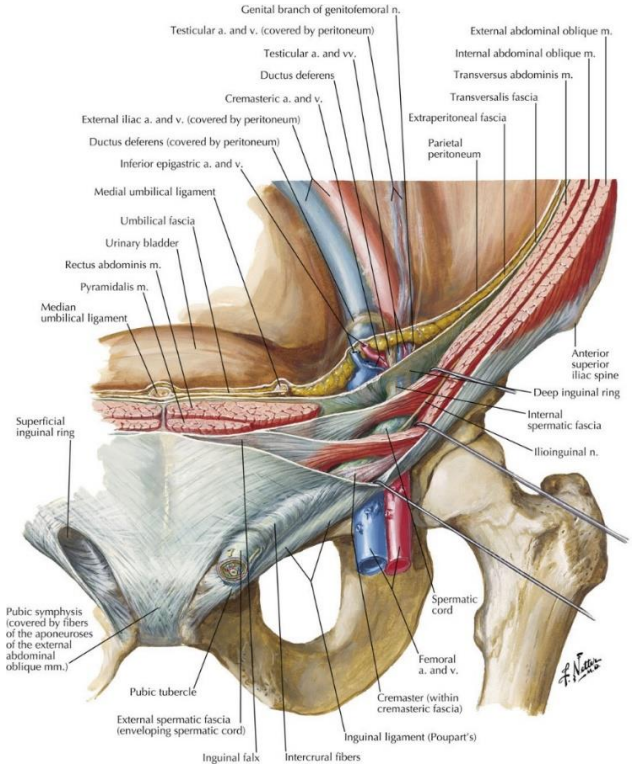


Figure 1. Groin anatomy. (Reprinted from Netter Atlas of Human Anatomy, 8th edition, with permission from Elsevier.)

Nerves

The nerve supply to the inguinal region consists of a network of peripheral sensory nerves originating mainly from the ileohypogastric, the ilioinguinal and the genitofemoral nerves.

The ileohypogastric nerve emerges from the L1 root, passes between the transverse muscle and the internal oblique muscle and exits from the abdominal wall into the subcutaneous tissue in the semilunar line area, innervating the skin of the lower anterior abdominal wall.

The ilioinguinal nerve arises from the L1 root and runs caudal to the ileohypogastric nerve. The nerve enters the inguinal canal through the abdominal wall and supplies the skin of the groin and lateral scrotum after exiting through the external inguinal ring.

The genitofemoral nerve emanates from the L1 and L2 roots and follows a course through and, distally, on the surface of the psoas muscle. The nerve divides into the femoral branch that enters the abdominal wall lateral of the inguinal canal and supplies the skin of the thigh, and the genital branch that passes through the abdominal wall at the internal inguinal ring and joins the spermatic cord, innerving the cremaster muscle (12).

The lateral femoral cutaneous nerve is formed from the L2 and L3 roots and runs parallel and inferior to the femoral branch of the genitofemoral nerve in the iliac fossa. It provides sensation to the lateral side of the thigh.

Several sensory nerve fibers emanating from different nerves cover the lamina propria of the vas deferens and supply the testicle in men, and to some extent cover the round ligament in women (13).

Blood vessels

The inferior epigastric artery branches from the external iliac artery inferomedial to the internal inguinal orifice and, accompanied by the corresponding vein, run vertically in the retromuscular space behind the rectus muscle. These vessels are the anatomical landmark that separates a direct hernia through the abdominal wall (medial to the epigastric vessels), from an indirect hernia through the internal ring (lateral to the epigastric vessels).

The gonadal arteries are branches of the abdominal aorta; the veins drain into the inferior vena cava and the left renal vein. They enter the iliac fossa preperitoneally from the posterior, joining vas deferens caudally and deep to the internal inguinal orifice, forming the spermatic cord that enters the abdominal wall through the internal orifice. The external iliac vessels that supply the leg enter the iliac fossa posteriorly and exit under the inguinal ligament, becoming the femoral vessels. The external iliac vein is located medially to the iliac artery, while the femoral nerve is located lateral to the iliac artery (10).

Muscles and fascia

The aponeurosis emanating from the external oblique muscle, the internal oblique muscle and the transverse abdominis muscle constitute the layers surrounding the inguinal canal.

Important landmarks of the groin area are the inguinal ligament that attach to the anterior superior iliac spine and runs medial and attaches to the pubic tubercle; the conjoint tendon which is formed by the internal oblique and the transverse oblique muscles and attaches to the pubic crest caudally, to the linea alba medially and has a free border laterally where the inguinal canal exits superficially; Coopers ligament that attaches on the pubic tubercle and runs inferodorsally along the pubic bone; and the arcuate line that is the caudal lining of the posterior rectus sheet (10).

Classification

The lateral (indirect) hernia is the most common type constituting 55% of all inguinal hernias in men and 53% in women (14). Lateral hernia can develop from a patent processus vaginalis with a persisting communication between the intraabdominal cavity and the scrotum (11). The herniation originates at the internal orifice of the inguinal canal. A lateral hernia consists of a hernia sac formed of the peritoneum, protruding alongside the spermatic cord through the inguinal canal. The vaginal process normally closes with age but persists in approximately 20% of adults, contributing to the risk for development of a lateral hernia (15). Closure of the processus vaginalis is delayed on the right side resulting in more frequently occurring lateral hernias on the right side (15).

A cord lipoma consists of preperitoneal fatty tissue protruding alongside the spermatic cord. It presents similar to a lateral hernia even though it does not entail the risk of intestinal strangulation (16, 17).

The second most common hernia type is the medial (direct) hernia protruding through a defect in the weak medial area of the MPO. It constitutes 35% of all inguinal hernias for men and 18% for women (14). The hernia protrudes directly through an abdominal wall defect consisting of a weakened transversalis fascia in Hesselbach’s triangle, medial to the epigastric vessels (7).

Femoral hernia accounts for approximately 4% of all groin hernias. Femoral hernias protrude through the femoral canal and typically consists of preperitoneal fat or visceral contents. The female pelvis is broader and flatter than in men resulting in a wider femoral orifice (18). Femoral hernias are, as a consequence, more common in women; accounting for 25% of all groin hernias in women but only for 1.4% in men at the time of repair (14).

A combination of two or more of the hernia types is defined as a combined inguinal hernia. There are also several fewer common hernias in the groin region, such as the Spigelian hernia or the obturator hernia (19, 20). Different hernias are illustrated in Figure 2.

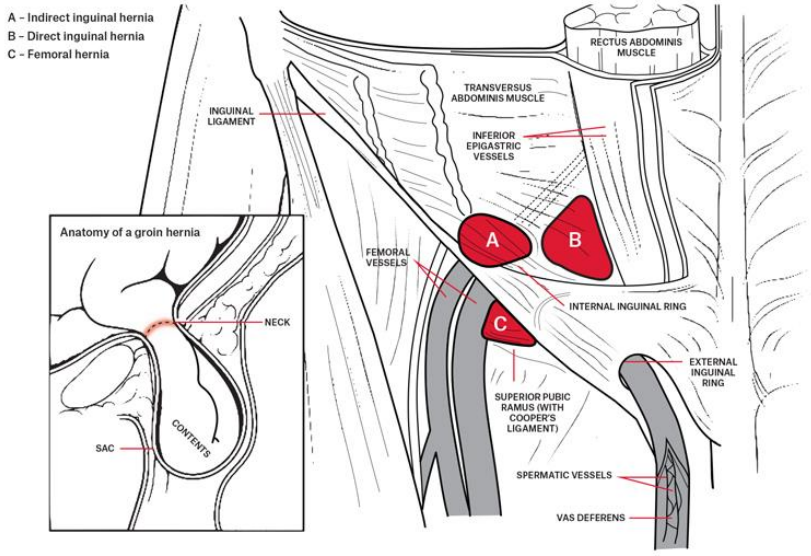


Figure 2. Classification of groin hernias. Illustration of the most common groin hernias. A: lateral (indirect) hernia; B: medial (direct) hernia; C: femoral hernia. (Reproduced with permission from The RACGP from: Turner RC. A general practitioner primer on groin hernias. Aust J Gen Pract 2018 Aug;47(8):530–33. doi: 10.31128/AJGP04-18-4546)

1.1.2 Epidemiology

The art of epidemiology includes the ability of obtaining reasonable answers from imperfect data (Lorena González-García).

Approximately 9 out of 10 patients with an inguinal hernia are men and the incidence increases with age. Prevalence studies shows similar frequencies in differing regions and differing socioeconomic circumstances worldwide. The lifetime risk for inguinal hernia in men has been estimated to 27%, while the 20-year cumulative incidence in middle-aged men is 14 and the prevalence in men over 75 years of age is 47% (1, 21-23).

1.1.3 Risk factors

The strongest risk factors for developing an inguinal hernia are male sex and high age (21). The inguinal canal in men is wider as it encircles the spermatic cord, and the tissues lose strength and tension with age (21). A patent processus vaginalis is a risk factor for developing a lateral inguinal hernia for men (15), while a decreased type I/III collagen ratio increases the risk for hernias in both men and women (24-26). There is a considerable variability regarding the insertion of the transverse aponeurosis to the pubic tubercle in men which may have an impact on the risk for developing medial hernias (18). Low BMI has been shown to increase the risk for femoral hernias in women (27), while obesity seems to be a protective factor (28).

Other predisposing factors are, increased intra-abdominal pressure such as heavy labor, obesity, pregnancy or chronic obstructive pulmonary disease; structural collagen changes due to aging, connective tissue diseases such as Ehlers-Danlos syndrome and Marfan syndrome; or tobacco smoking (29, 30).

Contralateral hernia

Some patients operated for a unilateral inguinal hernia, later develop a contralateral inguinal hernia which may need a new hernia repair. The prevalence of a concurrent contralateral undiagnosed inguinal hernia at the time of a unilateral repair has been estimated to 10-32 % (31, 32). There is no consensus regarding best management for asymptomatic contralateral hernias. Some support prophylactic repair (33) while others recommend the watchful waiting approach (34).

Risk factors for the development of a subsequent contralateral inguinal hernia are not well studied. Available literature reports a similar pattern of risk factors as for a primary hernia, i.e., male sex, high age (35), and possibly also a decreased collagen I/III ratio as well as both high and low BMI.

1.2 MANAGEMENT OF INGUINAL HERNIA

1.2.1 Symptoms

An inguinal hernia often presents as a local bulging in the groin. It can appear with or without pain but is commonly combined with a dull sensation and groin discomfort. Symptoms range from completely asymptomatic to strangulated hernias with secondary peritonitis. If the hernia is reducible, symptoms typically resolve as the hernia is pushed back into the abdomen. Hernias can result in numbness in the groin region caused by compression or damage to the sensory nerves in or close to the inguinal canal.

A strangulated hernia is painful. The incarcerated contents get trapped in the hernia neck which reduces venous outflow causing edema, reduced perfusion and finally ischemia. An untreated incarcerated hernia may result in necrosis and tissue loss. A hernia containing part of the bowel, illustrated in Figure 3, may result in intestinal obstruction and ischemia followed by necrosis and intestinal perforation with peritonitis. Therefor a strangulated inguinal hernia needs prompt medical attention (29).

All groin hernias are at risk for strangulation, but it is much more common in femoral hernias (29). Over 20% of incarcerated femoral hernias that undergo acute repairs also require a bowel resection due to intestinal strangulation. Consequently, there is a ten-fold increased mortality risk compared to elective inguinal hernia repair (36, 37).

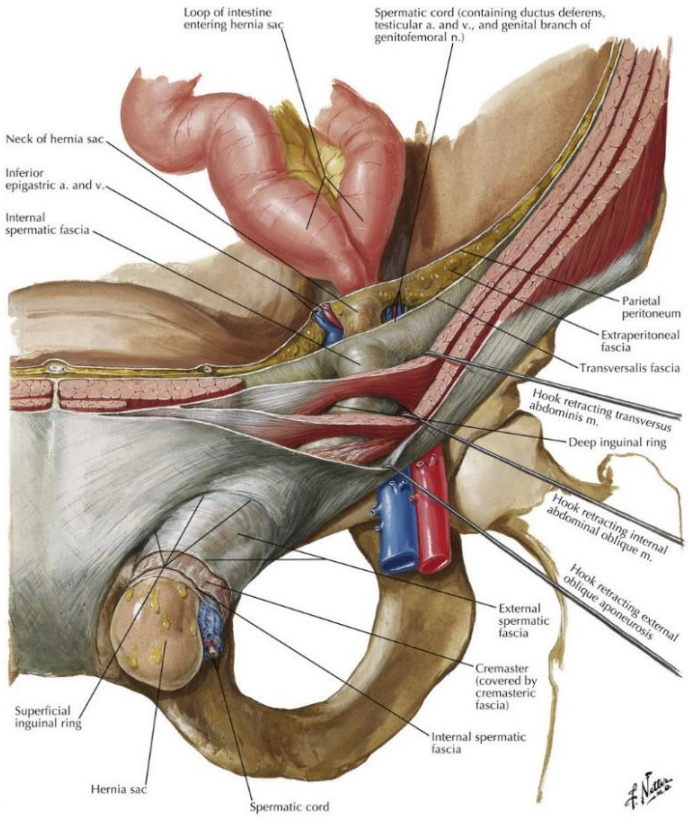


Figure 3. Illustration of a lateral (indirect) hernia with incarcerated small bowel. (Reprinted from Netter Atlas of Human Anatomy, 8th edition, with permission from Elsevier)

1.2.2 Assessment

Clinical examination

The clinical presentation of a groin hernia varies. A focused history uptake and a thorough physical examination are the key assessment instruments to establish a correct diagnosis. The groin region should be examined both in standing and supine position as abdominal pressure may reveal a protrusion of an inguinal hernia. Examination using a gentle finger in the groin during a Valsalva maneuver can detect a protruding hernia.

A patient complaining of a painful groin bulging which is reducible at clinical examination usually does not represent a diagnostic dilemma and render further examinations superfluous. Cases with inguinal pain without any detectable bulging and non-reducible bulges are more challenging and may need further diagnostic methods for an adequate diagnosis. The patient's body habitus can also cause challenges in the diagnostic procedure. Small, yet symptomatic hernias may not be clinically detectable,

Imaging diagnostics

Ultrasound (US) is a useful method to detect protruding hernias as well as to classify the type of hernia and to describe hernia contents i.e. fat, bowel, or other tissues. US has the advantage of being dynamic and provides the ability to examine motion of tissues in different positions (38). It is furthermore a cost-effective assessment method without any ionizing radiation. On the other hand, US is operator-dependent and may be limited by the patient's habitus (39).

CT-scan provides more details of the anatomy, but without the possibility to capture motion of the tissues. Extraperitoneal herniation such as a cord lipoma or herniating bladder may however be better visualized with a CT scan. Drawbacks are the ionizing radiation as well as higher costs compared to US (39).

Herniography includes intra-abdominally injected radiopaque contrast fluid followed by plain x-ray. The method has proven to be superior to both US and CT in detecting small inguinal hernias (40). This method can also be performed as a CT-herniography. A disadvantage is the invasive intra-abdominal injection of radiopaque fluid and the risks that follow in terms of inadvertent injury to abdominal organs (39).

Magnetic resonance imaging (MRI) has proven to be superior to both US and CT in detecting occult inguinal hernias (41). Tendinitis or osteitis may also be detected with the MRI modality. This imaging modality does not generate ionizing irradiation but is more expensive than the others (39).

1.2.3 Treatment

The only definitive treatment for an inguinal hernia is surgical repair. The purpose of the operation is to reduce the hernia and to repair and reinforce the defect structures, as well as to prevent a future hernia recurrence (42).

Symptomatic treatment with a groin compression belt can reduce symptoms and delay further hernia development. Different designs of groin trusses have been used historically and has been reported long before the modern surgical repair technique was developed (43).

Asymptomatic inguinal hernias may be treated with watchful waiting approach. The benefit of this management is that the surgical hazards are avoided. Studies have on the other hand showed that approximately two thirds of these patients undergo a hernia repair within 10 years due to progressing symptoms, mainly pain (44-46).

If the watchful waiting approach fails, surgery is the next step of treatment. The most common surgical procedures today are open mesh repair with an anterior approach under local anesthesia or general anesthesia (2), and endo-laparoscopic mesh repair.

1.3 SURGERY

"The history of hernia repair is the history of surgery." Patino

A hernia is a permanent anatomical defect and will not heal or disappear by itself. Surgical repair aims to reconstruct and repair the anatomy permanently. Modern hernia repair history can be divided into the pre-mesh era and the mesh repair era.

1.3.1 Pre-mesh era

Surgical treatment of inguinal hernias has a long history. The first known report of an inguinal hernia repair emanates from approximately 300 BC, written on Egyptian papyrus rolls. Surgery with ligation of vessels under herb sedation was described. The surgical knowledge spread to the Greek and Roman empires and was preserved in the Byzantine and Arabic empires (47).

During the medieval period surgery was not considered as a part of the medical field but rather a skill performed by barbers which was developed at the battlefields. From the 15th Century anatomical studies were performed in Europe. The inguinal anatomy was described in detail by Sir Astley Cooper in 1844 (43) and the definition of direct and indirect inguinal hernias was presented.

Anesthesia or sedation is needed to be able to perform a surgical procedure. Opium, herbs, and alcohol are substances that have been well known and used over the centuries, combined with rapid surgical procedures including simplified technique. From the early 19th century nitrous oxide and ether were introduced. These substances could uphold a more stable and reliable sedation and were gradually applied and widely used in the surgical management. In the late 19th century Cocaine was introduced as the first local anesthetic agent used in hernia surgery (48). The use of cocaine inspired the development of synthetic local anesthetics. Lidocaine was introduced in the late 40´s and is still used for local anesthesia (49).

Edoardo Bassini (1844-1924), Figure 4, was an Italian surgeon that developed and described a repair technique involving ligation of the hernia sac and reconstruction of the posterior wall of the inguinal canal using the adjacent tissues in a three-layer repair using silk (50). Bassini presented his results after over four years observation time with a recurrence rate of only 4%. Bassini's technique was widely spread but attempts to reproduce his results regarding recurrences failed, with recurrence rates from 5-40%. The variation in outcome was probably due to different surgeons' own modifications of the technique (51).

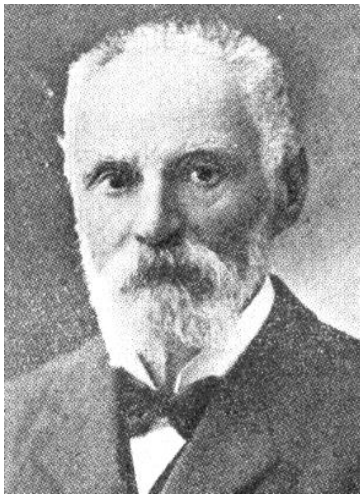


Figure 4. Dr Edoardo Bassini (1844-1924). "Padre de la cirugía herniaria moderna". Father of the modern hernia surgery. (Picture licensed from Pinterest.)

Henry O Marcy (1837-1924) was an American surgeon practicing in Chicago, who described a further developed technique including a high ligation of the hernia sac and narrowing of the internal inguinal ring.

Edward Shouldice (1890-1965), a Canadian surgeon, introduced a more complex open repair where the hernia sac was ligated proximally, while the posterior floor of the inguinal canal was repaired and reinforced thoroughly using adjacent tissues in four layers. Shouldice described his method in the 1950s (52). Follow-up studies in specialized clinics such as the Shouldice clinic in Canada have reported recurrence rates of 0.5-2.8% after more than five years (8, 53).

1.3.2 Mesh repair era

Several prosthesis materials have been tried throughout the history such as silver filigrees in the early 1900s, stainless steel, and tantrum gauze in the 1940s and early 1950s, all with varying side effects.

Seven criteria for the optimal prosthesis material was postulated in the 1950s, and are still valid (54). The prosthesis material should be chemically inert; easily sterilized; durable and in adequate size; relatively elastic to resist mechanical strains; smooth borders to prevent tissue trauma or inflammation; radio-translucent; easily obtainable and affordable.

In the 1960s polypropylene meshes were introduced by Usher and have been used and developed ever since (55). Polypropylene is still today the most widely used prosthesis material for hernia repair. Several other materials such as polyester, nylon,

polytetrafluorethylene (PTFE), polyvinyledine fluoride (PVDF), as well as biologic material such as porcine dermal grafts, autologous human grafts, have been introduced and used (56). Polypropylene mesh has been well studied regarding best properties of the material and design. A non-absorbable light-weight mesh with large pores has shown decreased risk for postoperative infections, less postoperative pain, as well as decreased patient reported postoperative discomfort without increased risk for recurrence (57).

1.3.3 Anterior approaches

Irving Lichtenstein (1920-2000), Figure 5, contributed to the inguinal hernia repair field with a method that fundamentally changed the management of inguinal hernias. Lichtenstein introduced the tension-free inguinal hernia repair using mesh reinforcement with the mesh placed anterior in the inguinal canal, between the internal and the external oblique aponeuroses, and with a slit for the spermatic cord (58), illustrated in Figure 6. This method provided a safe repair for both direct and indirect hernias.

The technique was announced in 1964, published in 1989 and contributed to the improvement of hernia repair outcome regarding recurrence rates (59). The tension-free mesh repair technique resulted in decreased recurrence rates to approximately 5%, and has been reported to have recurrence rates as low as 0.2% with a follow-up time of up to eight years, after optimization of the technique (60). Further developments and adjustments to the technique has been presented from the original authors (61).

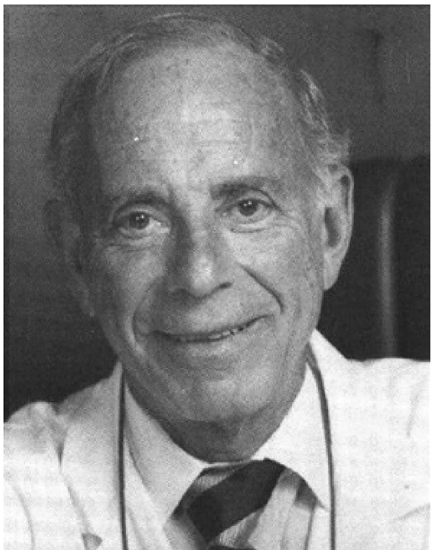


Figure 5. Dr Irving Lichtenstein (1920-2000), contributed to the inguinal hernia surgery field by introducing the "tension-free mesh repair technique". (Reprinted from Indian Journal of Surgery, 2021, with permission from Springer Nature.)

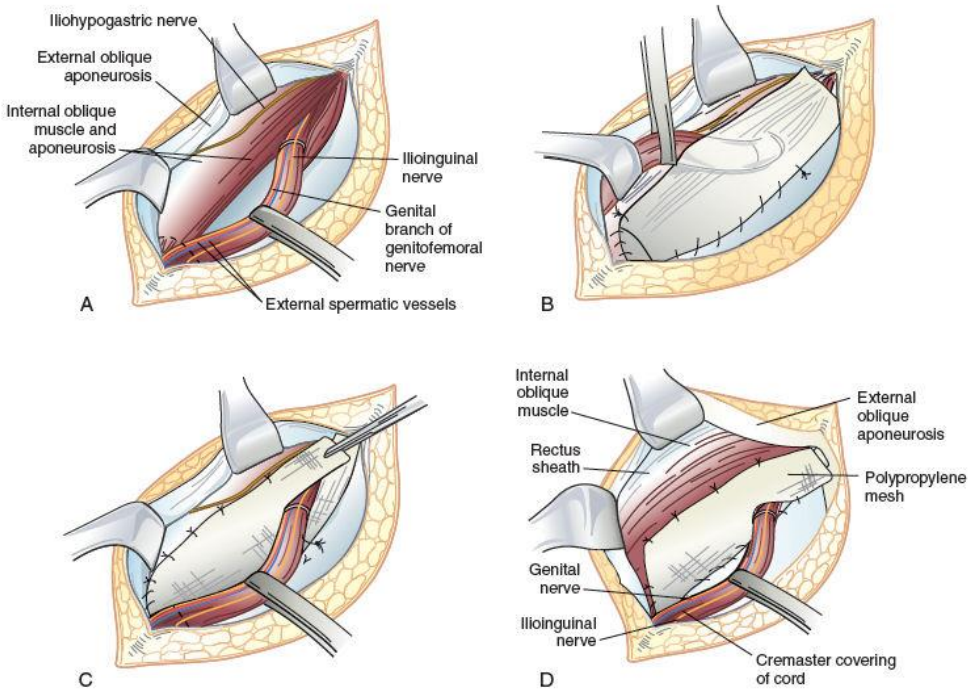


Figure 6. Illustrations of the Lichtenstein open anterior mesh repair technique, step by step. (Reprinted from Sabiston Textbook of Surgery, with permission from Elsevier Saunders.)

1.3.4 Posterior approaches

Lloyd Nyhus (1923-2008) was an American surgeon practicing in Chicago. Nyhus described a posterior approach using a transverse incision accessing the abdominal wall cranially to the inguinal canal and avoiding interference with the superficial structures of the inguinal canal. Placement of a mesh in the posterior plane made an entirely tension-free repair possible (62).

Rene Stoppa (1921-2006) was a French surgeon mainly practicing in Algeria. Stoppa described his technique of a posterior mesh reinforcement at the same time as Nyhus using a midline incision from where he had access to the posterior, preperitoneal plane. This method showed an even lower risk for interfering with the oblique or rectus abdominis muscles as well as the epigastric vessels compared to the transverse incision (63).

1.3.5 Endo-laparoscopic approaches

Laparoscopic techniques developed during the 1980s, initially for cholecystectomy and appendectomy. Different endo-laparoscopic techniques for hernia repair were presented in the early 1990s, and the first reported laparoscopic inguinal hernia repair was performed as an Intraperitoneal Onlay Mesh (IPOM) and was published in 1992 (64). Early results varied due to inadequate mesh sizes and early severe complications such as bleedings from major vessels. Outcomes improved gradually, with better understanding of the preperitoneal anatomy as well as increasing experience.

Trans Abdominal Preperitoneal repair (TAPP), is a technique accessing the inguinal space via an intraabdominal approach, illustrated in Figure 7. The first report of this method was published in 1993 (65). After accessing the abdominal cavity, the peritoneum covering the groin region is opened and pulled down to expose the inguinal structures. The hernia sac is either pulled back into the abdominal cavity or ligated and a mesh is placed on the posterior wall covered by the peritoneum that is closed with sutures or tackers. Advantages are a better view of the interior abdominal cavity and allowed inspection of the contralateral groin to identify any present contralateral hernias; a drawback is the necessity to traverse the abdominal cavity including risk for organ injuries.

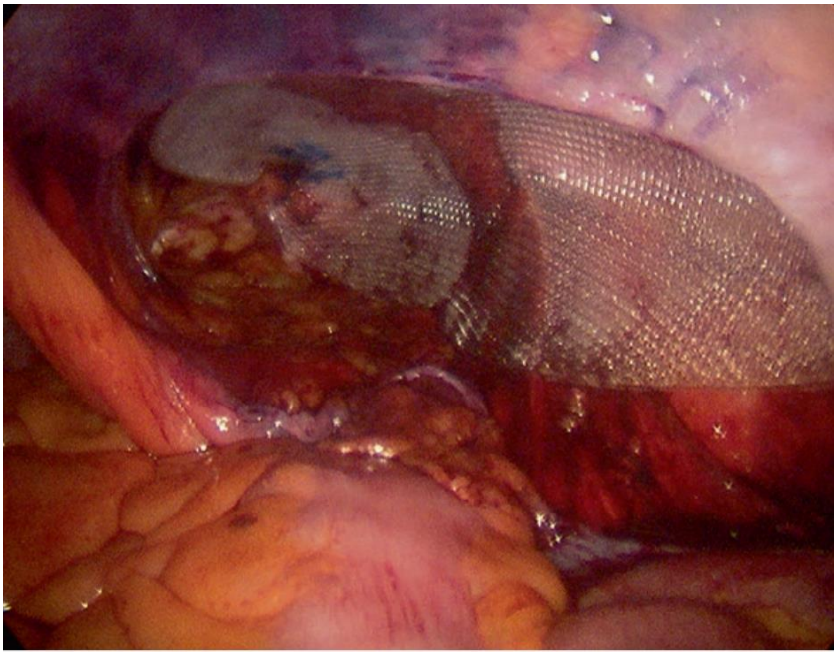


Figure 7. Illustration showing a hernia repair with the TAPP technique. Peritoneum incised and a mesh is placed in the extraperitoneal space. After mesh placement the peritoneum is closed. (Reprinted from Textbook of Hernia, Editor Hope, with permission from Springer.)

Total Endoscopic Preperitoneal repair (TEP), is a technique accessing the inguinal space through the rectus sheet and inflating carbon dioxide directly in to the preperitoneal space, illustrated in Figure 8. This developed endo-laparoscopic method was presented in 1993 (66, 67). The hernia sac is handled in a similar way as with the TAPP method. This method allows direct access to the groin without the need to traverse the abdominal cavity (68). Drawbacks are the limited space, the lack of direct control of the hernia contents, and lack of opportunity to inspect the contralateral groin without dissection of the area.

The endo-laparoscopic techniques have undergone multiple evaluations regarding recurrencies and postoperative complications (69-71). Early adverse outcomes have been addressed and the techniques have been modified and optimized during the years. One important contribution was the nine-step recommendation to achieve a “critical view” of the MPO region (72).

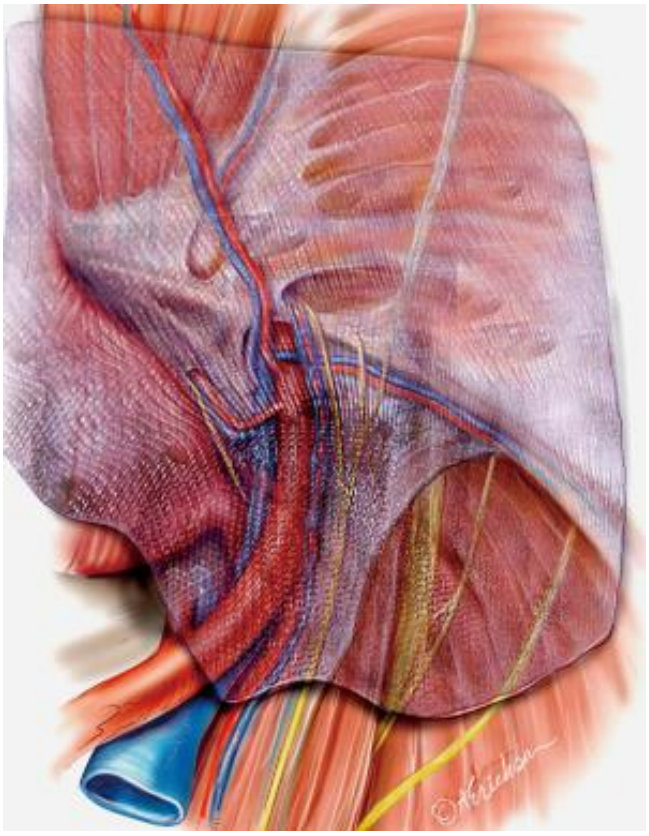


Figure 8. Illustration of the TEP procedure. The groin is exposed from the extraperitoneal space, and a mesh is placed on the posterior wall. (Reprinted from Slideshare, Laparoscopic Inguinal Hernia Repair Eminence-based or Evidence-based? Ferzli, 2011, with permission from Scribd.)

1.4 OUTCOME

"Good results come from experience. Experience comes from bad results." Unknown

Medical quality is determined by structure, process and outcome according to Donabedian (73). In surgery, outcome is the most frequent indicator of surgical quality. A negative outcome can be subdivided into complications, failure to cure and sequelae (74).

Surgical operations may come with side effects and possible temporary or persisting complications. Early and predictable side effects as surgery associated pain and wound healing manifestations can be treated with analgesic and anti-inflammatory drugs. Postoperative complications such as surgical site infections, hematomas, prolonged pain, urinary retention can often be treated with drugs such as analgesics or antibiotics while mechanical complications such as recurrence needs a reoperation.

Historically, hernia recurrence has been a common postoperative complication. After the introduction of mesh reinforcement hernia repairs, standardization of groin hernia management as well as introduction of quality registers, the recurrence rate has decreased and CPIP has become the most important postoperative adverse event. Health-Related Quality of Life (HRQoL) can be assessed with a variety of instruments, both to evaluate postoperative outcome as well as for preoperative risk stratification (75). Surgical outcome depends on preoperative, surgical, and postoperative factors such as comorbidities, surgical method, and approach as well as presence of postoperative complications.

1.4.1 Recurrence

A recurrence is a negative outcome and according to the Clavien-Dindo classification it constitutes a "failure to cure" (74). A relapse of the repaired hernia was a common adverse outcome following hernia repair during the pre-mesh era and was reported to occur in more than 20% of primary hernia repairs (76). Surgical repair during the pre-mesh era entailed an increased tension on already weakened tissue resulting in an increased risk for rupture. Absorbable suture material is also associated with increased recurrence rates (77).

The incidence of inguinal hernia recurrences is difficult to estimate. The frequency of diagnosed recurrences depends on follow-up time and validity of post-operative reporting. Reoperation rates are often used as a proxy to estimate the prevalence of hernia recurrences but the recurrence rate is assumed to exceed the reoperation rate with approximately 40% (76). Reoperations also entails a doubled risk for a new recurrence compared to a primary inguinal hernia repair (78). Studies have reported a population based reoperation rate after open inguinal hernia repair of 1.2-3.8%, and approximately 2.1-3.5% after endo-laparoscopic repair (79, 80), while reported recurrences in the SHR are 3% eight years after repair (14). Highly specialized hernia centers have on the other hand presented long-term reoperation rates below 1% (81), which supports specialization of hernia management and especially referring recurrent hernias and difficult cases to highly specialized centers (82).

1.4.2 Postoperative complications

A complication can be defined as “any deviation from the normal postoperative course” (74). Every invasive treatment comes with the risk for an adverse outcome, which depends on factors such as the extent of the procedure e.g., an extensive tumor resection or a minor hernia repair; as well as surgical situation e.g., acute or planned surgical procedure; level of experience of the surgeon. Furthermore, it depends on the medical health status of the patient. Diabetes, smoking, and atherosclerosis predisposes for a reduced perfusion and consequently an increased risk for impaired wound healing.

The general health anesthesiologic risk of the patient can be evaluated with the ASA (American Society of Anesthesiologists physical status) classification, which was introduced in the early 1940s (83). The ASA classification provides a preoperative prediction of risks for postoperative complications.

The five grade Clavien-Dindo classification was introduced in 1992 and has standardized reporting of surgical complications (84). This classification focuses on the medical aspect and is based on the level of therapy that is needed to treat a complication. The purpose of this classification was to avoid subjective interpretations of the complications from the patient or the physician, and instead record objective data. Since the introduction, this classification has been widely used as an instrument to grade the severity of postoperative complications (85).

Postoperative complications can also be subdivided into perioperative adverse events, such as nerve lesion, bleeding, or organ injury; and postoperative adverse events such as urinary retention, hematoma, surgical site infection and acute postoperative inguinal pain (APIP). Systemic postoperative complications such as respiratory difficulties, pneumothorax, pneumonia, sepsis, thromboembolic diseases, or renal failures may be even more complex but are not addressed in this thesis.

Hematoma

The definition of a postoperative hematoma is a blood collection at the site of the surgical procedure. Intraoperative bleeding can be managed immediately during the operation, but a slow bleeding following the procedure can result in a later hematoma. Postoperative hematomas after an inguinal hernia repair are often reported as secondary outcomes in the literature (2).

The reported incidence of postoperative hematomas following open repair is higher compared to endo-laparoscopic repairs (86). Symptoms such as subcutaneous swelling, pain and change of skin color are more common with hematomas after an open repair. A postoperative hematoma can cause a delayed healing, and increased risk for infection in the surgical site as well as seroma and excessive scar tissue formation.

Surgical Site Infection (SSI)

A postoperative infection in the surgical wound, often referred to as surgical site infection (SSI), can cause a delayed healing, rupture of the wound, excessive scar tissue formation and an increased risk for hernia recurrence (87). The risk factors for surgical site infections can also be separated into patient associated risk factors such as immunodepression, diabetes, obesity, and smoking (88), and surgery associated risk factors such as open hernia repair (89), and a present incarcerated hernia (90).

Postoperative Pain

Persistent pain is defined as pain for three months or longer (91). The international Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in the terms of such damage" (92). A functional classification of pain is acute or persistent pain. Acute pain is often caused by tissue damage while persistent pain can be entertained by an upregulated pain signaling system without any present stimulus. Pain is classified as nociceptive, neuropathic, psychological, or unknown. The cause of the perceived pain is important for decision on therapy.

The ilioinguinal and ileohypogastric nerves as well as the genital branch of the genitofemoral nerve may interfere with surgical dissection during an open anterior approach. Endo-laparoscopic dissection may interfere with the course of the femoral branch of the genitofemoral nerve or the lateral femoral cutaneous nerve in the iliac fossa.

Acute Postoperative Inguinal Pain (APIP)

APIP may increase the risk for a delayed mobilization resulting in venous thromboembolism and opioid-associated complications in the short-term perspective (93). Long-term risks are development of a CPIP which has been reported in 10-50% (91). Preoperative pain is a known predictor for both high-intensity postoperative pain and chronic postoperative pain (91, 94). Both pre-existing pain and acute postoperative pain have shown to predispose for chronic postoperative inguinal pain (95, 96).

Chronic Postoperative Inguinal Pain (CPIP)

Risk factors for developing CPIP can be sorted into either patient related risk factors such as age, sex, BMI, preoperative pain, and specific genotypes or as surgery related risk factors such as surgical approach, nerve handling, choice of mesh material and mesh fixation method. Several studies with the outcome chronic pain have been conducted. Young age, female sex, acute preoperative pain and specific genotypes have shown an association with CPIP (97-100). Open repair, hernia recurrence, postoperative complications such as acute postoperative pain, hematoma and SSI, have also been suggested, although their effect on the risk for CPIP have varied in the different studies (4, 95, 101, 102).

OUTCOME MEASUREMENT INSTRUMENTS

Outcome indicators can be either “objectively” measurable, surgeon-assessed, such as recurrence or postoperative complications; or patient-experienced such as HRQoL and pain. Surgery-assessed indicators can be recorded by postoperative follow-ups or by quality registers. Patient-experienced indicators can be recorded by patient registered outcome measurement forms (PROM).

1.5 QUALITY REGISTERS

National quality registers are typically data collected regarding a specific field or specific patient group such as patients with heart diseases, a pediatric population or patients undergoing an inguinal hernia repair. The advantage of a national register is the possibility to provide access to a large collection of information which reflect population-based conditions. As opposed to RCT settings, where the patient group may be narrowly selected, national quality registers provide unselected data. This allows for quality control as well as research that can complement the resource intense randomized studies in heavily controlled environments. The prospective inguinal hernia registration was pioneered in Sweden in 1992. There are today several national and regional registers available (103).

1.5.1 The Swedish Hernia Register (SHR)

The Swedish Hernia Register (SHR) was founded and introduced 1992 (14). Inguinal hernia repairs performed in adults, 15 years or older, in Sweden are recorded in the register. Today the register covers over 95% of all inguinal hernia repairs in Sweden and the register contains data on more than 350,000 performed inguinal hernia repairs (104). Approximately 16,000 inguinal hernia repairs are performed and registered in Sweden annually.

The register protocol collects data of the medical situation, performed operation, anatomical details, repair technique, prosthesis material and postoperative adverse events occurring within 30 days after the operation (105). The SHR is continuously evaluated and validated and develops regularly (104). The register protocol was updated 2015 with introduction of more detailed information regarding occurring postoperative complications, including grading of the severity using the Clavien-Dindo classification.

1.5.2 Other National and regional registers

The Danish Hernia Database (DHD) was founded in 1998 and includes data on both inguinal and ventral hernia repairs. The DHD is the only hernia register with a national compulsory participation by all surgeons performing inguinal hernia repairs. HerniaMed, a network of surgeons with a particular interest in hernia surgery, collects data on inguinal and abdominal wall hernias by an online registry in Germany, Italy, Austria, and Switzerland. The EuraHS register focusing on ventral abdominal wall hernias was launched by hernia surgeons from

several European countries, as an online registry platform in 2012, based on the EHS guidelines and including the novel EuraHS QoL questionnaire. The American Hernia Society Quality Collaborative (AHSQC) register was developed by a specialty group appointed by the American Hernia Society. Initial disease areas were incisional and parastomal hernias (106-109).

1.5.3 Patient Recorded Outcome Measurements (PROM)

The Patient Reporting of Outcome Measures (PROMs) is a method of evaluation from the patients perspective using a brief, self-completed form or questionnaire (110). There are numerous different locally and nationally designed outcome measurement instruments where the patient grades their subjective experience of the outcome following a treatment. The benefit with PROM questionnaires is the possibility to receive the patient's direct experience of outcome without filtering the data by a researcher or care giver. PROM questionnaires can be designed as paper forms or digital web-based forms (111).

1.5.4 The Inguinal Pain Questionnaire (IPQ)

The Inguinal Pain Questionnaire (IPQ) was developed and validated as a specific assessment questionnaire for evaluating groin pain associated with inguinal hernia and inguinal hernia repair (112). Pain intensity is assessed using a seven-step fixed point rating scale with steps operationally linked to pain behavior rather than to numbers or verbal pain descriptors and with additional monitoring of pain duration. The IPQ form is illustrated in Figure 10.

Pain is graded with a seven-step ordinal scale in the questionnaire *(0: no pain, 1: pain can be ignored, 2: pain cannot be ignored but does not affect everyday activities, 3: pain cannot be ignored and affects everyday activities, 4: pain prevents most activities, 5: pain necessitates bed rest, 6: pain requires immediate medical attention).*

Questions regarding the difficulty to perform six specific daily activities due to pain in the repaired groin are included (yes/no), as well as presence and intensity of preoperative pain, and furthermore a question regarding presence of testicular pain on the side of the inguinal repair. The IPQ has been used in several scientific studies and is widely referred to. It covers several aspects of groin pain and pain behavior which makes it well-suited for research situations.

1.5.5 Other specific questionnaires

There are several available questionnaires and forms regarding outcomes following specific diseases or specific treatment methods.

Carolinas Comfort Scale (CCS) questionnaire was developed in 2007 in the US as a quality-of-life assessment instrument specified for patients undergoing hernia repair with mesh reinforcement. Evaluation of the CCS has shown that it provides a more disease specific

assessment of quality-of-life among hernia patients than the SF-36 questionnaire (113). The questionnaire includes 23 items measuring severity of pain, sensation, and movement limitations from the mesh in eight categories.

The EuraHS QoL questionnaire was developed 2009 by a multinational group of experts as a numeric three-dimensional QoL instrument designed for both inguinal and abdominal wall hernias. It is included in the EuraHS platform which is an international web-based hernia register platform (108).

The McGill Pain Questionnaire was developed in 1971 and is a validated instrument for measuring general pain and has since then been widely used in a variety of clinical situations (114). The benefit of the instrument is the long and widespread use which make it suitable as a reference instrument. It is on the other hand not specific for inguinal pain. A short form was developed in 1987 (115), and was translated to Swedish in 1994 (116).

1.6 EUROPEAN HERNIA SOCIETY (EHS) GUIDELINES

The European Hernia Society commissioned a working group of hernia specialists to present guidelines regarding management of inguinal hernia and the HerniaSurge Group was founded (2). The purpose of the evidence-based guidelines was to compile present knowledge to use in daily clinical practice. Evidence from the present literature and outcomes based on register studies were analyzed. The present guidelines were published in 2018 and clarifies several aspects of assessment methods, surgical repair techniques and postoperative regimens.

The guidelines state that symptomatic inguinal hernias should be repaired surgically, while asymptomatic hernias in male patients may be managed with "watchful waiting". Mesh repair is recommended as first choice method, either by open anterior or endo-laparoscopic technique, depending on available resources and expertise. “Surgical treatment should be tailored to the surgeon's expertise, patient- and hernia-related characteristics and local/national resources.”

Furthermore, patient health-related, lifestyle and social factors should all influence the shared decision-making process leading up to hernia management. It is recommended that surgeons/surgical services provide both anterior and posterior approach options. Lichtenstein and endo-laparoscopic repair are the best evaluated methods provided that resources and expertise are available,

It is concluded that endo-laparoscopic methods provide quicker recovery time, decreased risk for chronic pain as well as being cost effective. The EHS guidelines suggest stratifying inguinal hernia patients for tailored treatment, research, and clinical evaluation. It provides in total 136 statements and 88 recommendations and constitutes an important consensus statement of several basic steps in inguinal hernia management.

2 AIMS OF THE THESIS

The overall aim of this thesis was to improve the understanding of the etiology of adverse outcomes following inguinal hernia repair such as postoperative chronic pain and risk for a subsequent contralateral repair following a unilateral inguinal hernia repair.

Specific aims were as follows:

Paper I

The purpose of this study was to determine if there is a relationship between specific postoperative complications and risk for chronic pain after open inguinal hernia repair.

Paper II

The aim of this study was to develop and a condensed version of the IPQ in order to facilitate its use in daily clinical practice, and to evaluate if it provided outcome values consistent with the IPQ.

Paper III

The purpose of this study was to further clarify the association between specific postoperative complications and the risk of developing long-term groin pain.

Paper IV

The aim of the fourth study was to investigate the incidence as well as factors predictive for a subsequent hernia repair on the contralateral side following a primary unilateral hernia repair.

3 MATERIALS AND METHODS

All four studies included in this thesis used study populations from the Swedish Hernia Register. Advantages with a population-based material include the possibility to collect data from a large population as well as the generalizability of the results to the normative population.

3.1 PAPER I

This was an observational study investigating aspects of CPIP following inguinal hernia repair. The design was a long-term follow-up of a previously studied cohort (117), with the aim to investigate the association between patient-reported postoperative complications and the prevalence of long-term postoperative pain. The study sample was a patient cohort of 1448 individuals that had undergone inguinal hernia repair during a two-month period in 2002 (117).

Participants were originally identified in the SHR and responded in the previous study to a locally designed questionnaire regarding self-reported postoperative complications. One or more complications within the first month of the hernia repair was reported by 23.8%. The most common postoperative complications were hematoma, acute severe pain in the operated groin, testicular pain, and surgical site infection (117).

Surgical technique was limited to open repairs due to differences in the pattern of post-operative complications between open and endo-laparoscopic repairs, and to the fact that only 2% of repairs during the study period were performed using endo-laparoscopic technique.

Recruited participants that had responded to the previous complication questionnaire were eligible for participation. After exclusion of endo-laparoscopic repairs, deceased and emigrated patients there were 1155 individuals included in the study. Recruitment and participation are shown in Figure 9. Included participants were asked to complete the IPQ by mail. One reminder was sent to non-responders. Results from the IPQ questionnaire were linked individually to the complication data from the preceding study.

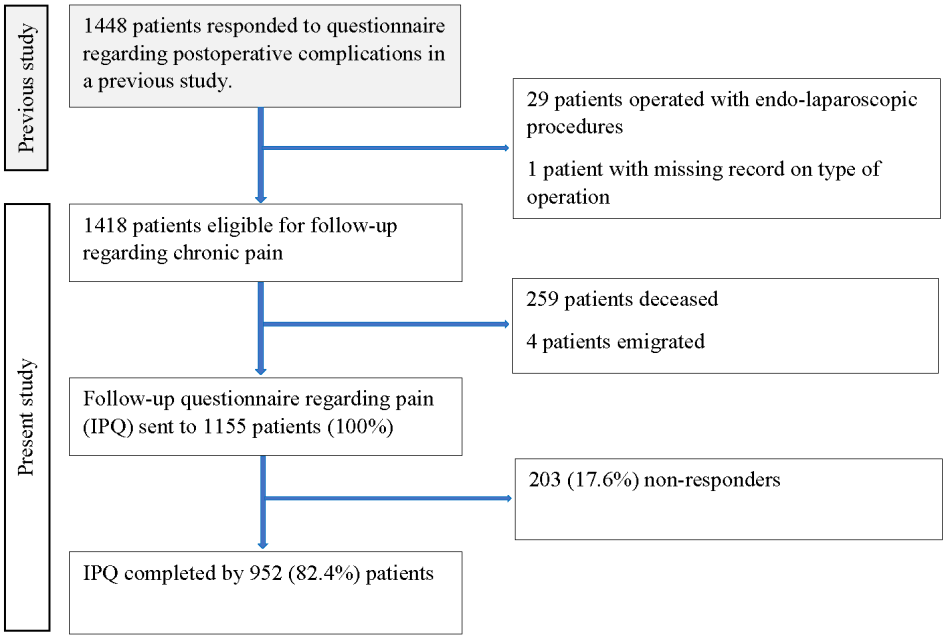


Figure 9. Recruitment procedure with inclusion and exclusion for paper I.

Statistical analyses

The primary outcomes "pain in the operated groin" and "testicular pain on the side of hernia surgery" were analyzed with separate logistic regression models against possible risk factors. The outcome "pain" was defined as answer to the IPQ item "pain intensity past week" and divided into "no pain" versus all other gradings of pain intensity.

Possible risk factors were: sex; age at the time for hernia repair; pre-operative pain (reported retrospectively in the IPQ questionnaire in a seven-grade ordinal scale); method of anesthesia (local, regional or general); method of hernia repair (anterior mesh, posterior mesh, plug repair or suture repair); suture fixation material (non-absorbable, slowly absorbable or rapidly absorbable) as well as patient reported postoperative complications (hematoma, infection, wound dehiscence, severe postoperative pain, thrombosis, testicular pain, anesthetic complications, urinary tract complications, voiding problems and constipation).

Potential risk factors were analyzed with univariable logistic regression models. Risk factors showing significance in the univariable analysis were included in the multivariable logistic regression model together with the already established risk factors age and sex.

3.2 PAPER II

The design of the short form of the IPQ was based on experience from using the original version of IPQ. After evaluation of several studies using the original version of IPQ, there were two main items emerging as the two most clinically relevant questions for evaluating postoperative inguinal pain. Identified items were extracted from the original IPQ to design the sf-IPQ.

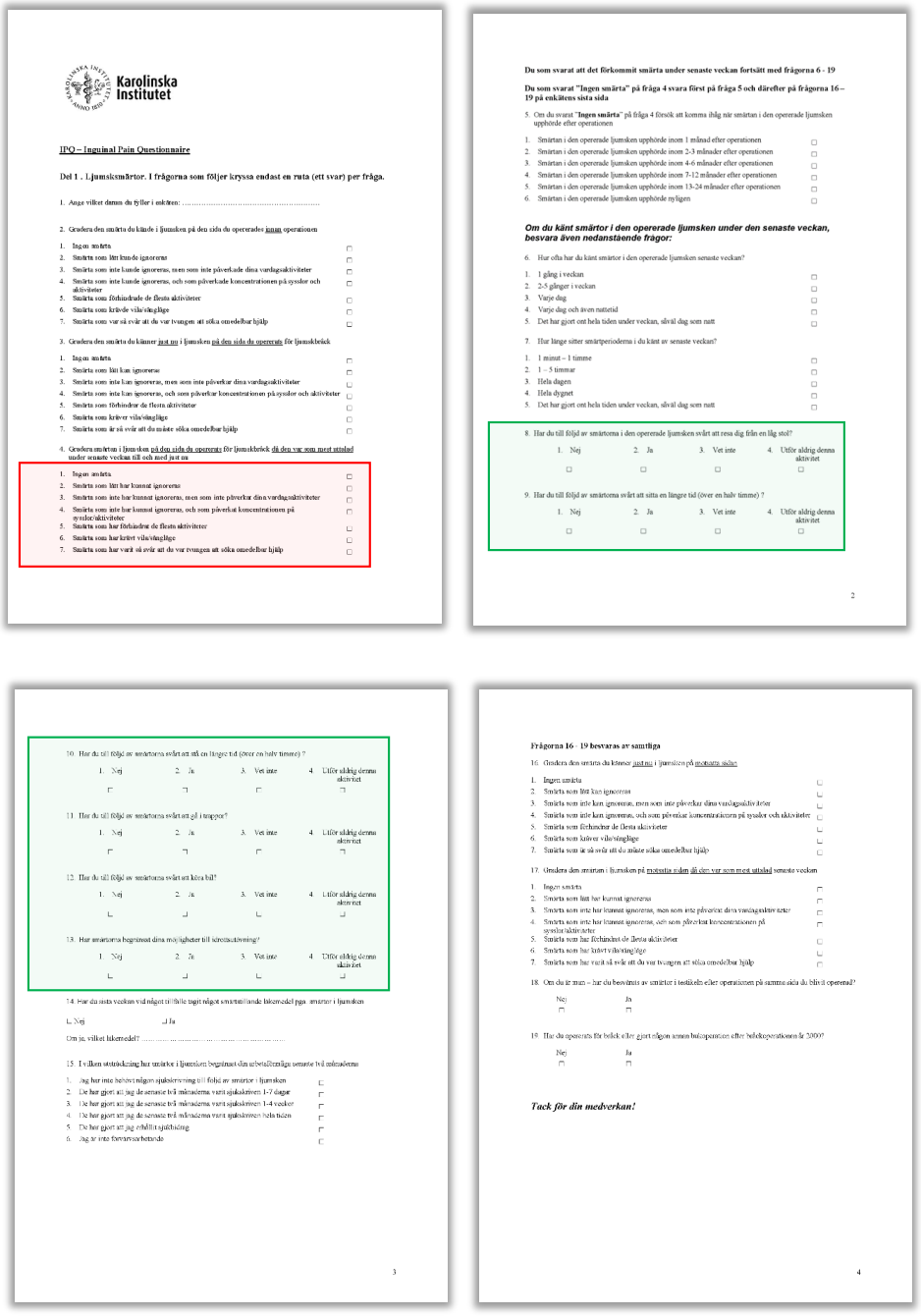
The first item was a question regarding pain intensity which was transferred from the IPQ without any changes, while the second item was a compilation of six separate questions regarding inguinal pain interference with different daily activities. The final sf-IPQ thus consisted of two questions on a one-page form which took less than a minute to complete.

The process of designing the sf-IPQ is illustrated with the original IPQ including the two main items marked in red and green in Figure 10. The final sf-IPQ is shown in Figure 11.

This study was designed as a cross-sectional analysis of a cohort of 400 patients with hernia repairs consecutively registered in the SHR during March 2013. Three years later, during spring 2016, eligible participants received a letter with information regarding the study and a form for written consent to participate as well as three questionnaires assessing pain: the original IPQ (112); the sf-IPQ; and the short form of the McGill Pain Questionnaire (SF-MPQ) (115).

The purpose was to evaluate if sf-IPQ registered the relevant modality, pain, and the comparison reflected the agreement in perception of pain between these two instruments. SF-MPQ was included as a reference tool to compare the distribution of registered pain as well as any differences between the sf-IPQ and SF-MPQ.

After exclusion of non-responders, deceased patients, and incomplete questionnaires there were 279 valid responses available for analysis, illustrated in Figure 14.



IPQ – Inguinal Pain Questionnaire

Del 1 . Ljumsksmärtor. I frågorna som följer kryssa endast en ruta (ett svar) per fråga.

1. Ange vilket datum du fyller i enkäten: ……

2. Gradera den smärta du kände i ljumsken på den sida du opererades innan operationen

1. Ingen smärta
2. Smärta som lätt kunde ignoreras
3. Smärta som inte kunde ignoreras, men som inte påverkade dina vardagsaktiviteter
4. Smärta som inte kunde ignoreras, och som påverkade koncentrationen på sysslor och aktiviteter
5. Smärta som förhindrade de flesta aktiviteter
6. Smärta som krävde vila/sängläge
7. Smärta som var så svår att du var tvungen att söka omedelbar hjälp

3. Gradera den smärta du känner just nu i ljumsken på den sida du opererats för ljumskbrråck

1. Ingen smärta
2. Smärta som lätt kan ignoreras
3. Smärta som inte kan ignoreras, men som inte påverkar dina vardagsaktiviteter
4. Smärta som inte kan ignoreras, och som påverkar koncentrationen på sysslor och aktiviteter
5. Smärta som förhindrar de flesta aktiviteter
6. Smärta som kräver vila/sängläge
7. Smärta som är så svår att du måste söka omedelbar hjälp

4. Gradera smärtan i ljumsken på den sida du opererats för ljumskbrråck då den var som mest utbredd under senaste veckan till och med just nu

1. Ingen smärta
2. Smärta som lätt kan ignoreras
3. Smärta som inte har kunnat ignoreras, men som inte påverkar dina vardagsaktiviteter
4. Smärta som inte har kunnat ignoreras, och som påverkat koncentrationen på sysslor/aktiviteter
5. Smärta som har förhindrat de flesta aktiviteter
6. Smärta som har krävt vila/sängläge
7. Smärta som har varit så svår att du var tvungen att söka omedelbar hjälp

Du som svarat att det förkommit smärta under senaste veckan fortsätt med frågorna 6 - 19

Du som svarat "Ingen smärta" på fråga 4 svara först på fråga 5 och därefter på frågorna 16 – 19 på enkätens sista sida

5. Om du svarat "**Ingen smärta**" på fråga 4 försök att komma ihåg när smärtan i den opererade ljumsken upphörde efter operationen

1. Smärtan i den opererade ljumsken upphörde inom 1 månad efter operationen
2. Smärtan i den opererade ljumsken upphörde inom 2-3 månader efter operationen
3. Smärtan i den opererade ljumsken upphörde inom 4-6 månader efter operationen
4. Smärtan i den opererade ljumsken upphörde inom 7-12 månader efter operationen
5. Smärtan i den opererade ljumsken upphörde inom 13-24 månader efter operationen
6. Smärtan i den opererade ljumsken upphörde nyligen

Om du känt smärtor i den opererade ljumsken under den senaste veckan, besvara även nedanstående frågor:

6. Hur ofta har du känt smärtor i den opererade ljumsken senaste veckan?

1. 1 gång i veckan
2. 2-5 gånger i veckan
3. Varje dag
4. Varje dag och även nattetid
5. Det har gjort ont hela tiden under veckan, såväl dag som natt

7. Hur länge sitter smärtperioderna i du känt av senaste veckan?

1. 1 minut – 1 timme
2. 1 – 5 timmar
3. Hela dagen
4. Hela dygnet
5. Det har gjort ont hela tiden under veckan, såväl dag som natt

8. Har du till följd av smärtorna i den opererade ljumsken svårt att resa dig från en låg stol?

1. Nej 2. Ja 3. Vet inte 4. Utför aldrig denna aktivitet

9. Har du till följd av smärtorna svårt att sitta en längre tid (över en halv timme) ?

1. Nej 2. Ja 3. Vet inte 4. Utför aldrig denna aktivitet

10. Har du till följd av smärtorna svårt att stå en längre tid (över en halv timme) ?

1. Nej 2. Ja 3. Vet inte 4. Utför aldrig denna aktivitet

11. Har du till följd av smärtorna svårt att gå i trappor?

1. Nej 2. Ja 3. Vet inte 4. Utför aldrig denna aktivitet

12. Har du till följd av smärtorna svårt att köra bil?

1. Nej 2. Ja 3. Vet inte 4. Utför aldrig denna aktivitet

13. Har smärtorna begränsat dina möjligheter till idrottsutövning?

1. Nej 2. Ja 3. Vet inte 4. Utför aldrig denna aktivitet

14. Har du sista veckan vid något tillfälle tagit något smärtstillande läkemedel pga. smärtor i ljumsken

Nej Ja

Om ja, vilket läkemedel? ……

15. I vilken utsträckning har smärtor i ljumsken begränsat din arbetsförmåga senaste två månaderna

1. Jag har inte behövt någon sjukskrivning till följd av smärtor i ljumsken
2. De har gjort att jag de senaste två månaderna varit sjukskriven 1-7 dagar
3. De har gjort att jag de senaste två månaderna varit sjukskriven 1-4 veckor
4. De har gjort att jag de senaste två månaderna varit sjukskriven hela tiden
5. De har gjort att jag erhållit sjukbidrag
6. Jag är inte förvärvsarbetande

Frågorna 16 - 19 besvaras av samtliga

16. Gradera den smärta du känner just nu i ljumsken på motsatta sidan

1. Ingen smärta
2. Smärta som lätt kan ignoreras
3. Smärta som inte kan ignoreras, men som inte påverkar dina vardagsaktiviteter
4. Smärta som inte kan ignoreras, och som påverkar koncentrationen på sysslor och aktiviteter
5. Smärta som förhindrar de flesta aktiviteter
6. Smärta som kräver vila/sängläge
7. Smärta som är så svår att du måste söka omedelbar hjälp

17. Gradera den smärtan i ljumsken på motsatta sidan då den var som mest utbredd senaste veckan

1. Ingen smärta
2. Smärta som lätt har kunnat ignoreras
3. Smärta som inte har kunnat ignoreras, men som inte påverkat dina vardagsaktiviteter
4. Smärta som inte har kunnat ignoreras, och som påverkat koncentrationen på sysslor/aktiviteter
5. Smärta som har förhindrat de flesta aktiviteter
6. Smärta som har krävt vila/sängläge
7. Smärta som har varit så svår att du var tvungen att söka omedelbar hjälp

18. Om du är man – har du besvärats av smärtor i testikeln eller operationen på samma sida du blivit opererad?

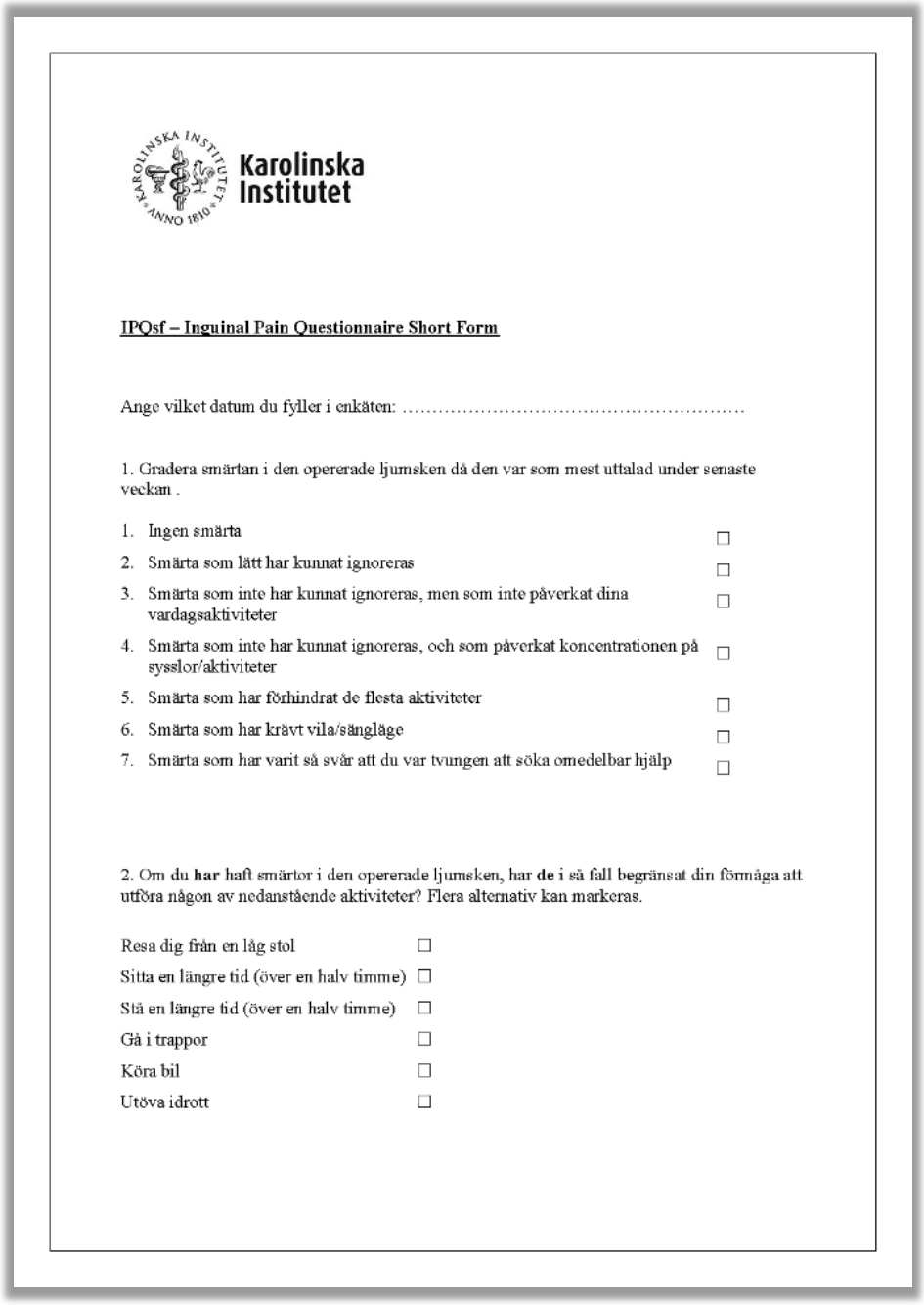
Nej Ja

19. Har du opererats för bråck eller gjort någon annan bukoperation efter bråckoperationen år 2000?

Nej Ja

Tack för din medverkan!

Figure 10. The original IPQ consisting of four pages and including 19 questions. Question 4 (marked red) was transferred without changes to item 1 in the sf-IPQ. Questions 8-13 (marked green) were compiled to item 2 in the sf-IPQ.



Karolinska Institutet

IPQsf – Inguinal Pain Questionnaire Short Form

Ange vilket datum du fyller i enkäten: .....

1. Gradera smärtan i den opererade ljumsken då den var som mest uttalad under senaste veckan .

1. Ingen smärta ☐
2. Smärta som lätt har kunnat ignoreras ☐
3. Smärta som inte har kunnat ignoreras, men som inte påverkat dina vardagsaktiviteter ☐
4. Smärta som inte har kunnat ignoreras, och som påverkat koncentrationen på sysslor/aktiviteter ☐
5. Smärta som har förhindrat de flesta aktiviteter ☐
6. Smärta som har krävt vila/sängläge ☐
7. Smärta som har varit så svår att du var tvungen att söka omedelbar hjälp ☐

2. Om du **har** haft smärtor i den opererade ljumsken, har **de** i så fall begränsat din förmåga att utföra någon av nedanstående aktiviteter? Flera alternativ kan markeras.

Resa dig från en låg stol ☐
Sitta en längre tid (över en halv timme) ☐
Stå en längre tid (över en halv timme) ☐
Gå i trappor ☐
Köra bil ☐
Utöva idrott ☐

Figure 11. The single page sf-IPQ including two items. Item 1 was transferred from the original IPQ without changes. Item 2 was created by a compilation of questions 8-13 in the original IPQ.

At three years after surgery the postoperative healing process was assumed to be completed and to not have any impact on the presence of pain. The questionnaires were sorted in two different orders where half of the participants received questionnaires in the sequence: IPQ, Sf-IPQ and SF-MPQ while the other half received questionnaires in the sequence: Sf-IPQ, IPQ and SF-MPQ.

A scoring system, previously defined for the original IPQ, was used to quantify the severity of registered pain in the Sf-IPQ (37). In item 1, the worst level of pain during the past week was registered, in a scale from 0 points (no pain) to 6 points (pain so severe that prompt medical advice was sought). In item 2, six different activities were listed where each activity limited by groin pain rendered one point.

The total score range was thus 0-12 points. Score 0-2 was considered as negligible pain while score 3-12 was considered as pain interfering with daily activities for both the IPQ and the Sf-IPQ. Returned questionnaires were considered as valid for inclusion in the study if all items necessary for calculating the scores for both IPQ and sf-IPQ were completed.

Statistical analyses

Statistical analyses on this equivalent study were based on 80% power, 95% significance level and 15% expected dropouts. Based on the power calculation, 379 participants, including the expected 15% dropouts, were required. The IPQ and sf-IPQ scores were compared using three different analysis methods with the purpose to study the association from three different views.

Cohen's kappa was used to analyze agreement regarding the frequency of substantial pain. The intraclass correlation coefficient test (ICC) with the two-way mixed effects model (type ICC[3,1]) was used to analyze the correlation and consistency of the pain score generated by the questionnaires (118). McNemar's test was used to analyze any systemic incoherence between the tests in grading pain as substantial or negligible.

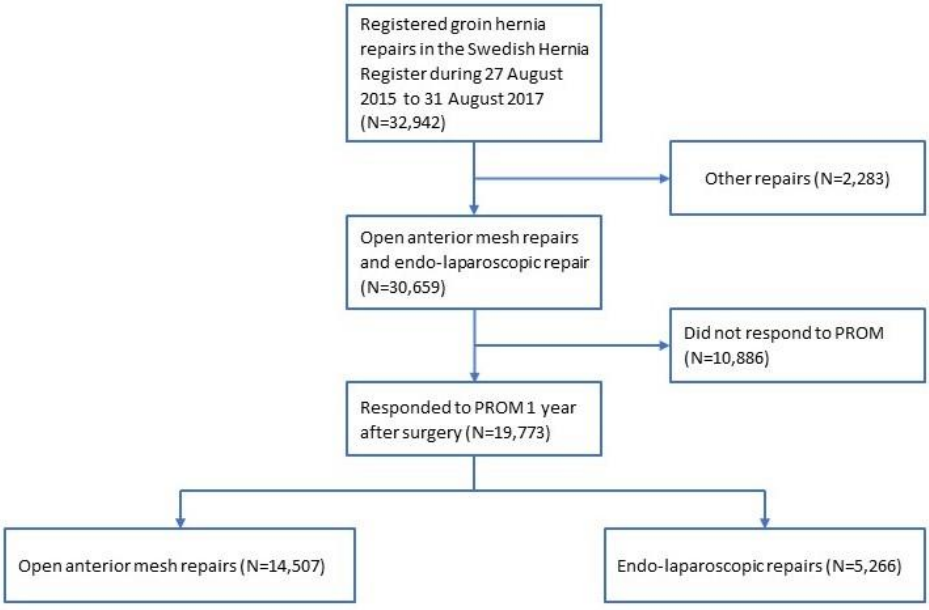
The responder's v/s non-responders as well as the two different questionnaire order groups were compared with respect to the factors age, sex, surgical repair technique, method of anesthesia, emergency hernia repair and bilateral hernia repair. Differences between the groups were analyzed with Mann-Whitney U test and Pearson's Chi-square test. The distribution of SF-MPQ score associated to the sf-IPQ and IPQ scores was visualized in a population distribution diagram showing the pain perception of the two instruments.

3.3 PAPER III

This study was designed as a population-based cohort study with prospective data obtained from the SHR. Collected information included patient characteristics, hernia characteristics, method of repair, details of the surgical procedure and information regarding postoperative complications known to the clinic and occurring within 30 days after surgery. Open anterior mesh repairs and endo-laparoscopic repairs were considered eligible for inclusion.

The study period was August 27, 2015, to August 31, 2017. In August 2015, the SHR registry form was updated to include more detailed data on postoperative complications. Information on present CPIP was collected using a PROM questionnaire that was developed by the SHR and was distributed one year after surgery, to all patients operated on between September 2012 and August 2017. It inquired about persisting inguinal pain, groin complaints, perceived result of the operation and the overall experience of the surgical procedure.

Inclusion criteria were a hernia repair registered in the SHR during the study period and a completed PROM questionnaire. The questionnaire was sent and administrated by the SHR. No reminders were sent to non-responders according to the large number of patients and to the SHR design. Inclusion procedure is illustrated in Figure 12.



Figur 12. Recruitment, inclusion, and exclusion criteria. (Reprinted from Olsson et al, Hernia 2021, with permission from Springer.)

Open anterior mesh repairs and endo-laparoscopic repairs were analyzed as separate groups, due to the expected differences in postoperative complications between the two groups. The primary outcome was the reported intensity grade of inguinal pain during the past week registered in the PROM questionnaire. The pain registration in the PROM questionnaire consisted of a seven-grade scale with rating of persistent pain on the side of operation, similar to the IPQ questions. The grading of pain is shown in Table 1.

0	No pain
1	Pain can be ignored
2	Pain cannot be ignored but does not affect daily activities
3	Pain cannot be ignored and affect daily activities
4	Pain prevents most activities
5	Pain necessitates bed rest
6	Pain requires immediate medical attention

Table 1. The pain intensity grades in the PROM questionnaire.

Evaluated postoperative complications included all local adverse events in the operated groin that hypothetically could increase the risk for CPIP. Systemic postoperative complications such as cardiovascular events or systemic infections were not analyzed. Rare complications such as postoperatively diagnosed iatrogenic injuries to the testis, bladder or intestine were not analyzed due to the very rare occasions. Analyzed postoperative complications were grouped into five categories: hematoma, surgical site infection, seroma, urinary tract complication and acute postoperative pain, illustrated in Table 2.

Statistical analyses

Ordered logistic regression analyses were performed, with self-reported pain one year after surgery as the dependent variable. Self-reported pain was obtained from the seven-grade scale in the PROM questionnaire. Assessed potential risk factors were the postoperative complication categories (hematoma, surgical site infection, urinary tract complication, seroma, and acute postoperative pain) as well as age, sex, smoking habits, and BMI.

Risk factors that showed an increased risk for CPIP in univariable analyses were included in the multivariable analysis. Separate models were used for open anterior mesh repair and endo-laparoscopic repair.

Characteristics for non-responders were compared to the responders regarding age, sex, smoking habits, BMI as well as surgical technique and reported postoperative complications. Chi-square test was used to analyze categorical variables while t-test was used for analyzing continuous variables.

Postoperative complications ≤30 days	**Definition in the SHR**	**Category of complication**
Recurrence	Recurrent hernia on the same side.	
Urinary retention	Urinary retention requiring catheterisation.	Urinary Tract Complication
Superficial hematoma	Bleeding from a minor vessel in the incision or dissection area, ventral of the transversalis fascia, incl port incision.	Hematoma
Deep hematoma	Bleeding from a major vessel intraabdominal or preperitoneal dorsal of the transversalis fascia.	Hematoma
Superficial surgical site infection	Wound infection in the surgical incision or port incision.	Surgical Site Infection
Deep surgical site infection/abscess	Infection dorsal of the transversalis fascia, preperitoneal or intraabdominal.	Surgical Site Infection
Systemic infection	Sepsis.	
Pain	Severe pain demanding prolonged pharmacological treatment, readmission, or reoperation.	Acute Postoperative Pain
Intestinal obstruction	Intestinal obstruction.	
Intestinal Damage	Iatrogenic intestinal damage diagnosed postoperatively.	
Urinary bladder damage	Iatrogenic bladder damage diagnosed postoperatively.	
Testicular damage	Iatrogenic damage on vas deferens, testicular vessels, pain/atrophy of the testicle diagnosed postoperatively.	
Cardiovascular event	Cardio or pulmonary event occurring postoperatively.	
Seroma	Collection of fluid (blood, lymph) expanding the space of the pseudo hernia.	Seroma
Death	Death occurring within 30 days postoperatively without any of above complications	

Table 2. showing the arrangement of postoperative complications into the categories: urinary tract complications, hematomas, surgical site infection, acute postoperative pain and seroma.

3.4 PAPER IV

This population-based prospective cohort study comprised data from the SHR on primary inguinal hernia repairs carried out January 2007 to December 2019. Inclusion criteria were adult patients (≥ 18 years at time for surgery) undergoing a primary groin (lateral, medial, femoral, or combined) hernia repair. Other hernias or indications for surgery, such as sportsman hernia or chronic pain were excluded. Recruitment procedure with inclusion and exclusion criteria is shown in Figure 13.

To ensure that only the first groin hernia repair was registered as an index repair, data for 1994-2006 was also obtained from the SHR and participants with a registered previous ipsilateral or contralateral hernia repair during this period were excluded. Primary bilateral hernia repairs were included and studied as a separate subgroup. The cohort of unilaterally operated patients was further investigated regarding any subsequent contralateral repair.

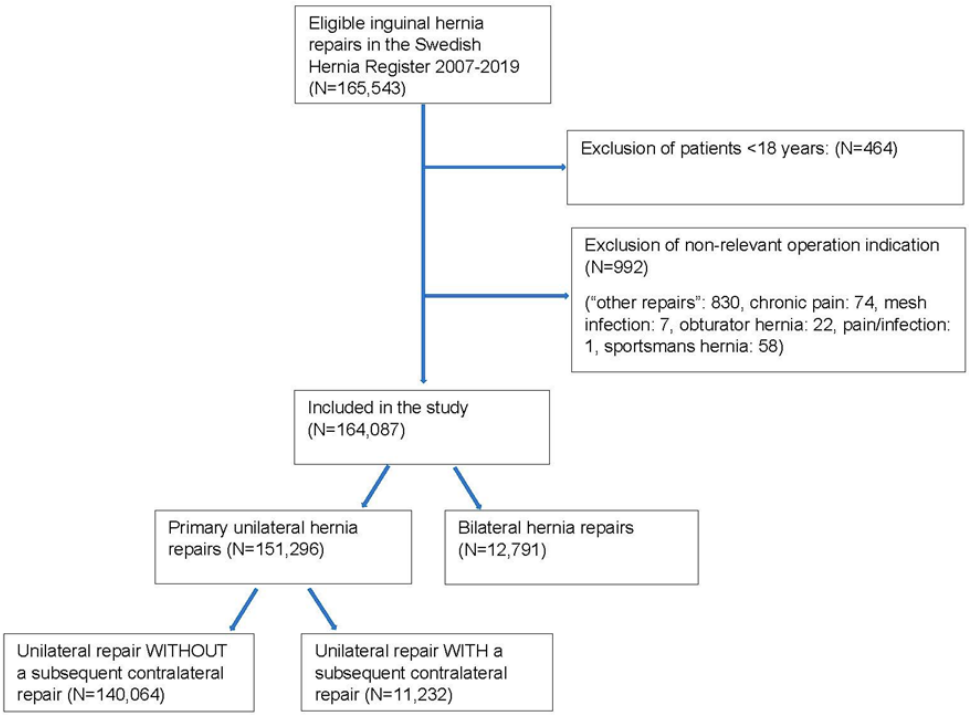


Figure 13. Recruitment process with inclusion and exclusion criteria.

Age was analyzed as a continuous variable. BMI was divided into the four categories underweight (BMI <18.5), normal weight (BMI 18.5-25), overweight (BMI 25-30), obesity + morbid obesity (BMI >30). Obesity and morbid obesity formed a common category due to the low number of morbidly obese patients. ASA classification score was grouped into the categories ASA 1, ASA 2, ASA 3, and ASA 4 + ASA 5. ASA 4 + 5 was combined into one category due to the low frequency in the studied cohort.

Additional variables were: side (left/right); emergency surgery (yes/no); hernia anatomy (medial/lateral/femoral or combined – any combination of the aforementioned defects); hernia defect size (<1.5 cm/ 1.5-3 cm/ >3 cm); sliding hernia (yes/no). The surgical methods were categorized into open or endo-laparoscopic approach. Endo-laparoscopic repairs were subdivided into TEP or TAPP repairs.

Statistical analyses

The primary endpoint was a later registered contralateral hernia repair. Factors regarded as potential risk factors for a future contralateral inguinal hernia repair during the study period were analyzed with a univariable Cox proportional hazards regression analysis. Considered risk factors were age, sex, BMI, ASA classification, side of repair, hernia anatomy, hernia defect size, presence of a sliding hernia as well as method of repair.

Factors identified as predictors for a later contralateral repair were included in a multivariable Cox proportional hazard model as independent variables. The risk for a later contralateral hernia repair following a unilateral hernia repair was calculated. Participants were followed until a contralateral hernia repair was registered (the terminal event), death (censored event) or the end of follow-up time (censored event).

3.5 ETHICAL CONSIDERATIONS

Ethical considerations were discussed during the initial phase of planning for each study.

Study participants were recruited from the SHR. All patients operated and registered in the SHR are to be informed and give consent to be registered in the SHR. Data in the SHR is considered sensitive personal data since it concerns health issues. When possible, data was anonymized by the SHR prior to extraction. In the studies where full identification possibilities were needed to be able to administer questionnaires to the eligible study persons pseudonymization was performed as soon as possible and analyses were performed on pseudonymous data, which was stored safely after completed analyses.

In study I and II, participants received written information regarding the studies and actively completed and returned responses to questionnaires together with a written consent to participate in the studies. Questions in the survey could be perceived as a breach of privacy,

while answering the questionnaires offered an occasion to express satisfaction or dissatisfaction with the treatment in a way that was not otherwise routinely provided.

Participation in study III and IV entailed no physical risks as it only involved analyses of already existing data. The risk of privacy breaches was considered low as only anonymized data were used for analysis.

There was no personal benefit from participating in the studies, but a possibility that knowledge gathered will benefit future patients with groin hernias (either other patients or the study participants themselves in case of contralateral hernia or a recurrence). The opportunity to give feedback on the given treatment could possibly ameliorate feelings of privacy infringement.

Potential results from the studies were considered to contribute with increased knowledge regarding the natural course of inguinal hernia development, possible causes of postoperative adverse events, and risk factors for subsequent contralateral hernias. This knowledge could benefit a large proportion of the population and justify the risk for experienced privacy breach.

Ethical approval for Paper I was granted by the Regional Ethics Review Board in Stockholm (no. 2010/583-31/2).

Ethics approval for Paper II was granted by the Regional Ethics Review Board in Stockholm (No. 2009/44- 31/3).

Ethical approval for the Paper III was granted by the Regional Ethical Review Board in Stockholm (dnr: 2019–02,487).

Ethical approval for Paper IV was granted by the Swedish Ethical Review Authority (dnr: 2021-00410).

4 RESULTS

4.1 PAPER I

The IPQ was completed by 82.4% (952/1155) of the participants. Eight hundred and ninety-four (93.9%) of the responders were men, and the median age at time of surgery was 58 years (interquartile range 48-67 years). Hernia repair was performed under general anesthesia in 61.2% (583/1155) of cases, regional anesthesia in 12.7% (121/1155) of cases and local anesthesia in 26.1% (248/1155) of cases.

Postoperative complications had in the previous study been reported by 35.7% (340/952) of the responders in this study. CPIP was reported by 17.9% (170/952), whereof 3.0% (29/952) reported pain with the IPQ intensity grade 3-6, limiting their ability to perform daily activities. Testicular pain on the side of the hernia repair was reported by 8.6% (77/894) of the male responders.

Multivariable regression analysis showed an increased odds ratio for developing CPIP on the side of the hernia repair for patients who had reported severe acute postoperative inguinal pain (APIP) in the operated groin. The level of preoperative pain was positively associated to the risk for CPIP. Results are shown in Table 3.

Age was negatively associated with the risk for developing CPIP with decreasing risk for every one-year increase in age at the time of hernia repair. Rapidly absorbable suture material, either in a suture repair or used as a mesh fixation, showed an increased risk for CPIP compared to non-absorbable suture material.

An association between postoperative urinary tract complications and the risk for CPIP was indicated in the univariable analysis, but the difference between groups did not persist in the multivariable analysis. Postoperatively reported testicular pain increased the risk for CPIP in the univariable analysis but was not included in the multivariable analysis, as it would have excluded women from the model.

Acute postoperative testicular pain (OR 5.77; 95% CI 2.97-11.22) and urinary tract complications (OR 2.67; 95% CI 1.06-6.73) were found to be predictors for persistent testicular pain on the side of the hernia repair. High age was negatively associated with the probability of chronic testicular pain (OR 0.97; 95% CI 0.95-0.98).

Reported preoperative inguinal pain, APIP and the postoperative complication hematoma were associated with an increased risk for developing chronic testicular pain in the univariable analyses, but no significant association was seen in the multivariable analysis. There was no association between anesthetic method, method of repair, fixation technique, or other postoperative complications in the univariable analysis.

	Frequencies	Univariate analysis		Multivariate analysis	
	Patients with chronic pain, n/no. at risk (%)	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
Sex					
Male	156/894 (17.5)				
Female	14/58 (24.1)	1.53 (0.82-2.88)	0.182	1.76 (0.88-3.49)	0.11
Age		0.99 (0.97-0.996)	0.009	0.99 (0.98-1.00)	0.05
Anesthesia					
Local	40/248 (16.1)				
Regional	28/121 (23.1)	1.53 (0.89-2.64)	0.124		
General	102/583 (17.5)	1.06 (0.71-1.59)	0.769		
Preoperative groin pain*					
0	12/163 (7.4)	Ref		Ref	
1	22/164 (13.4)	1.94 (0.92-4.06)	0.080	2.08 (0.98-4.41)	0.07
2	37/186 (19.9)	3.13 (1.57-6.23)	0.001	3.14 (1.55-6.36)	0.001
3	54/266 (20.3)	3.17 (1.64-6.14)	0.001	3.11 (1.59-6.11)	0.001
4	29/103 (28.2)	4.83 (2.33-10.01)	<0.001	4.50 (2.13-9.53)	<0.001
5	6/21 (28.6)	4.93 (1.62-15.04)	0.005	5.29 (1.66-16.90)	0.005
6	9/34 (26.5)	4.63 (1.76-12.15)	0.002	3.49 (1.25-9.75)	0.02
Hematoma					
No	136/777 (17.5)				
Yes	31/148 (21.0)	1.24 (0.80-1.93)	0.329		
Infection					
No	151/860 (17.6)				
Yes	14/68 (20.6)	1.20 (0.65-2.22)	0.555		
Wound rupture					
No	160/901 (17.8)				
Yes	8/38 (21.1)	1.24 (0.56-2.78)	0.597		
Severe postoperative pain in the groin					
No	135/832 (16.2)				
Yes	33/104 (31.7)	2.48 (1.57-3.91)	<0.001	2.09 (1.28-3.41)	0.003
Thrombosis					
No	162/924 (17.5)				
Yes	4/10 (40.0)	3.66 (0.97-13.78)	0.055		
Testicular pain postop (only males)				Omitted due to collinearity	
No	130/797 (16.3)				
Yes	23/84 (27.4)	1.98 (1.18-3.33)	0.010		
Complication to anesthesia					
No	160/911 (17.6)				
Yes	7/26 (26.9)	1.68 (0.69-4.06)	0.249		
Urinary tract complication					
No	153/897 (17.1)				
Yes	14/40 (35.0)	2.65 (1.34-5.21)	0.005	1.94 (0.94-4.00)	0.07
Constipation					
No	159/911 (17.5)				
Yes	6/26 (23.1)	1.53 (0.60-3.93)	0.372		

Table 3. Logistic regression analyses regarding chronic postoperative inguinal pain (CPIP) in the operated groin. Results from the multivariable analysis showed that preoperative pain, severe acute postoperative pain, and high age predisposed for CPIP. (Reprinted from Olsson et al, Surgery, 2016, with permission from Elsevier.)

PAPER II

The response rate was 69.8% (279/400 participants), after two reminders and exclusion of deceased patients, non-responders, and incomplete questionnaires, illustrated in Figure 14. Median age of the responders was 64 years (23-94 years). There were 92.5% (258/279) men and 7.5% (21/279) women. The hernia repairs were elective procedures in 96.4% (269/279), and acute operations in 3.6% (10/279). There were 75.6% (211/279) open hernia repairs and 24.4% (68/279) endo-laparoscopic repairs, whereof two cases were converted from endo-laparoscopic to open technique.

General anesthesia was used in 80.3% (224/279), local anesthesia in 13.3% (37/279), and spinal or epidural anesthesia in 6.5% (18/279) of the included operations. There were 7.2% (20/279) bilateral hernia repairs. Non-responders were analyzed regarding age, sex, surgical technique, method of anesthesia, emergency repair and bilateral repair, and compared to responders. Only age differed between the groups where median age for responders was 64 (23-94) years, and for non-responders 55 (18-90) years. There was no detected difference in characteristics between the two groups with different order of the questionnaires.

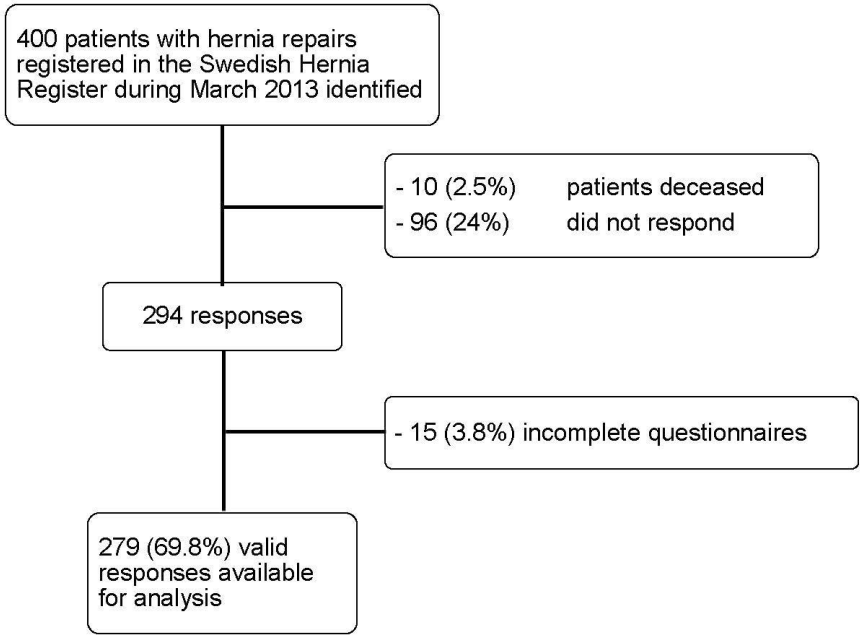


Figure 14. Flowchart of the recruitment process, inclusion and exclusion of participants.

The IPQ-score and the sf-IPQ-score were calculated and analyzed. Reported persistent pain in the operated groin, interfering with daily activities (score ≥3) was reported by 7.9% (22/279) with the IPQ, and by 11.8% (33/279) with the sf-IPQ, illustrated in Figure 15.

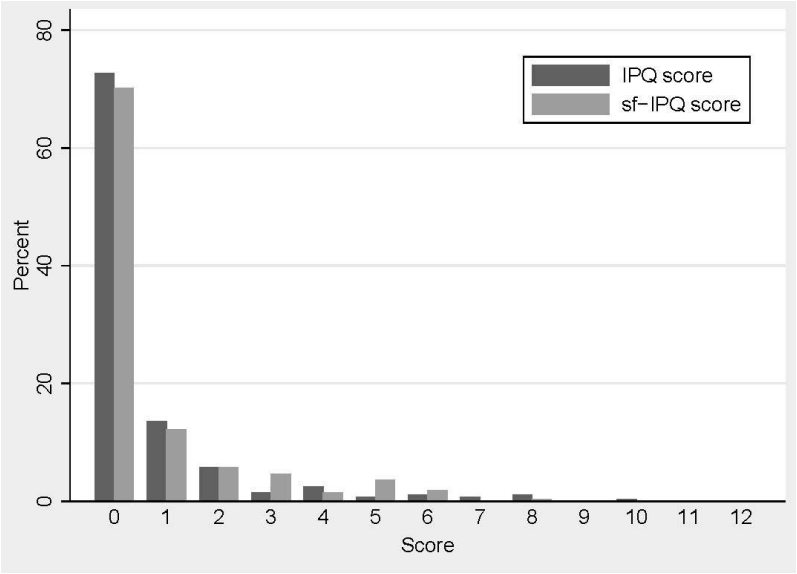


Figure 15. Distribution of IPQ score and sf-IPQ score, respectively, for 279 patients three years after inguinal hernia repair. IPQ score ≥3: 7,9% (n=22), Sf-IPQ score ≥3: 11.8% (n=33). (Reprinted from Olsson et al, World J surg, 2018, with permission from Springer.)

The observed agreement regarding reported pain between the IPQ and the sf-IPQ was 93.9%. Cohen's kappa was 0.66 (95% CI 0.55-0.77, p<0.001). Correlation and consistency between the two scores were evaluated using the Intraclass Correlation Coefficient, ICC, yielding a coefficient of 0.78 (95% CI 0.73-0.82, p<0.001). A difference for reported pain intensity between the IPQ and the sf-IPQ was shown with McNemar´s test (p=0.013). Differences in distribution of the SF-MPQ was shown between patients reporting sf-IPQ-score <3, and patients reporting sf-IPQ-score ≥3, illustrated in Figure 16.

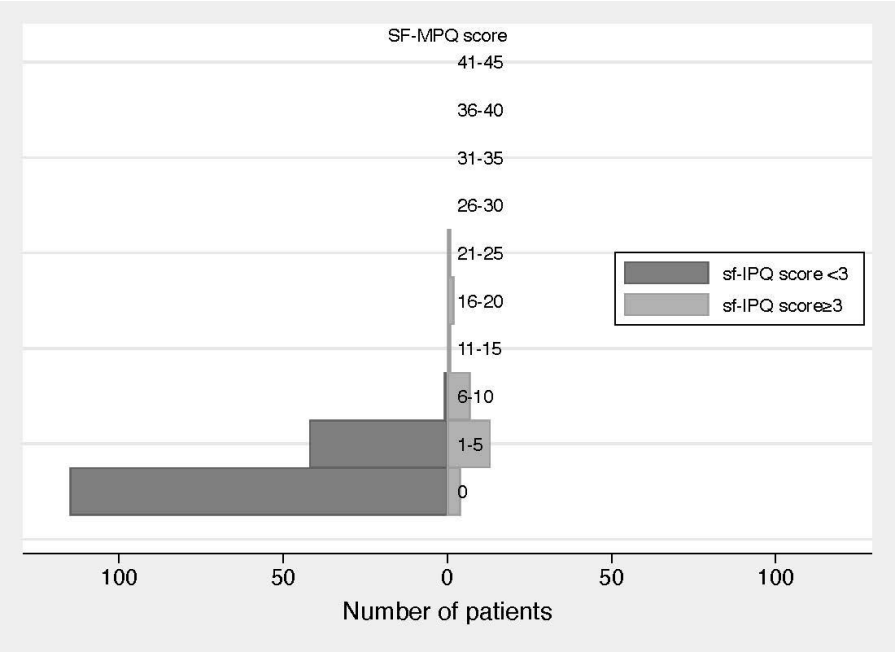


Figure 16. Comparison of SF-MPQ score distribution for study participants with sf-IPQ score <3 and sf-IPQ score ≥ 3, respectively. (Reprinted from Olsson et al, World J Surg, 2018, with permission from Springer.)

4.2 PAPER III

There were 32,942 inguinal hernia repairs registered in the SHR during the study period. After exclusion of 2283 operations carried out with other methods than anterior open repair or endo-laparoscopic repair, 30,659 cases remained. Response rate to the PROM was 64.5% (19,773/30,659).

Sex distribution of the responder group, including both open anterior mesh repairs and endo-laparoscopic repairs, were 91.4% men and 8.6% women. Mean age at the time of surgery was 62.3 years. There were 4.1% smokers. Mean BMI was 25.2 kg/m^2. The hernia repair was performed with open anterior mesh technique in 73.4%, and with endo-laparoscopic repair in 26.6% of the cases. Response rates stratified for sex were 60.3% (1694/2809) for women, and 64.9% (18,079/27,850) for men.

Complication rates registered in the SHR, separating between responders (Table 4), and non-responders, were 2.2% vs 2.4% for hematoma (p=0.450), 1.5% vs 1.6% for surgical site infection (p=0.485), 1.1% vs 1.2% for seroma (p=0.682), 3.7% vs 3.6% for urinary tract complication(p=0.691), and 1.2% vs 2.2% for acute postoperative pain (p<0.001).

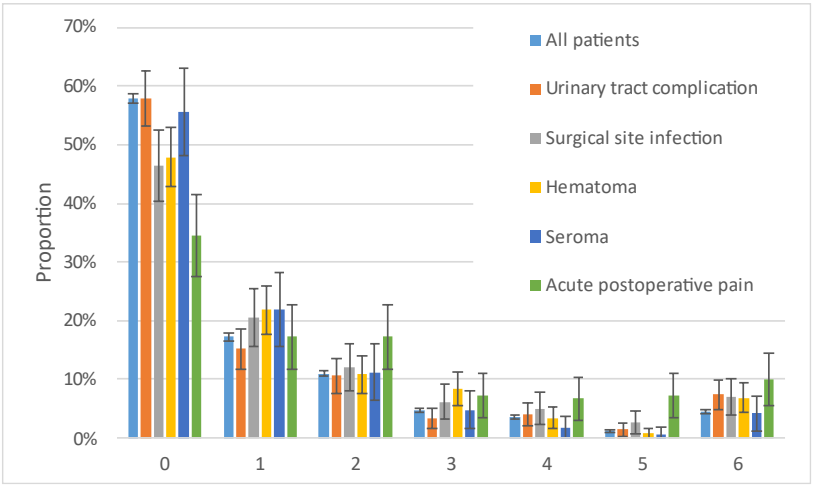
Baseline data	**Open anterior mesh repairs (N=14507)**	**Endo-laparoscopic mesh repairs (N=5266)**	**All eligible responders (N=19773)**
Mean age, years (standard deviation)	65.5 (12.9)	60.4 (14.3)	62.3 (13.5)
Sex			
Male	14170 (97.7%)	3909 (74.2%)	18079 (91.4%)
Female	337 (2.3%)	1357 (25.8%)	1694 (8.6%)
Smokers	602 (4.1%)	200 (3.8%)	802 (4.1%)
Mean BMI, kg/m^2 (standard deviation)	25.3 (3.1)	24.9 (3.2)	25.2 (3.1)
Urinary tract complication	416 (2.9%)	321 (6.1%)	737 (3.7%)
Surgical site infection	258 (1.8%)	29 (0.6%)	287 (1.5%)
Hematoma	380 (2.6%)	62 (1.2%)	442 (2.2%)
Seroma	169 (1.2%)	55 (1.0%)	224 (1.1%)
Acute postoperative pain	180 (1.2%)	62 (1.2%)	242 (1.2%)

Table 4. Baseline characteristics and frequency of registered postoperative complications for open anterior mesh repairs, endo-laparoscopic repairs as well as for all eligible responders.

Distribution of self-reported CPIP according to the seven-grade scale one year after open anterior mesh repair was: grade 0: 57.9%; grade 1: 17.2%; grade 2: 11.0%; grade 3: 4.7%; grade 4: 3.6%; grade 5: 1.2%; and grade 6: 4.4%, illustrated in Figure 17 a.

Corresponding rates for self-reported CPIP after endo-laparoscopic hernia repair was distributed as follows: grade 0: 58.0%; grade 1: 16.0%; grade 2: 11.4%; grade 3: 5.1%; grade 4: 4.0%; grade 5: 1.3%; and grade 6: 4.2%, illustrated in Figure 17 b.

a



b

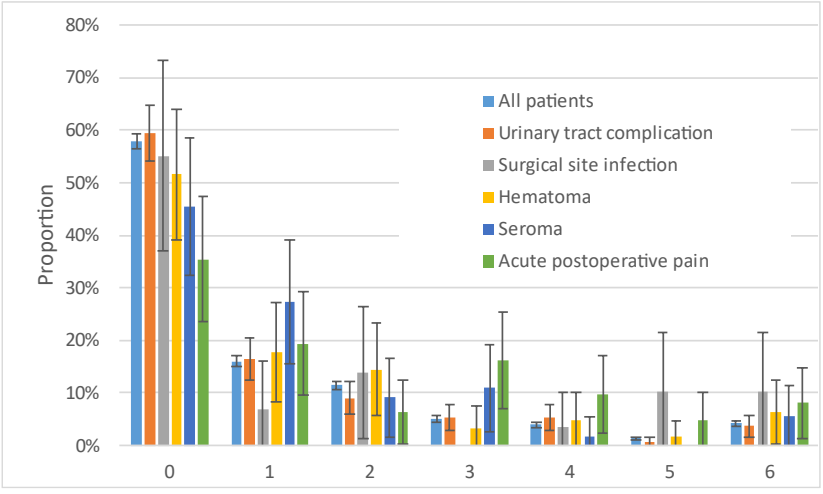


Figure 17. Illustration showing the distribution of graded intensity of CPIP for patients with open anterior mesh repair (a), and endo-laparoscopic repair (b); bars represent all patients and patients with each specified postoperative complication, respectively.

Statistical analyses using uni- and multivariable ordered logistic regression models for the open anterior mesh repairs showed that APIP, hematoma, and SSI were associated with level of CPIP one year after surgery, shown in Table 5. Urinary tract complications and seroma were not associated with CPIP.

	Univariable analysis		Multivariable analysis	
	Ordered regression odds ratio (95% confidence interval)	*P*	Ordered regression odds ratio (95% confidence interval)	*p*
Age (years)	0.97 (0.964–0.975)	<0.001	0.97 (0.964–0.975)	<0.001
Female	2.08 (1.306–3.304)	0.002	2.60 (1.596–4.227)	<0.001
Smoker	1.73 (1.212–2.460)	0.002	1.52 (1.059–2.178)	0.023
BMI (kg/m^2)	1.09 (1.062–1.114)	<0.001	1.07 (1.047–1.099)	<0.001
Urinary tract complication	1.16 (0.751–1.780)	0.508	1.50 (0.953–2.350)	0.079
Surgical site infection	2.90 (1.722–4.887)	<0.001	2.18 (1.271–3.733)	<0.001
Hematoma	2.37 (1.531–3.656)	<0.001	2.03 (1.300–3.184)	<0.001
Seroma	1.03 (0.524–2.023)	0.932	0.88 (0.435–1.762)	0.707
Acute post-operative pain	10.84 (5.929–19.815)	<0.001	7.46 (4.018–13.868)	<0.001

Table 5. Ordered logistic regression analysis for CPIP one year after open anterior mesh repair of inguinal hernia in 14 507 patients.

Analyses for the endo-laparoscopic group with uni- and multivariable ordered logistic regression models showed that APIP was significantly associated with CPIP, while none of the other complications showed any association, shown in Table 6.

	Univariable analysis		Multivariable analysis	
	Ordered regression odds ratio (95% confidence interval)	P	Ordered regression odds ratio (95% confidence interval)	p
Age (years)	0.98 (0.975–0.991)	<0.001	0.98 (0.973–0.989)	<0.001
Female	1.69 (1.288–2.218)	<0.001	2.13 (1.603–2.844)	<0.001
Smoker	4.35 (2.404–7.852)	<0.001	4.84 (2.655–8.810)	<0.001
BMI (units)	1.13 (1.081–1.167)	<0.001	1.15 (1.102–1.191)	<0.001
Urinary tract complication	0.85 (0.512–1.416)	0.537	1.10 (0.652–1.866)	0.715
Surgical site infection	2.47 (0.524–11.695)	0.253	2.33 (1.478–11.402)	0.296
Hematoma	1.77 (0.600–5.224)	0.301	1.85 (0.614–5.585)	0.275
Seroma	2.18 (0.700–6.808)	0.179	2.40 (0.746–7.727)	0.141
Acute post-operative pain	9.75 (3.483–27.290)	<0.001	9.35 (3.184–27.479)	<0.001

Table 6. Ordered logistic regression regarding CPIP one year after endo-laparoscopic mesh repair of inguinal hernia in 5 266 patients. (Table 5 and 6 are reprinted from Olsson et al, Hernia 2021, with permission from Springer.)

Female sex and smoking were significant predictors for developing CPIP, after both open anterior and endo-laparoscopic repairs. BMI was also associated with CPIP, with increasing odds for every increased step (kg/m^2) of BMI, while age at the time of surgery was negatively associated with CPIP, with decreasing odds for each one-year increase of age.

4.3 PAPER IV

There were 165,543 patients without a prior groin repair in the SHR registered during the study period. After applying the exclusion criteria 164,087 remaining patients were included in the study, whereof 151,296 were unilateral repairs and 12,791 bilateral repairs.

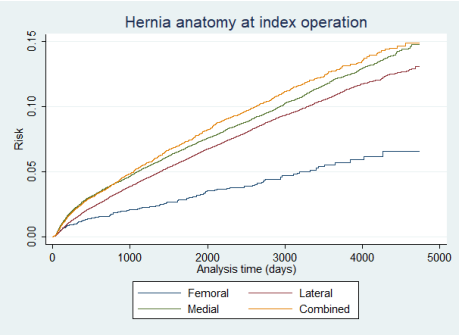
Sex distribution among patients with a primary unilateral hernia repair was 89.9% men and 10.1% women. Median age at the time of surgery was 63.7 years (range 18.0-102.4 years). There were 0.9% underweight, 50.5% normal weight, 41.8% overweight, and 6.8% obese or morbidly obese patients. Hernia repairs on the right side (58.1%) were more common than on the left side (41.9%). Lateral inguinal hernias accounted for 57.7% of cases, while 30.9% were medial inguinal, 2.7% were femoral and 8.8% were combined hernias. The index operation was performed as open anterior mesh repair in 87.7% while TEP technique was used in 10.6% and TAPP technique in 1.8%. The cumulative risks are illustrated with Kaplan Meyer curves in Figure 18.

There were 11,232 (7.4%) registered subsequent contralateral repairs among the patients that had undergone a primary unilateral hernia repair with a median follow-up time (time from index operation to either contralateral repair, death, or end-of-study) of 5.5 years (range 0-13 years). The median time to subsequent contralateral repair was 2.7 years.

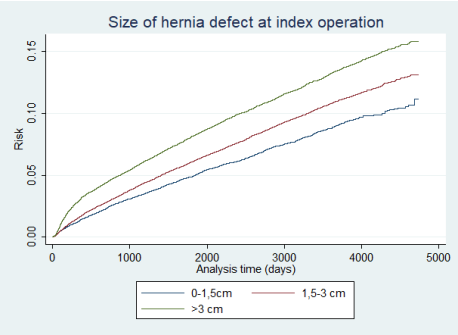
Of patients having undergone open anterior mesh repair, 8.6% were later operated in the contralateral groin. Corresponding cumulative incidence for TEP repair was 3.4% and for TAPP repair 4.2%.

Univariable Cox regression analyses showed that male sex, increased age, hernia repair on the left side, medial or combined hernia, hernia defect size over 1.5 cm, and repair with an open anterior mesh technique had a positive association with a subsequent contralateral hernia repair. Low and high BMI (underweight and obesity + morbid obesity) as well as femoral hernia were associated with a decreased risk for a subsequent contralateral inguinal hernia repair.

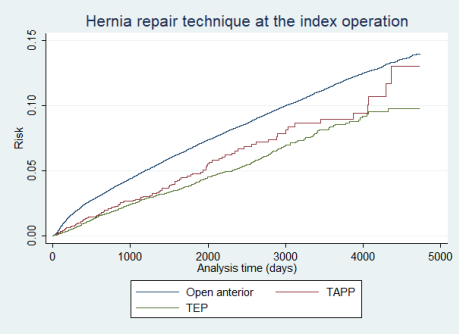
a



b



c



d

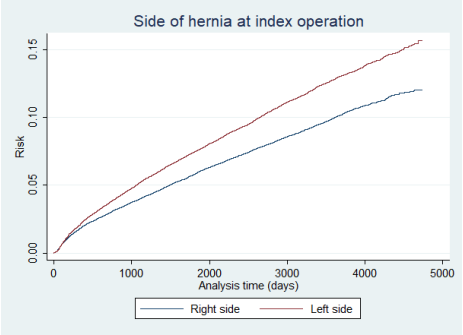


Figure 18. *Kaplan Meyer curves showing cumulative risk for subsequent contralateral hernia depending on hernia anatomy (a), and hernia defect size (b), hernia repair techniques (c), and side of the index unilateral repair (d).*

In the multivariable Cox regression (proportional hazards model) persisting risk factors for a subsequent contralateral hernia repair were; male sex ($p<0.001$); hernia repair on the left side ($p<0.001$); medial inguinal hernia ($p=0.045$); combined inguinal hernia ($p=0.006$); hernia defect size of 1.5-3.0 cm ($p=0.011$); hernia defect size of > 3 cm ($p<0.001$), and high age ($p<0.001$).

Analyses also showed that patients with BMI 25-30 ($p<0.001$); patients with BMI>30 ($p<0.001$); and patients operated with TEP ($p<0.001$) or TAPP technique ($p<0.001$) had a decreased risk for a future contralateral repair, shown in Table 7.

	Univariable Cox regression model			Multivariable Cox regression model		
	HR	(95% CI)	P	HR	(95% CI)	P
Sex						
Female	1 (ref)					
Male	2.13	(1.96-2.32)	p<0.001	1.74	(1.57-1.92)	p<0.001
Age	1.01	(1.008-1.011)	p<0.001	1.01	(1.006-1.009)	p<0.001
BMI						
normal	1 (ref)					
under	0.71	(0.55-0.91)	p=0.008	0.85	(0.66-1.11)	p=0.234
over	0.99	(0.95-1.03)	p=0.579	0.93	(0.89-0.97)	p<0.001
obese + morbid	0.71	(0.65-0.78)	p<0.001	0.68	(0.62-0.75)	p<0.001
ASA						
1	1 (ref)					
2	1.10	(1.05-1.14)	p<0.001	0.97	(0.93-1.02)	p=0.323
3	1.11	(1.04-1.19)	p=0.002	0.94	(0.87-1.01)	p=0.094
4 + 5	1.19	(0.87-1.62)	p=0.273	0.97	(0.68-1.36)	p=0.841
Side						
Right	1 (ref)					
Left	1.30	(1.25-1.35)	p<0.001	1.30	(1.25-1.35)	p<0.001
Anatomy						
Lateral	1 (ref)					
Medial	1.15	(1.11-1.20)	p<0.001	1.05	(1.001-1.096)	p=0.044
Combined	1.22	(1.14-1.30)	p<0.001	1.10	(1.03-1.18)	p=0.006
Femoral	0.50	(0.42-0.59)	p<0.001	0.85	(0.69-1.04)	p=0.116
Defect size						
<1.5 cm	1 (ref)					
1.5-3 cm	1.22	(1.16-1.29)	p<0.001	1.09	(1.03-1.16)	p=0.004
>3 cm	1.64	(1.54-1.73)	p<0.001	1.35	(1.27-1.45)	p<0.001
Operation approach						
Open	1 (ref)					
Endo-laparoscopic	0.53	(0.49-0.58)	p<0.001			
Operation method						
Open	1 (ref)					
TAPP	0.61	(0.50-0.74)	p<0.001	0.77	(0.63-0.94)	p=0.011
TEP	0.52	0.48-0.57)	p<0.001	0.64	(0.58-0.70)	p<0.001
Sliding						
No	1 (ref)					
Yes	1.20	(1.13-1.27)	p<0.001	1.03	(0.97-1.10)	p=0.304
Emergency						
Yes	1 (ref)					
No	1.01	(0.93-1.11)	p=0.758			

Table 7. Cox proportional hazards regression for a subsequent contralateral inguinal hernia repair in 151,296 patients with an index unilateral hernia repair January 2007-December 2019.

5 DISCUSSION

"Half knowledge is more victorious than whole knowledge. It understands things as being more simple than they are, and this renders its opinions more easily intelligible and more convincing." (F. Nietzsche)

5.1 PAPER I AND III

There was a strong association between patient-perceived occurrence of the postoperative surgical complication APIP and CPIP in the long-term follow-up cohort study (Paper I). APIP was also a strong predictor for CPIP affecting daily activities after both open anterior and endo-laparoscopic repair in the one-year follow-up study (Paper III).

Previous studies have suggested postoperative complications as a risk factor for CPIP. In these two studies we were able to investigate specific adverse events, and to demonstrate which complications are in fact associated with CPIP. The questionnaire regarding complications that study persons in Paper I had completed provided more detailed information regarding complications than the SHR could provide at the time. The more elaborate registration of complications in the SHR, used in later years, together with the routine administration of PROM one year after surgery provided a possibility to investigate the same issue in a three-year cohort of Swedish groin hernia patients.

The strongest predictor, by far, for CPIP was severe pain in the direct post-operative period. There was also a strong association between the complications "postoperative testicular pain" and "urinary tract complication", and chronic testicular pain in Paper I. In Paper III, the postoperative complications hematoma and SSI were predictors for CPIP after open repair but not after endo-laparoscopic repair.

This differing risk pattern depending on the specific postoperative complication has not been shown before. Study persons were furthermore stratified according to hernia repair technique in Paper III. The difference between open repair and endo-laparoscopic repair regarding postoperative complications as predictors for CPIP is novel knowledge. Smoking was associated with CPIP after both open and endo-laparoscopic repair. Smoking has shown to be a predictor for poor postoperative pain control (119), and increases the risk for transition from acute to chronic back pain, which may be applicable also on inguinal pain (120).

There was a difference in patient characteristics between the group that underwent endo-laparoscopic repair, who were younger and more often female, and the group that underwent open repair. Since younger age and female sex are known risk factors for CPIP (4, 121), that is a likely reason for surgeons to more often choose endo-laparoscopic repair technique in

this patient group. Open anterior mesh repair increased the risk for CPIP, which is in concordance with previous studies that have shown that endo-laparoscopic approaches have a reduced risk for CPIP (122). The correlation between non-specific postoperative complications and CPIP has been previously reported in a small study (123), as well as in a population based cohort study (4): these results prompted the idea behind Paper I.

Our findings are supported by other research that shows associations between intense acute postoperative pain and adverse outcome, such as long-term pain. The CPIP prevalences in other studies are comparable to ours (96, 124-127), which confirm the external validity.

The crucial question which these studies cannot answer, is whether there is a causal relationship between these postoperative complications and CPIP. A potential confounder is the surgical technique. Technical difficulties related to the method of repair may be correlated to a poor outcome such as the presence of postoperative complications.

Patient-associated factors such as age, anatomical variations, previous surgery and concomitant diseases increase the risk for CPIP (4), while obesity is not associated with increased rate of complications (128). Surgery-associated factors such as approach, mesh material, fixation method, technique and experience are important factors for the risk for postoperative complications, CPIP and recurrence (129, 130). The summary of these assumptions may be that a thorough, gentle and precise surgical dissection technique could decrease the risk for postoperative complications as well as chronic postoperative inguinal pain. Postoperative complications are thus not necessarily risk factors for CPIP *per se*, but rather proxies for careless and traumatic surgical technique.

Considering the moderate influence and the relatively low rates of these specific complications, their role in the pathogenesis of CPIP is probably limited. On the other hand, the large number of hernia patients justifies further striving to improve surgical management and proceed with a firm and focused action plan to reduce the prevalence of CPIP.

The results of these studies emphasize the importance of a strict indication for inguinal hernia repair and individualized preoperative information regarding the risk for possible adverse outcome. APIP was identified as a strong predictor for CPIP in our studies and needs to be addressed early in the postoperative course to be able to provide an optimal treatment. Our findings suggest that other strategies are required to reduce the problem of CPIP, in particular atraumatic surgical technique or an alternative repair technique i.e., endo-laparoscopic technique, which had a lower rate of the postoperative complications hematoma and SSI compared to open anterior repair, in paper III, where they were significantly associated with CPIP. Surgeons should choose operative techniques with a low risk for pain in the immediate postoperative period and be very active in managing severe postoperative pain. Intraoperative Transversus Abdominis Plane blocking has shown to be an effective technique to reduce postoperative pain (131). Early adequate pain management has shown good results regarding the long-term outcome of postoperative pain (91), while surgical neurectomy might be the final solution if pharmacological and conservative treatment fails (132, 133)

5.2 PAPER II

The sf-IPQ was demonstrated to be a robust disease-specific instrument for the assessment of groin pain, well suited to be used in in daily clinical practice. It showed significant agreement, correlation and consistency with the original IPQ. Advantages of the sf-IPQ included its simplified design, condensed form, and user-friendliness. These characteristics make the sf-IPQ well suited for daily use, with the primary purpose to identify pain or discomfort that warrant further clinical evaluation management.

Disease-specific outcome reporting instruments are together with disease-specific registries indispensable in clinical research that continuously strive to improve outcome (103). Other hernia repair-specific instruments have been developed, such as the Carolinas Comfort Scale (113); and the EuraHS-QoL (108). These instruments similarly to the original IPQ are very well suited for research purposes. They may not be as ideal for convenient routine clinical use. The validated sf-IPQ is the first hernia specific PROM that has been designed specifically for such use and constitutes an important contribution to improve the postoperative outcome measurement, in daily practice.

A main difference between the sf-IPQ and the IPQ is the complexity of the questionnaires. The sf-IPQ does not include detailed information required for research but provided concise outcome information entirely comparable with that from the original IPQ. The sf-IPQ showed a consistently higher registered pain score compared to the original IPQ. This finding indicates a further advantage compared to the comprehensive IPQ, allowing identification of patients with mild to moderate pain that may not actively seek care but that could benefit from clinical consultation. Considering the sensitivity and user-friendliness of the sf-IPQ, it could be recommended as a standard instrument for routine hernia management.

5.3 PAPER IV

Identified risk factors for a later contralateral repair were pre- and intraoperative findings such as a medial or combined hernia, a large hernia defect size as well as a left sided hernia and male sex. Medial hernias and large defect size could possibly be associated to confounding factors such as the patient’s collagen composition, which affects the general fascia constitution, including an increased risk for a future contralateral hernia formation. A patent processus vaginalis is more common on the right side which would explain the increase in risk for a future lateral hernia on the right side, after a left sided primary hernia repair.

Our findings provide an ability to better identify patients at risk for contralateral hernias. A male patient with a large medial hernia in the left groin could preferably be referred to a preoperative imaging examination with the purpose to identify any occult, asymptomatic contralateral hernia. In these specific cases a bilateral hernia repair could be considered.

A subsequent contralateral hernia repair was performed in 7.4 % of patients operated for a primary unilateral inguinal hernia within a median time of 2.9 years after the index operation. The frequency of contralateral repairs and the time to contralateral operation found in our study were comparable to other studies. Rates of later contralateral repairs was seen in 10.5% in a retrospective Taiwanese study (35), and incidence of a later developed contralateral hernia of 8.1% after exploration with negative findings during a unilateral hernia repair (32). One study that systematically explored the asymptomatic contralateral side laparoscopically identified an occult hernia in a rate of 11.2% (134). The present study contributes with both an incidence rate and identified risk factors in a large population based prospective cohort.

There is an ongoing discussion whether to explore the contralateral groin or not. Endo-laparoscopic methods provide an opportunity to explore and repair an occult inguinal hernia on the other side without the need of a complementary incision in the contralateral groin, and with a limited expected increase of operation time. The benefit of a contralateral exploration including prophylactic repair of an occult hernia is the advantage of a bilateral repair during one surgical procedure (134, 135). Proponents usually base their arguments on the reported turn-over rate of two-thirds from watchful-waiting to a future repair (136, 137). Opponents highlight the risk with unnecessary procedures and base their arguments on the reported incidence of only 20-30% of occult hernias that will lead to future surgery (33, 138, 139).

Considering the fact that postoperative complications increase the risk for CPIP, which was shown in Paper I and III, an excessive surgical exploration could not be generally recommended. The TAPP technique provides access to explore the contralateral groin without any further dissection while the TEP approach necessitates further dissection on the contralateral side but still within the same surgical access. In specific cases, such as presence of the risk factors identified in this study, a medial or combined hernia; a large defect; a left sided hernia and male sex; a contralateral exploration including a repair in cases with an occurring contralateral hernia could be considered. Patient factors should be included in the preoperative decision-making. Hernia patients with comorbidities increasing the risks of general anaesthesia could benefit from a bilateral repair instead of two repeated repairs. Further research to more effectively pin-point patients at risk should be conducted.

In the EHS hernia guidelines, endo-laparoscopic hernia repairs are recommended as first line approach in women, bilateral repairs, recurrent hernias and in young patients (2). Considering our findings, it might also be prudent to offer patients with the identified risk factors for contralateral hernia, who are fully informed and have given consent, an endo-laparoscopic repair as a first line approach.

5.4 INTERPRETATION OF MAIN FINDINGS

APIP was a strong predictor for the development of CPIP after both open anterior repair and endo-laparoscopic repair, where the findings in paper I was confirmed in paper III. Preoperative groin pain was also a significant predictor for CPIP after open anterior mesh postoperative course, to be able to treat the pain adequately, as well as to prevent a possible transition from acute to chronic pain. Reflecting the prevalence of CPIP affecting daily activities, of approximately 14% after both open anterior and endo-laparoscopic repairs, these findings are important and further research on this topic is warranted.

Postoperative hematoma and SSI were also significant predictors for CPIP after open anterior mesh repairs. Although the incidence of these postoperative complications was fairly low and the association with the risk for developing CPIP was moderate, the total number of patients undergoing inguinal hernia repair is huge. Even a marginal improvement of the outcome will have an impact on the total prevalence of CPIP. The large population undergoing hernia repair surgery is sufficient to warrant improvement of the surgical technique, even if the benefit for the individual patient may be limited.

Considering the findings in paper I and III, and how they may relate to risks with ungentle or excessive surgery, the decision process prior to surgery requires serious attention. A thorough preoperative assessment is crucial for evaluation of present risk factors, including an optimized planning, an adequate choice of an individualized operation technique as well as any indication for contralateral exploration. The choice of surgical technique could preferably be minimally invasive if appropriate. It is further paramount that the patient is involved in this decision-making based on understandable scientific knowledge.

CPIP results in suffering for a large number of patients and needs to be better characterized as well as better assessed prior to hernia repair. The sf-IPQ could serve as a suitable instrument for assessing both preoperative and postoperative inguinal pain. This part of the inguinal hernia management deserves to be standardized in the daily routine at surgical clinics, and not only as part of research projects.

The risk for a subsequent contralateral hernia repair following a unilateral primary hernia repair was found to be relatively low. Hence, perioperative active contralateral exploration or prophylactic contralateral hernia repair is of limited value, especially considering the potential risks for postoperative complications possibly resulting in long-term pain. It should be avoided as routine but could be considered in select cases.

Surgical intervention can be hazardous and comes with risk for postoperative adverse events; this holds true for groin hernia surgery too. The large number of patients with a benign condition such as an inguinal hernia, facing potential benefits as well as harms from surgery, motivates thorough risk analysis prior to surgery. The risk for possible postoperative complications should be weighed against a careful evaluation of complaints prior to surgery. An occult hernia or a hernia with mild symptoms may be managed with a watchful-waiting

approach to minimize the risk for postoperative adverse events. The watchful waiting approach has shown to be safe even though 2/3 of the patients undergo a hernia repair within ten years, mainly due to increasing pain (45).

Decision-making based on thorough preoperative assessment and a careful patient-selection combined with adequate choice of repair technique, may be far more valuable for the patient than a quick procedure. An interpretation of the quote "if it´s not broken – don´t fix it" (140), could be; If the patient doesn't have any symptoms – don't put the patient at risk for a long-term suffering.

5.5 METHODOLOGICAL CONSIDERATIONS

Random errors may cause indistinct results while systematic errors may affect validity and can result in erroneous conclusions. Bias is an event occurring during inference leading the result to systematically deviate from the true value. Errors and bias might have had an impact on the included studies to some extent.

Population-based prospective cohorts

The included studies in this thesis are based on study populations from the SHR. A benefit of research on population-based cohorts with a high coverage rate, compared to consecutively included study participants in a more local setting, is the presumably closer similarity to the full population which makes the results more generalizable with a higher degree of external validity.

The generalizability does not only depend on a more unselected group of study subjects. Participation of a large group of surgeons with varying experience and degree of specific interest in the subject at hand, working in different types of surgical units provides a closer reflection of the true national clinical situation.

Data sets with a very large number of observations allow detection of statistically significant differences, even when the numerical differences are small. This needs to be considered when working with large population-based study samples; clinical relevance of findings should always be contemplated.

Selection bias

The risk for selection bias is low due to the relatively large study samples gathered from a national quality register with a very high coverage rate. Although the data derived from population-based registers can be generalized to the entire population, there is still a risk of selection bias when comparing the outcomes from different approaches. We have aimed to limit our exclusion criteria in the studies in order to minimize selection bias. In Paper I, there is some risk for selection bias due to the fact that patients were only eligible for the

study if they had partaken in the prior study, which may affect the generalizability to the main population. In Papers II-IV the risk is on the other hand lower due to the larger and unselected study population derived from the SHR.

In all four papers, there is a skewed distribution of sex. A majority of the participants are men, which limits the generalizability to a female population. Inguinal hernia is on the other hand much more common in men and the distribution of sex in these papers by and large reflects the population of hernia patients. The total population of hernia patients have a similar predominance of men, which may strengthen the possible clinical benefit of the results from the studies.

Information bias

Inappropriate data collection or incorrect measurement of variables may cause information bias. Information bias can be divided into differential and non-differential misclassification.

In Paper I, there was a risk for information bias due to the participants self-registering of the questionnaires at two different occasions. Instructions on how to respond to the questionnaires were attached with the purpose to avoid any information bias. Thus, the probable impact of information bias is considered low.

In Paper II, a possible risk of information bias was identified during the study planning. The order of the three posted questionnaires could possibly lead to a tendency of lack of focus when fulfilling the forms, the study person encountered last. This potential risk was managed by sorting the three questionnaires in two different orders and comparing the results of the groups.

In Paper III and IV there was no considered risk for information bias due to the already existing data acquired from the SHR. The register has an established annual routine for validation of data entered in order to address this possibility; data have been found to be consistently of high validity with 98% correctly entered variables (104).

Confounding

Factors that can be associated with both exposure and outcome may distort the effect and blur the result; they are labeled as confounding factors. In all four papers statistical analyses were adjusted for possible confounders, such as age, sex, and BMI, in multivariable analyses. However, the studies cannot account for possible confounders outside of the investigated variables and they cannot prove causality.

In Paper I, III and IV constituting data from the SHR, we adjusted for all available known confounders in the multivariable analyses. A sensitivity analysis was made by comparing characteristics between responders and non-responders.

In Paper II, which was a small study cohort, we sorted the three questionnaires in in two different orders to avoid both information bias and impact from any confounding factors.

Generalizability

Generalizability or external validity is the extent to which result from the study population can be extrapolated to a larger population. Inclusion from national disease-specific registers such as the SHR provides a valid study sample but is on the other hand mainly generalizable on a male population. This should however not be considered negative considering the sex profile of inguinal hernia prevalence. The generalizability may also be limited outside the Western countries and in areas with limited resources.

Precision

Type I error is an incorrect rejection of the null hypothesis. Type II error is an incorrect acceptance of the null hypothesis.

In Paper I and III the low frequency of registered and self-reported complications could be considered to limit far-reaching conclusions from the results. Considering the large number of observations in Paper III one must be observant on the risk for a type I error. However, the differences found in the study were statistically highly significant.

6 CONCLUSIONS

Paper I: Severe acute postoperative pain and preoperative pain are significant risk factors for development of CPIP, lasting eight years after open anterior mesh repair.

Paper II: The sf-IPQ questionnaire is a simple disease-specific pain instrument that provides concise outcome information comparable to the original IPQ. The sf-IPQ is highly appropriate for routine clinical use.

Paper III: APIP predisposes for CPIP after both open anterior and endo-laparoscopic repair. Postoperative hematoma and SSI predispose for CPIP after open anterior repair.

Paper IV: Direct, large and left-sided inguinal hernias predispose for a subsequent contralateral inguinal hernia repair. Hernia patients with the present risk factors should be adequately examined preoperatively for an optimized surgical decision-making.

7 FUTURE PERSPECTIVES

Papers included in this thesis have provided results that were both expected and unexpected which has resulted in new knowledge as well as confirmed outcomes from previous studies.

There are many repair techniques described and possibly an even greater variety of the application of these techniques. Considering the large number of patients undergoing hernia repair, the surgical methods need to be well defined and preferably standardized to enable comparing of outcomes between different clinics and surgeons as well as providing a good quality repair to more patients.

There is a large variety of anatomical conditions and characteristics among patients in need of hernia surgery. An abdominal wall surgical clinic should ideally be able to provide a toolbox of surgical repair methods to offer the best designed repair to each patient. "One standard repair technique for all groin hernias does not exist" (2). In daily clinical practice it is on the other hand reasonable to limit the toolbox of hernia repair techniques to a number of methods based on the available competence as well as technical resources at the clinic.

Complicated cases may need to be referred to a specialist center with experience from difficult hernias and with a larger experience of different surgical methods including more advanced techniques such as robot-assisted laparoscopic repairs.

Improving surgical management to avoid long-term adverse outcome is a continual process. Continuing education and training of both junior and senior hernia surgeons, ceaseless evaluation of outcomes and further research, as well as an open mind for innovation and technology are needed. Surgical technique is crucial and needs to be continuously improved. Future research could preferably be focused on developing minimally invasive surgical methods to reduce the surgical trauma. Studying the effect of dissection technique is interesting but presumably difficult, as is investigating surgeon-related variability in outcomes. The area may need to be approached by exploring the effect of controlled standardization of treatment and procedure.

Occurrence of preoperative inguinal pain in hernia patients is frequent but not always fully addressed regarding the genesis. Further research on this topic and possibly a development of a pain classification could facilitate the decision of surgery or an alternative management. While some risk factors for contralateral hernia were found, they may not be considered specific enough to provide a solid basis for prophylactic treatment. Further studies to determine more precise factors, and hopefully markers to identify those patients who are very likely to develop a contralateral hernia, may provide guidance. The influence of collagen alterations could be one of the areas to investigate in this context.

Hernia patients would benefit from a systematic risk stratification regarding present preoperative pain, presumed collagen alteration, anatomical findings, and symptoms, in facilitating the design of an optimal and individualized hernia repair.

8 SAMMANFATTNING PÅ SVENSKA

8.1 INLEDNING

Ett ljumskbråck är en bristning av den försvagade bukväggen i ljumsken och drabbar framför allt män. Den enda permanenta behandlingen är kirurgisk reparation av bråcket. Varje år utförs uppskattningsvis 20,000,000 ljumskbråcksoperationer globalt och ca 16,000 i Sverige. En förbättrad kirurgisk teknik, användning av nät som förstärkning samt införandet av ett kvalitetsregister, Svenskt Bråckregister (SBR), har medfört en betydande minskning, från 30–50% till <5%, av återfall av bråck efter operation.

Ett allt viktigare utfallsmått är idag kronisk smärta i den opererade ljumsken. Studier har visat att uppemot 1/3 av alla patienter som opererats för ljumskbråck har kvarstående ljumsksmärta av någon grad. Titthålskirurgi har under de senaste decennierna börjat användas alltmer vid ljumskbråckskirurgi. Denna metod har medfört en viss minskning av kronisk ljumsksmärta samt också givit möjlighet att operera båda ljumskarna vid ett och samma ingrepp, utan att behöva öppna huden på båda sidorna. Metoden innebär också en möjlighet att inspektera den andra ljumsken vid misstanke om ett symtomfritt ljumskbråck som då kan opereras i förebyggande syfte.

Med tanke på den stora mängden patienter som drabbas av ljumskbråck är det mycket viktigt att bättre förstå orsakerna till och uppkomsten av kronisk smärta i den opererade ljumsken. Det är också viktigt att utvärdera riskerna och nyttan med en utvidgad titthålsoperation och en eventuell operation i förebyggande syfte.

De övergripande målen med avhandlingsarbetet var att:

1. Undersöka om det finns ett samband mellan komplikationer till operation av förstagångsljumskbråck och utvecklandet av kronisk smärta i den opererade ljumsken.

2. Utveckla ett förenklat formulär för att registrera ljumsksmärta i rutinsjukvård.

3. Undersöka förekomst av en senare operation för ljumskbråck i den motsatta ljumsken samt att värdera risker och nytta med en dubbelsidig operation.

8.2 ARBETE I

I det första arbetet studerades sambandet mellan olika kirurgiska komplikationer och kronisk ljumsksmärta. Vår hypotes var att vissa kirurgiska komplikationer ökade risken för att utveckla en kronisk smärta i den opererade ljumsken. 1155 patienter som opererats för ljumskbråck samt var registrerade i SHR inkluderades i studien. I SHR finns uppgifter om det

förekommit några komplikationer i anslutning till operationen såsom; blödning, sårinfektion, svår smärta, urinstämma eller testikelsmärta. Studiedeltagarna hade i en tidigare studie i anslutning till ljumskbråcksoperationen besvarat en enkät om komplikationer under den första månaden efter operationen. De fick i denna studie besvara en enkät, Inguinal Pain Questionnaire (IPQ), avseende smärta i ljumsken ca 8 år efter ljumskbråcksoperationen.

Av de 952 studiedeltagare som besvarade IPQ uppgav 170 st (17,9%) att de hade en kvarvarande smärta i den opererade ljumsken och 29 st (3%) att de led av en svår kvarvarande ljumsksmärta. Statistiska beräkningar visade att svår smärta innan eller under månaden efter operationen ökade risken för kronisk ljumsksmärta. Beräkningarna visade också att risken för kronisk smärta minskade med ökande ålder.

8.3 ARBETE II

I det andra arbetet utvecklade vi en förenklad version av smärtformuläret IPQ, short form IPQ (sf-IPQ). Avsikten var att skapa ett formulär som var enklare att använda i daglig verksamhet. Originalformuläret IPQ är ett standardiserat och validerat formulär där patienten själv registrerar smärta och obehag i den ljumske som opererats. Formuläret består av 19 frågor på fyra sidor och tar ca 10 minuter att besvara. Sf-IPQ utformades genom att sammanställa de två viktigaste frågorna från IPQ till ett kort enkelsidigt formulär.

400 patienter som opererats för ljumskbråck tre år tidigare och som var registrerade i SBR inkluderades i studien. Formulären IPQ, sf-IPQ samt ett kontrollformulär, McGill Pain Questionnaire, skickades till studiedeltagarna. Statistiska beräkningar visade en systematisk skillnad för digniteten av angiven smärta där sf-IPQ visade en något högre smärta vilket vi tolkade som att sf-IPQ kan vara ett känsligare smärtinstrument. Därutöver visade de statistiska analyserna en god överensstämmelse mellan IPQ och sf-IPQ. De två formulären bedömdes vara utbytbara.

8.4 ARBETE III

I det tredje arbetet undersökte vi en stor samling av patienter opererade för ljumskbråck avseende sambandet mellan specifika kirurgiska komplikationer och ljumsksmärta ett år efter operationen. 30,659 patienter som registrerats i SBR för en ljumskbråcksoperation med öppen eller med titthålsteknik under 2015–2017 inkluderades i studien. Under studieperioden registrerades kirurgiska komplikationer på alla patienter i SBR på samma detaljnivå som i det speciella formuläret som hade använts för deltagarna i den första studien. Därutöver skickades en smärtenkät ut från SBR till alla opererade patienter ett år efter operationen.

Registrerade kirurgiska komplikationer kategoriserades som blödning, sårinfektion, inkapslad vätskeansamling, urinvägskomplikation eller svår smärta efter operationen. Statistiska analyser visade att svår smärta efter operationen var en stark riskfaktor för kronisk smärta vid

operation både med öppen och titthålsteknik. Sårinfektion och blödning var signifikanta riskfaktorer för kronisk smärta efter öppen operation.

8.5 ARBETE IV

I det fjärde arbetet undersökte vi aspekter av ett efterföljande bråck i den motsatta (kontralaterala) ljumsken. Vi undersökte förekomsten av en senare operation i den kontralaterala ljumsken, tiden mellan den första och den andra operationen samt riskfaktorer för utvecklande av ett kontralateralt bråck. En kohort på 151,297 patienter som opererats för ett ensidigt ljumskbråck, med öppen metod eller med titthålsteknik under perioden 2007–2019, och registrerats i SBR inkluderades i studien.

Statistiska beräkningar visade att 7,4% av studiedeltagarna senare genomgick ytterligare en operation i den kontralaterala ljumsken. Mediantiden till den senare operationen var 2,7 år. Analyserna visade att män, äldre personer, direkt ljumskbråck, kombinerat ljumskbråck, bråckstorlek >1,5 cm och bråckstorlek >3 cm samt bråckoperation på vänster sida var riskfaktorer för en senare kontralateral operation. Risken för en senare kontralateral operation var mindre hos patienter som hade opererats med titthålsteknik och hos överviktiga patienter.

8.6 SLUTSATSER AV DE FYRA STUDIERNA

Kronisk smärta efter en ljumskbråcksoperation innebär ett lidande för en stor patientgrupp. Uppföljning och utvärdering av kvarstående postoperativ smärta är viktigt för att bättre förstå uppkomstmekanismer och att kunna utveckla och förbättra kirurgiska metoder och därmed minska problematiken. Den förenklade versionen av smärtformuläret sf-IPQ är ett bra instrument för utvärdering av postoperativ smärta och kan med fördel användas i vardagligt arbete.

De kirurgiska komplikationerna svår postoperativ smärta, blödning och sårinfektion var signifikanta riskfaktorer för kronisk smärta. Dessa riskfaktorer kan ha en koppling till kirurgisk teknik. En möjlig slutsats kan vara att en optimerad och mer försiktig kirurgisk teknik kan minska förekomsten av komplikationer och därmed minska risken att utveckla kronisk smärta.

Andelen patienter som senare opererats i den motsatta sidans ljumske var förhållandevis låg. Med tanke på risken för kronisk smärta efter kirurgi så kan vi inte rekommendera att rutinmässigt operera den motsatta sidans ljumske i samband med titthålsoperation av ett ensidigt ljumskbråck annat än i utvalda fall. Om det föreligger riskfaktorer för ett bråck också på motsatt sida samt om patienten givit samtycke kan en utvidgad operation med undersökning av den motsatta ljumsken övervägas.

9 ACKNOWLEDGEMENTS

Beside all hernia patients around the globe, I am forever grateful to everyone who contributed to making this thesis possible. Thank you,

Ursula Dahlstrand, my head supervisor, for your endless patience, always professional approach and never letting me get away easy, or give up; **Gabriel Sandblom** for your always positive attitude, availability, open mindset and fundamentally important support; Professor **Ulf Gunnarsson** for recruiting and training me into the highest academic level; **Ulf Fränneby**, my former colleague, for your kindness and academic inspiration; **Anders Sondén** for your skills to make difficult things simple; **Linda, Jessica** and **Johanna** at the **Clister** office; everyone in the **research group** for tough but friendly professional academic training; **KI-SÖS** for all support during the years;

All colleagues at **Södersjukhuset, UAS, Västerås** and elsewhere, **Jerzy Lewin**, my former colleague and NYC roommate, for introducing me to both rectus diastasis surgery and to the academic world; **Lennart Boström**, for hiring me in both Västerås and Stockholm as well as supporting my PhD training and local clinical studies; **Thorhallur Agustsson**, my former colleague and roommate (I miss our chats); **Göran Rietz**, my former colleague and "wing man" from both Västerås and Södersjukhuset, (let´s do more robotics); **Leonard, Gunnar, Martin, Karin, Per, Anna, Anders, Kjell et al** from the 36an-team.

Katarina Woxnerud, naphrapath and inspirer, for your invaluable experience, open mindset and positive curiosity; **Otto Stackelberg**, vascular surgeon and brilliant statistician; **Olivia Kiwanuka**, former colleague and mind-blowing academic writer;

CFTK, with **Richard Segerlund Rex** and crew, for making plans come true; **Yngve Raab**, my first registrar supervisor, for the "always have a B-plan" rule; **Claes Rudberg**, my second registrar supervisor, for teaching me to keep things in order; **Bengt A, Lennart E, Claes S, Catharina E, Adam B, Stefan S, Sadettin K, Per H, Tim H, Jeffrey M,** for being promotive role models.

The Balint troop: **Henrik Oppelstrup** (the Dane), **Andreas Fischer** (the Austrian), **Olof Rydin** (the New Zealander), **Anders Stenbäck** (the Uplander), **Johan Hagberg** (the Mind), **Christopher Hedbeck** (the Nobleman) and **Kim Stranger** (the American), for all years with life supporting traditions, academic, intellectual and funny personal development;

Karolina & Tobias and **Erik & Anna**, my dearest sister and brother, with beautiful families, for your love, stability and warm support;

Mom and Dad, **Monica** and **Gunnar**, for your endless love and incomprehensible support;

Camilla, my love, companion and life partner, for your crucial faith, patience, curiosity and for always keeping me alive;

Benjamin, Rebecka and **Jonathan**, my pride, my hope, my future, my everything.

10 REFERENCES

1. Primatesta P, Goldacre MJ. Inguinal hernia repair: incidence of elective and emergency surgery, readmission and mortality. Int J Epidemiol. 1996;25(4):835-9.

2. HerniaSurge G. International guidelines for groin hernia management. Hernia. 2018;22(1):1-165.

3. Lange JF, Kaufmann R, Wijsmuller AR, Pierie JP, Ploeg RJ, Chen DC, et al. An international consensus algorithm for management of chronic postoperative inguinal pain. Hernia. 2015;19(1):33-43.

4. Fränneby U, Sandblom G, Nordin P, Nyrén O, Gunnarsson U. Risk factors for long-term pain after hernia surgery. Ann Surg. 2006;244(2):212-9.

5. Eklund A, Montgomery A, Bergkvist L, Rudberg C, group SMToIHRbLSs. Chronic pain 5 years after randomized comparison of laparoscopic and Lichtenstein inguinal hernia repair. Br J Surg. 2010;97(4):600-8.

6. Sandblom G, Kalliomäki ML, Gunnarsson U, Gordh T. Natural course of long-term postherniorrhaphy pain in a population-based cohort. Scand J Pain. 2010;1(1):55-9.

7. Rutkow IM, Robbins AW. Classification systems and groin hernias. Surg Clin North Am. 1998;78(6):1117-27, viii.

8. Schumpelick V, Treutner KH, Arlt G. Inguinal hernia repair in adults. Lancet. 1994;344(8919):375-9.

9. FRUCHAUD H. [The effect of the upright position proper to man upon the anatomy of the inguinal region: surgical consequences; anatomic bases of surgical treatment of inguinal hernia]. Mem Acad Chir (Paris). 1953;79(25-66):652-61.

10. Paulsen F, Waschke J, editors. Sobotta Atlas of Human Anatomy. 15th Edition ed: Elsevier; 2013.

11. Rowe MI, Copelson LW, Clatworthy HW. The patent processus vaginalis and the inguinal hernia. J Pediatr Surg. 1969;4(1):102-7.

12. Liu WC, Chen TH, Shyu JF, Chen CH, Shih C, Wang JJ, et al. Applied anatomy of the genital branch of the genitofemoral nerve in open inguinal herniorrhaphy. Eur J Surg. 2002;168(3):145-9.

13. Amid PK, Chen DC. Surgical treatment of chronic groin and testicular pain after laparoscopic and open preperitoneal inguinal hernia repair. J Am Coll Surg. 2011;213(4):531-6.

14. Swedish Hernia Register. Available from: wwwsvensktbrackregisterseAnnual report 2019, accessed June 2020.

15. van Veen RN, van Wessem KJ, Halm JA, Simons MP, Plaisier PW, Jeekel J, et al. Patent processus vaginalis in the adult as a risk factor for the occurrence of indirect inguinal hernia. Surg Endosc. 2007;21(2):202-5.

16. Köckerling F, Schug-Pass C. Spermatic Cord Lipoma-A Review of the Literature. Front Surg. 2020;7:39.

17. Piga E, Oberg S, Andresen K, Rosenberg J. Intraoperative handling of spermatic cord lipomas during inguinal hernia repair: a nationwide survey. Hernia. 2021;25(5):1331-7.

18. Condon RE, Carilli S. The Biology and Anatomy of Inguinofemoral Hernia. Semin Laparosc Surg. 1994;1(2):75-85.

19. Skandalakis PN, Zoras O, Skandalakis JE, Mirilas P. Spigelian hernia: surgical anatomy, embryology, and technique of repair. Am Surg. 2006;72(1):42-8.

20. Skandalakis LJ, Androulakis J, Colborn GL, Skandalakis JE. Obturator hernia. Embryology, anatomy, and surgical applications. Surg Clin North Am. 2000;80(1):71-84.

21. de Goede B, Timmermans L, van Kempen BJ, van Rooij FJ, Kazemier G, Lange JF, et al. Risk factors for inguinal hernia in middle-aged and elderly men: results from the Rotterdam Study. Surgery. 2015;157(3):540-6.

22. Ruhl CE, Everhart JE. Risk factors for inguinal hernia among adults in the US population. Am J Epidemiol. 2007;165(10):1154-61.

23. Abramson JH, Gofin J, Hopp C, Makler A, Epstein LM. The epidemiology of inguinal hernia. A survey in western Jerusalem. J Epidemiol Community Health. 1978;32(1):59-67.

24. Henriksen NA, Mortensen JH, Sorensen LT, Bay-Jensen AC, Agren MS, Jorgensen LN, et al. The collagen turnover profile is altered in patients with inguinal and incisional hernia. Surgery. 2015;157(2):312-21.

25. Henriksen NA, Yadete DH, Sorensen LT, Agren MS, Jorgensen LN. Connective tissue alteration in abdominal wall hernia. Br J Surg. 2011;98(2):210-9.

26. Meyer AL, Berger E, Monteiro O, Alonso PA, Stavale JN, Gonçalves MP. Quantitative and qualitative analysis of collagen types in the fascia transversalis of inguinal hernia patients. Arq Gastroenterol. 2007;44(3):230-4.

27. Rosemar A, Angerås U, Rosengren A, Nordin P. Effect of body mass index on groin hernia surgery. Ann Surg. 2010;252(2):397-401.

28. Rosemar A, Angerås U, Rosengren A. Body mass index and groin hernia: a 34-year follow-up study in Swedish men. Ann Surg. 2008;247(6):1064-8.

29. Rusko J, Pancotti R, Brown R, editors. Maingot´s Abdominal Operations. Eleventh Edition ed: McGraw-Hill companies; 2007.

30. Cobb WS, Burns JM, Kercher KW, Matthews BD, James Norton H, Todd Heniford B. Normal intraabdominal pressure in healthy adults. J Surg Res. 2005;129(2):231-5.

31. Koehler RH. Diagnosing the occult contralateral inguinal hernia. Surg Endosc. 2002;16(3):512-20.

32. Zendejas B, Onkendi EO, Brahmbhatt RD, Greenlee SM, Lohse CM, Farley DR. Contralateral metachronous inguinal hernias in adults: role for prophylaxis during the TEP repair. Hernia. 2011;15(4):403-8.

33. van den Heuvel B, Beudeker N, van den Broek J, Bogte A, Dwars BJ. The incidence and natural course of occult inguinal hernias during TAPP repair: repair is beneficial. Surg Endosc. 2013;27(11):4142-6.

34. Jacob DA, Hackl JA, Bittner R, Kraft B, Kockerling F. Perioperative outcome of unilateral versus bilateral inguinal hernia repairs in TAPP technique: analysis of 15,176 cases from the Herniamed Registry. Surg Endosc. 2015;29(12):3733-40.

35. Lee CH, Chiu YT, Cheng CF, Wu JC, Yin WY, Chen JH. Risk factors for contralateral inguinal hernia repair after unilateral inguinal hernia repair in male adult patients: analysis from a nationwide population based cohort study. BMC Surg. 2017;17(1):106.

36. Dahlstrand U, Wollert S, Nordin P, Sandblom G, Gunnarsson U. Emergency femoral hernia repair: a study based on a national register. Ann Surg. 2009;249(4):672-6.

37. Dahlstrand U, Sandblom G, Nordin P, Wollert S, Gunnarsson U. Chronic pain after femoral hernia repair: a cross-sectional study. Ann Surg. 2011;254(6):1017-21.

38. Robinson A, Light D, Nice C. Meta-analysis of sonography in the diagnosis of inguinal hernias. J Ultrasound Med. 2013;32(2):339-46.

39. Piga E, Zetner D, Andresen K, Rosenberg J. Imaging modalities for inguinal hernia diagnosis: a systematic review. Hernia. 2020;24(5):917-26.

40. Robinson A, Light D, Kasim A, Nice C. A systematic review and meta-analysis of the role of radiology in the diagnosis of occult inguinal hernia. Surg Endosc. 2013;27(1):11-8.

41. Miller J, Cho J, Michael MJ, Saouaf R, Towfigh S. Role of imaging in the diagnosis of occult hernias. JAMA Surg. 2014;149(10):1077-80.

42. Arvidsson D, Smedberg S. Laparoscopic compared with open hernia surgery: complications, recurrences and current trends. Eur J Surg Suppl. 2000(585):40-7.

43. Cooper A. The anatomy and surgical treatment of abdominal hernia. London: Lea & Blanchard; 1844. p. 427.

44. McBee P, Fitzgibbons jR. The current status of watchful waiting for inguinal hernia management: a review of clinical evidence. Mini-invasive Surgery2021.

45. Reistrup H, Fonnes S, Rosenberg J. Watchful waiting vs repair for asymptomatic or minimally symptomatic inguinal hernia in men: a systematic review. Hernia. 2021;25(5):1121-8.

46. Fitzgibbons RJ, Giobbie-Hurder A, Gibbs JO, Dunlop DD, Reda DJ, McCarthy M, et al. Watchful waiting vs repair of inguinal hernia in minimally symptomatic men: a randomized clinical trial. JAMA. 2006;295(3):285-92.

47. Lascaratos JG, Tsiamis C, Kostakis A. Surgery for inguinal hernia in Byzantine times (A.D. 324-1453): first scientific descriptions. World J Surg. 2003;27(10):1165-9.

48. Olch PD. William S. Halsted and local anesthesia: contributions and complications. Anesthesiology. 1975;42(4):479-86.

49. GORDH T. Xylocain, a new local analgesic. Anaesthesia. 1949;4(1):4-9.

50. Raymond C. The Centenary of Bassini´s Contribution to Inguinal Herniorraphy. The American Journal of Surgery1987. p. 324-6.

51. Mair GB. Criticism of the Bassini Operation and its Modifications. Br Med J. 1945;2(4414):178-81.

52. Shouldice EB. The Shouldice repair for groin hernias. Surg Clin North Am. 2003;83(5):1163-87, vii.

53. Hay JM, Boudet MJ, Fingerhut A, Poucher J, Hennet H, Habib E, et al. Shouldice inguinal hernia repair in the male adult: the gold standard? A multicenter controlled trial in 1578 patients. Ann Surg. 1995;222(6):719-27.

54. CUMBERLAND VH. A preliminary report on the use of prefabricated nylon weave in the repair of ventral hernia. Med J Aust. 1952;1(5):143-4.

55. USHER FC, OCHSNER J, TUTTLE LL. Use of marlex mesh in the repair of incisional hernias. Am Surg. 1958;24(12):969-74.

56. Ibrahim AM, Vargas CR, Colakoglu S, Nguyen JT, Lin SJ, Lee BT. Properties of meshes used in hernia repair: a comprehensive review of synthetic and biologic meshes. J Reconstr Microsurg. 2015;31(2):83-94.

57. Conze J, Kingsnorth AN, Flament JB, Simmermacher R, Arlt G, Langer C, et al. Randomized clinical trial comparing lightweight composite mesh with polyester or polypropylene mesh for incisional hernia repair. Br J Surg. 2005;92(12):1488-93.

58. Lichtenstein IL, Shore JM. Exploding the myths of hernia repair. Am J Surg. 1976;132(3):307-15.

59. Lichtenstein IL, Shulman AG, Amid PK, Montllor MM. The tension-free hernioplasty. Am J Surg. 1989;157(2):188-93.

60. Shulman AG, Amid PK, Lichtenstein IL. The safety of mesh repair for primary inguinal hernias: results of 3,019 operations from five diverse surgical sources. Am Surg. 1992;58(4):255-7.

61. Amid PK. How to avoid recurrence in Lichtenstein tension-free hernioplasty. Am J Surg. 2002;184(3):259-60.

62. Nyhus LM, Pollak R, Bombeck CT, Donahue PE. The preperitoneal approach and prosthetic buttress repair for recurrent hernia. The evolution of a technique. Ann Surg. 1988;208(6):733-7.

63. Stoppa R, Verhaeghe P. [Tension and suture free repair of groin hernias using a large, bilateral prosthesis and by the pre-peritoneal way]. J Chir (Paris). 1998;135(2):71-3.

64. Filipi CJ, Fitzgibbons RJ, Salerno GM, Hart RO. Laparoscopic herniorrhaphy. Surg Clin North Am. 1992;72(5):1109-24.

65. Arregui ME, Navarrete J, Davis CJ, Castro D, Nagan RF. Laparoscopic inguinal herniorrhaphy. Techniques and controversies. Surg Clin North Am. 1993;73(3):513-27.

66. McKernan JB. Laparoscopic extraperitoneal repair of inguinofemoral herniation. Endosc Surg Allied Technol. 1993;1(4):198-203.

67. Phillips EH, Carroll BJ, Fallas MJ. Laparoscopic preperitoneal inguinal hernia repair without peritoneal incision. Technique and early clinical results. Surg Endosc. 1993;7(3):159-62.

68. Bringman S, Ramel S, Heikkinen TJ, Englund T, Westman B, Anderberg B. Tension-free inguinal hernia repair: TEP versus mesh-plug versus Lichtenstein: a prospective randomized controlled trial. Ann Surg. 2003;237(1):142-7.

69. Phillips EH, Rosenthal R, Fallas M, Carroll B, Arregui M, Corbitt J, et al. Reasons for early recurrence following laparoscopic hernioplasty. Surg Endosc. 1995;9(2):140-4; discussion 4-5.

70. Bittner R, Leibl B, Kraft K, Däubler P, Schwarz J. [Laparoscopic hernioplasty (TAPP)--complications and recurrences in 900 operations]. Zentralbl Chir. 1996;121(4):313-9.

71. Felix E, Scott S, Crafton B, Geis P, Duncan T, Sewell R, et al. Causes of recurrence after laparoscopic hernioplasty. A multicenter study. Surg Endosc. 1998;12(3):226-31.

72. Daes J, Felix E. Critical View of the Myopectineal Orifice. Ann Surg. 2017;266(1):e1-e2.

73. Donabedian A. The quality of care. How can it be assessed? JAMA. 1988;260(12):1743-8.

74. Clavien PA, Sanabria JR, Strasberg SM. Proposed classification of complications of surgery with examples of utility in cholecystectomy. Surgery. 1992;111(5):518-26.

75. Gutacker N, Street A. Use of large-scale HRQoL datasets to generate individualised predictions and inform patients about the likely benefit of surgery. Qual Life Res. 2017;26(9):2497-505.

76. Kald A, Nilsson E, Anderberg B, Bragmark M, Engström P, Gunnarsson U, et al. Reoperation as surrogate endpoint in hernia surgery. A three year follow-up of 1565 herniorrhaphies. Eur J Surg. 1998;164(1):45-50.

77. Nordin P, Haapaniemi S, Kald A, Nilsson E. Influence of suture material and surgical technique on risk of reoperation after non-mesh open hernia repair. Br J Surg. 2003;90(8):1004-8.

78. Sevonius D, Gunnarsson U, Nordin P, Nilsson E, Sandblom G. Recurrent groin hernia surgery. Br J Surg. 2011;98(10):1489-94.

79. Eklund AS, Montgomery AK, Rasmussen IC, Sandbue RP, Bergkvist LA, Rudberg CR. Low recurrence rate after laparoscopic (TEP) and open (Lichtenstein) inguinal hernia repair: a randomized, multicenter trial with 5-year follow-up. Ann Surg. 2009;249(1):33-8.

80. Burcharth J, Andresen K, Pommergaard HC, Bisgaard T, Rosenberg J. Recurrence patterns of direct and indirect inguinal hernias in a nationwide population in Denmark. Surgery. 2014;155(1):173-7.

81. Scheuerlein H, Schiller A, Schneider C, Scheidbach H, Tamme C, Köckerling F. Totally extraperitoneal repair of recurrent inguinal hernia. Surg Endosc. 2003;17(7):1072-6.

82. Köckerling F, Jacob D, Wiegank W, Hukauf M, Schug-Pass C, Kuthe A, et al. Endoscopic repair of primary versus recurrent male unilateral inguinal hernias: Are there differences in the outcome? Surg Endosc. 2016;30(3):1146-55.

83. Mayhew D, Mendonca V, Murthy BVS. A review of ASA physical status - historical perspectives and modern developments. Anaesthesia. 2019;74(3):373-9.

84. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205-13.

85. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg. 2009;250(2):187-96.

86. Simons MP, Aufenacker T, Bay-Nielsen M, Bouillot JL, Campanelli G, Conze J, et al. European Hernia Society guidelines on the treatment of inguinal hernia in adult patients. Hernia. 2009;13(4):343-403.

87. Jolissaint JS, Dieffenbach BV, Tsai TC, Pernar LI, Shoji BT, Ashley SW, et al. Surgical site occurrences, not body mass index, increase the long-term risk of ventral hernia recurrence. Surgery. 2020;167(4):765-71.

88. Sereysky J, Parsikia A, Stone ME, Castaldi M, McNelis J. Predictive factors for the development of surgical site infection in adults undergoing initial open inguinal hernia repair. Hernia. 2020;24(1):173-8.

89. Romero-Velez G, Lima DL, Pereira X, Farber BA, Friedmann P, Malcher F, et al. Risk Factors for Surgical Site Infection in the Undeserved Population After Ventral Hernia Repair: A 3936 Patient Single-Center Study Using National Surgical Quality Improvement Project. J Laparoendosc Adv Surg Tech A. 2022.

90. Yang L, Wang H, Liang X, Chen T, Chen W, Song Y, et al. Bacteria in hernia sac: an important risk fact for surgical site infection after incarcerated hernia repair. Hernia. 2015;19(2):279-83.

91. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet. 2006;367(9522):1618-25.

92. Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, et al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. Pain. 2020;161(9):1976-82.

93. Wheeler M, Oderda GM, Ashburn MA, Lipman AG. Adverse events associated with postoperative opioid analgesia: a systematic review. J Pain. 2002;3(3):159-80.

94. Althaus A, Arránz Becker O, Neugebauer E. Distinguishing between pain intensity and pain resolution: using acute post-surgical pain trajectories to predict chronic post-surgical pain. Eur J Pain. 2014;18(4):513-21.

95. Aasvang E, Kehlet H. Chronic postoperative pain: the case of inguinal herniorrhaphy. Br J Anaesth. 2005;95(1):69-76.

96. Peters ML, Sommer M, de Rijke JM, Kessels F, Heineman E, Patijn J, et al. Somatic and psychologic predictors of long-term unfavorable outcome after surgical intervention. Ann Surg. 2007;245(3):487-94.

97. Langeveld HR, Klitsie P, Smedinga H, Eker H, Van't Riet M, Weidema W, et al. Prognostic value of age for chronic postoperative inguinal pain. Hernia. 2015;19(4):549-55.

98. Romain B, Fabacher T, Ortega-Deballon P, Montana L, Cossa JP, Gillion JF, et al. Longitudinal cohort study on preoperative pain as a risk factor for chronic postoperative inguinal pain after groin hernia repair at 2-year follow-up. Hernia. 2021.

99. Dominguez CA, Kalliomäki M, Gunnarsson U, Moen A, Sandblom G, Kockum I, et al. The DQB1 *03:02 HLA haplotype is associated with increased risk of chronic pain after inguinal hernia surgery and lumbar disc herniation. Pain. 2013;154(3):427-33.

100. Belfer I, Dai F, Kehlet H, Finelli P, Qin L, Bittner R, et al. Association of functional variations in COMT and GCH1 genes with postherniotomy pain and related impairment. Pain. 2015;156(2):273-9.

101. Reinpold W. Risk factors of chronic pain after inguinal hernia repair: a systematic review. Innov Surg Sci. 2017;2(2):61-8.

102. Bjurstrom MF, Nicol AL, Amid PK, Chen DC. Pain control following inguinal herniorrhaphy: current perspectives. J Pain Res. 2014;7:277-90.

103. Kyle-Leinhase I, Köckerling F, Jørgensen LN, Montgomery A, Gillion JF, Rodriguez JAP, et al. Comparison of hernia registries: the CORE project. Hernia. 2018;22(4):561-75.

104. Axman E, Nordin P, Modin M, de la Croix H. Assessing the Validity and Cover Rate of the National Swedish Hernia Register. Clin Epidemiol. 2021;13:1129-34.

105. Nilsson E, Haapaniemi S. Hernia registers and specialization. Surg Clin North Am. 1998;78(6):1141-55, ix.

106. [The Danish hernia database--the first year]. Ugeskr Laeger. 2000;162(11):1552-5.

107. Stechemesser B, Jacob DA, Schug-Paß C, Köckerling F. Herniamed: an internet-based registry for outcome research in hernia surgery. Hernia. 2012;16(3):269-76.

108. Muysoms F, Campanelli G, Champault GG, DeBeaux AC, Dietz UA, Jeekel J, et al. EuraHS: the development of an international online platform for registration and outcome measurement of ventral abdominal wall hernia repair. Hernia. 2012;16(3):239-50.

109. Poulose BK, Roll S, Murphy JW, Matthews BD, Todd Heniford B, Voeller G, et al. Design and implementation of the Americas Hernia Society Quality Collaborative (AHSQC): improving value in hernia care. Hernia. 2016;20(2):177-89.

110. Sanders. http://www.hscic.gov.uk//proms-background 2014 [

111. Jensen KK, Henriksen NA, Harling H. Standardized measurement of quality of life after incisional hernia repair: a systematic review. Am J Surg. 2014;208(3):485-93.

112. Fränneby U, Gunnarsson U, Andersson M, Heuman R, Nordin P, Nyrén O, et al. Validation of an Inguinal Pain Questionnaire for assessment of chronic pain after groin hernia repair. Br J Surg. 2008;95(4):488-93.

113. Heniford BT, Walters AL, Lincourt AE, Novitsky YW, Hope WW, Kercher KW. Comparison of generic versus specific quality-of-life scales for mesh hernia repairs. J Am Coll Surg. 2008;206(4):638-44.

114. Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. Pain. 1975;1(3):277-99.

115. Melzack R. The short-form McGill Pain Questionnaire. Pain. 1987;30(2):191-7.

116. Burckhardt CS, Bjelle A. A Swedish version of the short-form McGill Pain Questionnaire. Scand J Rheumatol. 1994;23(2):77-81.

117. Fränneby U, Sandblom G, Nyrén O, Nordin P, Gunnarsson U. Self-reported adverse events after groin hernia repair, a study based on a national register. Value Health. 2008;11(5):927-32.

118. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. Psychol Bull.1979. p. 420-8.

119. Yang MMH, Hartley RL, Leung AA, Ronksley PE, Jetté N, Casha S, et al. Preoperative predictors of poor acute postoperative pain control: a systematic review and meta-analysis. BMJ Open. 2019;9(4):e025091.

120. Stevans JM, Delitto A, Khoja SS, Patterson CG, Smith CN, Schneider MJ, et al. Risk Factors Associated With Transition From Acute to Chronic Low Back Pain in US Patients Seeking Primary Care. JAMA Netw Open. 2021;4(2):e2037371.

121. Bjurström MF, Irwin MR, Chen DC, Smith MT, Montgomery A. Sex Differences, Sleep Disturbance and Risk of Persistent Pain Associated With Groin Hernia Surgery: A Nationwide Register-Based Cohort Study. J Pain. 2021;22(11):1360-70.

122. Dahlstrand U, Sandblom G, Ljungdahl M, Wollert S, Gunnarsson U. TEP under general anesthesia is superior to Lichtenstein under local anesthesia in terms of pain 6 weeks after surgery: results from a randomized clinical trial. Surg Endosc. 2013;27(10):3632-8.

123. Haapaniemi S, Nilsson E. Recurrence and pain three years after groin hernia repair. Validation of postal questionnaire and selective physical examination as a method of follow-up. Eur J Surg. 2002;168(1):22-8.

124. Kalliomäki ML, Meyerson J, Gunnarsson U, Gordh T, Sandblom G. Long-term pain after inguinal hernia repair in a population-based cohort; risk factors and interference with daily activities. Eur J Pain. 2008;12(2):214-25.

125. Bay-Nielsen M, Nilsson E, Nordin P, Kehlet H, Base SHDBtDHD. Chronic pain after open mesh and sutured repair of indirect inguinal hernia in young males. Br J Surg. 2004;91(10):1372-6.

126. Callesen T, Bech K, Kehlet H. Prospective study of chronic pain after groin hernia repair. Br J Surg. 1999;86(12):1528-31.

127. Nienhuijs S, Staal E, Strobbe L, Rosman C, Groenewoud H, Bleichrodt R. Chronic pain after mesh repair of inguinal hernia: a systematic review. Am J Surg. 2007;194(3):394-400.

128. Tjeertes EK, Tjeertes EE, Hoeks SE, Hoeks SS, Beks SB, Beks SS, et al. Obesity--a risk factor for postoperative complications in general surgery? BMC Anesthesiol. 2015;15:112.

129. Kraychete DC, Sakata RK, Lannes LeO, Bandeira ID, Sadatsune EJ. Postoperative persistent chronic pain: what do we know about prevention, risk factors, and treatment. Braz J Anesthesiol. 2016;66(5):505-12.

130. Tetik C, Arregui ME, Dulucq JL, Fitzgibbons RJ, Franklin ME, McKernan JB, et al. Complications and recurrences associated with laparoscopic repair of groin hernias. A multi-institutional retrospective analysis. Surg Endosc. 1994;8(11):1316-22; discussion 22-3.

131. Chamzin A, Frountzas M, Gkiokas G, Kouskouni E, Xanthos T, Michalopoulos NV. The Effect of Intraoperative Transversus Abdominis Plane Blocking on Postoperative

Pain After Laparoscopic Transabdominal Pre-peritoneal (TAPP) Groin Hernia Repair. Front Surg. 2022;9:834050.

132. Aasvang E, Kehlet H. Surgical management of chronic pain after inguinal hernia repair. Br J Surg. 2005;92(7):795-801.

133. Jensen EK, Ringsted TK, Bischoff JM, Petersen MA, Rosenberg J, Kehlet H, et al. A national center for persistent severe pain after groin hernia repair: Five-year prospective data. Medicine (Baltimore). 2019;98(33):e16600.

134. Sayad P, Abdo Z, Cacchione R, Ferzli G. Incidence of incipient contralateral hernia during laparoscopic hernia repair. Surg Endosc. 2000;14(6):543-5.

135. Ismail M, Nair S, Garg P. Is prophylactic laparoscopic total extraperitoneal inguinal hernia repair on the contralateral side justified in less developed regions? A comparative study of bilateral to unilateral repair. J Laparoendosc Adv Surg Tech A. 2010;20(6):533-6.

136. Fitzgibbons RJ, Ramanan B, Arya S, Turner SA, Li X, Gibbs JO, et al. Long-term results of a randomized controlled trial of a nonoperative strategy (watchful waiting) for men with minimally symptomatic inguinal hernias. Ann Surg. 2013;258(3):508-15.

137. Chung L, Norrie J, O'Dwyer PJ. Long-term follow-up of patients with a painless inguinal hernia from a randomized clinical trial. Br J Surg. 2011;98(4):596-9.

138. Dhanani NH, Olavarria OA, Wootton S, Petsalis M, Lyons NB, Ko TC, et al. Contralateral exploration and repair of occult inguinal hernias during laparoscopic inguinal hernia repair: systematic review and Markov decision process. BJS Open. 2021;5(2).

139. Thumbe VK, Evans DS. To repair or not to repair incidental defects found on laparoscopic repair of groin hernia: early results of a randomized control trial. Surg Endosc. 2001;15(1):47-9.

140. Flum DR. The asymptomatic hernia: "if it's not broken, don't fix it". JAMA. 2006;295(3):328-9.