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MESH IN HERNIA SURGERY

ASPECTS ON RECURRENCE AND PAIN OF DIFFERENT MESH TYPES IN GROIN HERNIA REPAIR AND MESH REPAIR IN SMALL UMBILICAL HERNIAS

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Mesh in Hernia Surgery - aspects on recurrence and pain of different mesh types in groin hernia repair and mesh repair in small umbilical hernias

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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"Life can only be understood backwards, but it must be lived forwards."

- *Søren Kierkegaard*

FOREWORD

I here present a thesis with four epidemiological papers in which I and colleagues have invested time to conduct research for the purpose to gain more clarity and knowledge about mesh in hernia surgery. The thesis is focused on the groin and umbilical hernia disease, and their surgical treatment with mesh. The thesis will hopefully add more elements to the current literature on recurrence and pain for different mesh types following groin hernia repair. Our scientific questions of interest were suitably addressed by using highly validated prospectively collected data from our unique Swedish nationwide hernia register. Furthermore, the thesis also includes a descriptive, retrospective study of mesh treatment for small umbilical hernias. The surgical method used in this study served as a basis for a national multicenter randomized clinical trial investigating treatment outcomes of small umbilical hernia repairs. The study protocol of this clinical trial is presented as Appendix A in this thesis. Indeed, many challenges arose while conducting this multicenter surgical intervention study.

The thesis begins by comprehensively, but at the same time in a selected manner, describing and discussing the already established, but yet deficient, scientific knowledge in the relevant field of mesh in hernia repair. Hopefully this introduction will increase the awareness of any outstanding questions and concerns in the field that was present at the very start of my research, and also facilitate to understand the aims of the thesis. Thereafter, the study methods and key results are described, where I also emphasize the ethical and methodological considerations of the studies. Finally, the significance of my research and its contribution to the field of mesh hernia repair is discussed. In addition to being scientific, objectively and critically evaluating the evidence in my writing, I also sometimes take sides, speculate and express my own honest views.

My aspiration is that this thesis will add novel evidence and contribute to the advancement in theoretical knowledge and clinical aspects of the field of mesh hernia repair, to ultimately benefit patient outcomes.

Maria Melkemichel

ABSTRACT

The groin hernia repair is one of the most common surgical procedure in Sweden with nearly 16,000 repairs performed annually. Including a mesh has become standard in the repair and the type of material and weight can influence the two main important postoperative complications; recurrence and pain. Lightweight meshes (LWM) have shown to have improved benefits compared to heavyweight meshes (HWM) in terms of less short-term pain and discomfort following both an open anterior mesh (OAM) groin hernia repair and a laparoscopic totally extra-peritoneal (TEP) hernia repair. A lighter mesh with less material could also be beneficial to reduce the risk of chronic pain after surgery. However, concerns exist whether LWM may be associated with higher recurrence rates. Furthermore, compared to groin hernias, small umbilical hernias continue to see a non-standardized practice and mostly limited use of mesh, despite recurrence rates considered to be high with a simple suture repair.

In **Paper I**, the aim was to compare the reoperation rate for recurrences of LWM versus HWM in TEP groin hernia repairs through an observational nationwide population-based cohort. 13,839 hernia repairs between year 2005 and 2013 were collected from the Swedish Hernia Register (SHR) and analyzed with a minimum of a 2-years follow-up. 491 (3.5 %) hernia repairs were reoperated for recurrence and the results demonstrated a significantly associated increased risk of reoperation for recurrence in repairs with LWM (HR 1.56, CI 1.29-1.88) compared to HWM. The risk of recurrence with the use of LWM in indirect and smaller hernia repairs were more comparable to HWM.

In **Paper II**, the aim was to compare the reoperation rate for recurrences of different types of LWMs versus HWM in OAM inguinal hernia repairs through an observational nationwide population-based cohort. Data on 76,495 hernia repairs on male patients undergoing an elective OAM inguinal hernia repair between year 2005 and 2013 was collected from the SHR and analyzed with a minimum of a 2-years follow-up. 1676 (2.1 %) hernia repairs were reoperated for recurrence and the results did not reveal an associated increased risk of reoperation for recurrence for the regular LWM-PP (polypropylene) (HR 1.12, CI 0.96-1.31) compared to HWM. Composite LWM-PP were however associated with an increased risk of recurrence compared to HWM.

In **Paper III**, the aim was to compare the chronic pain rate 1 year after surgery in different LWMs compared to HWM, following an OAM inguinal hernia repair, through an observational nationwide population-based cohort with prospectively assessed patient-reported outcome measures (PROMs). 23,259 male patients via the SHR (response rate 70.6 %) provided answers to the pain questionnaire and were analyzed. Rates of chronic pain were 15.8 % and 15.6 % for the two different LWM groups and the risk of developing significant chronic pain 1 year after surgery did not differ from the repairs with HWM (16.2 %). Younger male patients less than 50 years old had a significant increased risk of reporting chronic pain (19.4 %, OR 1.43, CI 1.29-1.60) compared to elderly patients.

In **Paper IV**, the aim was to investigate the surgical site complications within 30 days after surgery and recurrences of small umbilical hernias ≤ 2 cm that had undergone a repair with a small onlay mesh. Data on 80 elective small umbilical hernia repairs between 2015 and 2019 in a single surgical center at the department of Surgery in Södertälje Hospital (in the region of Stockholm) was collected retrospectively from the hospital's medical database. Patients were followed at least 4 months after surgery in the outpatient clinic documentation. 4

patients were identified to have had a surgical site complication and no cases of recurrence were registered in the outpatient clinic documentation.

In conclusion, while the use of HWM can have advantages to avoid increased recurrence rates in the TEP groin hernia repair, LWM can be recommended for cases of smaller and indirect hernia defects. However, there are no benefits of using HWM in OAM inguinal hernia repairs on male patients, irrespective of the size or the type of the hernia. Whereas recurrence rates in OAM inguinal repair on male patients were low, the chronic pain rates were unsatisfactorily high, particularly in younger patients, and was not found to be influenced by type of mesh used. The best surgical treatment for small umbilical hernia defects is still under research. Repairing small umbilical hernias with a small onlay-mesh seemed however safe with a low surgical site complication rate. Still, randomized controlled trials are warranted to assess whether mesh can reduce recurrences in comparison to a simple suture repair for the repair of umbilical hernias ≤2 cm.

LIST OF SCIENTIFIC PAPERS

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

I. **Lower recurrence rate with heavyweight mesh compared to lightweight mesh in laparoscopic totally extra-peritoneal (TEP) repair of groin hernia: a nationwide population-based register study.**
Melkemichel M, Bringman S, Widhe B.
Hernia, 2018 Dec;22(6):989-997

II. **Long-term Comparison of Recurrence Rates Between Different Lightweight and Heavyweight Meshes in Open Anterior Mesh Inguinal Hernia Repair: A Nationwide Population-based Register Study.**
Melkemichel M, Bringman SAW, Widhe BOO.
Annals of Surgery, 2021 Feb;273(2):365-372.

III. **Patient-reported chronic pain after open inguinal hernia repair with lightweight or heavyweight mesh: a prospective, patient-reported outcomes study.**
Melkemichel M, Bringman S, Nilsson H, Widhe B.
British Journal of Surgery, 2020 Nov;107(12):1659-1666

IV. **Onlay mesh repair for treatment of small umbilical hernias ≤ 2 cm in adults – A single-centre investigation.**
Melkemichel M, Stjärne L, Bringman S, Widhe B
Hernia, 2021 Sep

Related work presented as Appendix A – Study protocol for the SUMMER Trial

SUMMER Trial: Mesh versus Suture repair in small umbilical hernias in adults: A study protocol for a prospective randomized double-blind multicenter clinical trial.
Melkemichel M, Bringman S, Granåsen G, Widhe B
Trials, 2021 Jun 22;22(1):411.

LIST OF ABBREVIATIONS

ASA class	American Society of Anesthesiologists classification
BMI	Body mass index
CI	Conference interval
DVHD	Danish Ventral Hernia Database
EHS	European Hernia Society
FBR	Foreign Body Reaction
HWM	Heavyweight mesh
HR	Hazards ratio
IPOM	Intra-peritoneal onlay mesh
IPQ	Inguinal Pain Questionnaire
LWM	Lightweight mesh
LWM-PP/PG	Lightweight mesh polypropylene with polyglactin-910
LWM-PP/PGC	Lightweight mesh polypropylene with poliglecaprone-25
NNT	Number needed to treat
OAM	Open anterior mesh
OR	Odds ratio
PP	Polypropylene
PROM	Patient-Reported Outcome Measure
RCT	Randomized clinical trial
Regular LWM-PP	Regular lightweight mesh polypropylene
SHR	Swedish Hernia Register
SSI	Surgical site infection
TAPP	Trans-abdominal pre-peritoneal
TEP	Totally extra-peritoneal
VHPQ	Ventral Hernia Pain Questionnaire

CONTENTS

1 THESIS AT THE GLANCE

	Paper I	Paper II	Paper III	Paper IV
Aim	Comparison of reoperation risk for recurrence between LWM versus HWM following a TEP groin hernia repair.	Comparison of reoperation risk for recurrence between different LWMs versus HWM following an OAM inguinal hernia repair.	Comparison of patient-reported chronic pain between different LWMs versus HWM following an OAM inguinal hernia repair.	Investigation of surgical site complications and recurrences following an onlay mesh repair in small umbilical hernia defects.
Study population	13,839 TEP groin hernia repairs analyzed from the SHR, 2005-2013.	76,495 OAM inguinal hernia repairs on male patients analyzed from the SHR, 2005-2013.	23,259 OAM inguinal hernia repairs on male patients analyzed from the SHR with responded pain questionnaire, 2012-2016	80 small umbilical hernias ≤ 2 cm, repaired with a small onlay mesh in one surgical center between 2015 and 2019 was analyzed.
Methods	Nationwide prospective population-based study to assess recurrence.	Nationwide prospective population-based study to assess recurrence.	Nationwide prospective population-based PROM study to assess chronic pain.	Retrospective, descriptive study to assess surgical site complications within 30 days and recurrences.
Results	A significantly increased risk of reoperation for recurrence for the hernia repairs performed with LWMs, compared to HWM was found. The risk of recurrence with the use of LWM in indirect and smaller hernia repairs was more comparable to HWM.	No difference in the risk of reoperation for recurrence was found between HWM and regular LWM-PP. Composite LWM-PP was associated with an increased risk of recurrence compared to HWM.	No significant difference in of chronic pain was found between regular LWM-PP or composite LWM-PP compared to HWM.	4 patients were found to have had a surgical site complication within 30 days after surgery. No cases of recurrence were noticed.
Conclusion	While direct and larger hernia defects may benefit from HWM to avoid increased recurrence rates, LWM can be recommended for use in indirect and smaller hernia defects in TEP groin hernia repair.	Considering that regular LWM-PP also has less associated side effects there are no benefits of using HWM in OAM inguinal hernia repair.	Type of mesh did not influence the risk of developing chronic pain 1 year following an OAM inguinal hernia repair on male patients.	Repairing elective small umbilical hernias with a small onlay mesh was safe with a low surgical site complication rate. However, randomized trials are warranted to assess whether an onlay mesh can reduce the risk of recurrence for small umbilical hernia repairs.

2 BACKGROUND

2.1 INTRODUCTION

"The final word on hernia will probably never be written."

- *Sir John Bruce of Edinburgh, Professor of Surgery, 1905-1975*

Have you come to the point where you have placed your hand on your abdominal wall while coughing and wondered: Do I have a rupture? If yes, then I can tell you that;

A hernia is a widespread condition.

Operations for groin hernias are one of the most common and leading procedure in general surgery worldwide[1].

In 2015 almost 20 million people globally were estimated to have been affected by a groin hernia[1]. Therefore, continually improving and decreasing the occurrence of postoperative complications, such as recurrence and pain, are necessary to prevent impairment in many patients' lives.

A hernia is defined as an abnormal protrusion of the abdominal-cavity content through an area of weakness in the abdominal wall[2]. Preperitoneal, intraabdominal and retroperitoneal fat and visceral organs can therefore bulge out and cause pain for the patient. Occasionally, the contents can be incarcerated and strangulation of the blood circulation to the organs may occur. The latter can require emergency surgery with bowel resection and increased morbidity.

The most common types of hernias are groin, umbilical, epigastric and incisional hernia defects. Groin hernias can be either inguinal or femoral.

In Sweden, approximately 16,000 groin hernia repairs are performed annually[3]. The most frequent technique used for the repair is the so-called "tension-free hernioplasty", which can also

be referred to as the Lichtenstein method or the "Open anterior mesh" (OAM) groin hernia repair[3].

The next common hernia type is an umbilical hernia and accounts for at least 10 % of all the abdominal wall hernia defects[4]. Yet, the knowledge about umbilical hernia disease is still limited. Its repair is different worldwide; both between and within countries and without any gold standard treatment, particularly for small umbilical hernia defects.

2.2 THE GROIN HERNIA DISEASE

"A surgeon can do more for the community by operating on hernia cases and seeing that his recurrence rate is low than he can by operating on cases of malignant disease."

Sir Cecil Wakely, President, Royal Collage of Surgeons, 1948-

2.2.1 Epidemiology

Since the abdominal wall weakens with age, the prevalence of inguinal hernias is more common in the ageing population[5]. The exact incidence is not yet described, but the life-time risk of acquiring an inguinal hernia has been estimated to be 27% for men and 3 % for women[6]. This disparity can be explained by the different anatomical circumstances between the genders. A patent processus vaginalis is a well-known risk factor for developing an indirect hernia in men[7]. Furthermore, the opening of the external inguinal ring is naturally wider in men than in women (due to the presence of the spermatic cord), allowing the wall against the abdominal cavity to weaken and increasing the risk for intestine and peritoneum to protrude. Although indirect hernia defects are the most common groin hernias in both men and women, femoral hernias are more commonly diagnosed in women compared to men[7].

In addition to sex and age as risk factors for developing a groin hernia, abnormal metabolism of collagen/the extracellular matrix, family history, connective tissue diseases, abdominal wall deficiency after surgery (i.e., prostatectomy), chronic obstructive disorders and heavy work have also all been shown to be associated with an increased risk[8, 8-14]. Additionally, smoking may also affect the risk for groin hernia, by weakening the connective tissue[7]. Whereas some studies have

demonstrated obesity as a risk factor for developing an inguinal hernia, others have in contrast published conflicting data, presenting obesity as a protective variable[14,15].

2.2.2 Surgical treatment

Surgical repair is the only definitive cure for a groin hernia. Symptoms that present with a bulging resistance that limits daily physical activity and causes discomfort for the patient are the main indications for surgery. Groin hernias that do not cause any symptoms in men are not recommended to undergo a repair, due to concerns of postoperative chronic pain[16]. For women, however, surgery is always generally recommended, regardless of symptoms, due to the higher rate of femoral hernias which are associated with more complications[17].

The tension-free hernioplasty

Open mesh repair

Despite former well-known and excellent hernia surgeons' contributions to the hernia suture repair treatment, it was not until the tension-free hernioplasty was introduced in 1970's by the Los Angeles local Dr. Irving Lichtenstein, that the hernia repair took its stance. Without a doubt, the recurrence rates remarkably reduced widely internationally[18,19]. Consequently, also a significant reduction in pain after surgery was seen amongst these patients that underwent this new mesh repair[18]. A paradigm shift had come to the treatment of groin hernia repairs that included mesh reinforcement, without the need of muscles or tendons to be pulled under tension. As stated by Condon[20] and described by Lichtenstein[19]:

"A great deal of emphasis has been placed on the transversalis fascia and its role in hernia repair. Transversalis fascia is of varying density and is often quite thin, even transparent. It possesses little intrinsic strength, by itself, is a worthless material as far as the construction of a sound hernia repair is concerned."

Since the Lichtenstein procedure in 1988 was modified, the open tension-free hernioplasty has become the most used technique both worldwide and in Sweden for the repair of groin hernias, and is classified as the gold standard treatment for inguinal hernia repairs[3, 21-22]. Unlike the suture repairs, low recurrence rates were seen amongst both experienced and unexperienced young surgeons using the tension-free hernioplasty[23]. The method was described as structured,

reproducible, easy and safe, with zero recurrences within a 5 years follow-up while performing the technique in the Cedars-Sinai Medical Center[19,24]. Thereafter, several prospective studies have verified the superiority of the method compared to former suture repairs[25,26].

The main procedure step in the tension-free hernioplasty consists of an open anterior mesh (OAM) inguinal hernia repair with a sutured flat mesh to the inguinal ligament inserted over the entire inguinal floor (Figure 1). Repairs with techniques using plugs, patches, "Prolene Hernia System"/"UltraPro Hernia System" (simultaneous an anterior and a posterior mesh replacement) and an open posterior approach of placing the mesh are also included in the definition of the tension-free hernioplasty, but are less commonly used today in Sweden[3].

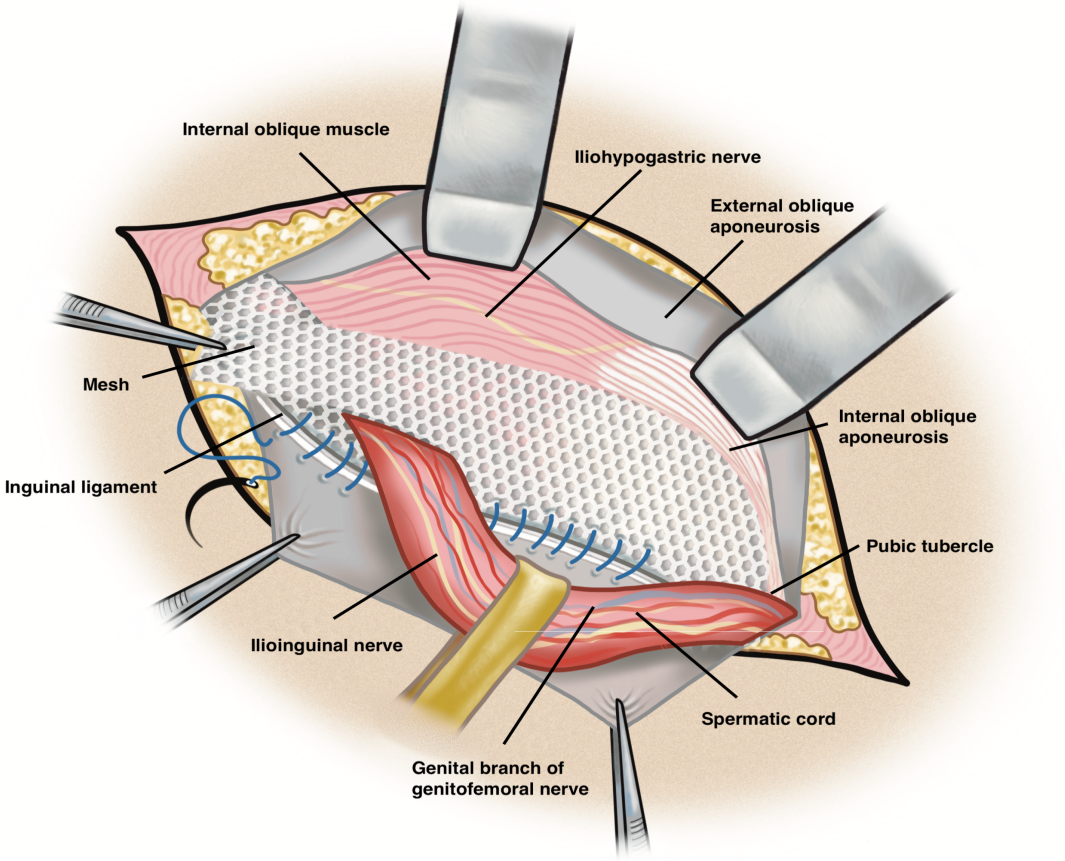

Figure 1. *Illustration of the Open anterior mesh groin hernia repair with anatomical important structures in the field.*

Laparoscopic mesh repair

In addition to advancing the surgical technique to achieve less tissue and nerve injury, the adoption of the laparoscopic approach increased among surgeons in the beginning of the 1990's. The method of repair has a huge advantage; enabling a great view of the pre-peritoneal space where all the potential hernia defects (a direct, indirect or a femoral defect) can occur both above and below the inguinal ligament (Figure 2). Also, the nerves in the groin will most of the time not come into conflict with the mesh insertion with the laparoscopic posterior approach, as compared to the open mesh repair. However, "the triangle of doom" (containing the large blood vessels) is more likely to be in your visualized dissection area.

In the Trans-Abdominal Pre-Peritoneal approach (TAPP) the pre-peritoneal space is reached by first entering the intraabdominal cavity where the peritoneum later on needs to be incised for the mesh replacement. In contrast, with the Totally Extra-Peritoneal approach (TEP), the pre-peritoneal space is reached directly by entering the pre-peritoneal space without passing the intraabdominal cavity. Although the risk of abdominal visceral complications has been theoretically considered to be lower with TEP compared to TAPP[27-29], the TEP technique has been described to be more challenging to master in the early years of practice, as it is deemed to have a longer learning curve[30]. The laparoscopic technique was initially criticized due to its complexity, need for general anesthetics, risk for potentially severe abdominal visceral, vascular complications and higher costs[31].

In Sweden, the dominating laparoscopic technique for groin hernia repairs is TEP and it accounts for approximately 20 % of all the groin hernia repairs[3]. In contrast, adoption of the laparoscopic technique is today been preferred as the first method of choice for primary groin hernia repairs in many other western countries. Both less short-term and chronic pain after surgery, along with low recurrence rates, has been confirmed[32-34]. Still, there are reports concerning that there might be an increased rate of recurrences with the laparoscopic approach compared to the traditional Lichtenstein repair[35]. Nevertheless, according to the European Hernia Society (EHS) guidelines, the laparoscopic technique of repairing a hernia defect is preferably recommended for all bilateral simultaneous repairs, for a recurrent surgery when the primary operation has been performed with an open anterior approach, and also for women with groin hernia defects[16].

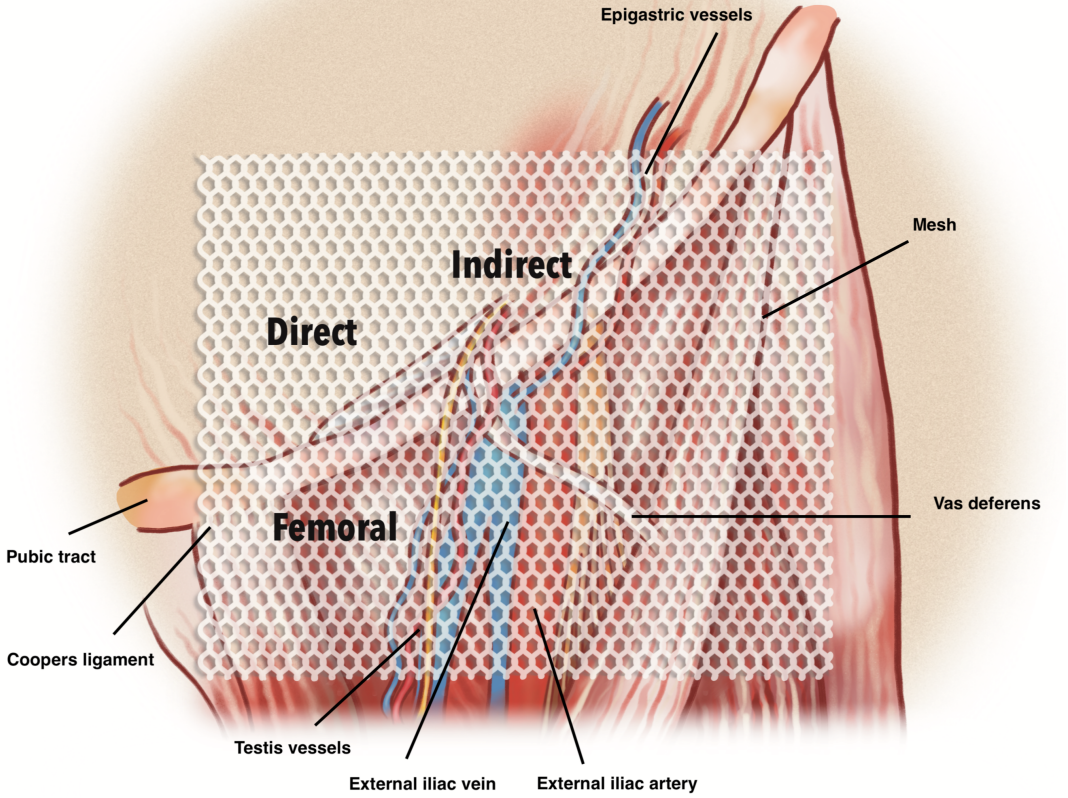

***Figure 2**. Illustration of the inserted mesh and important anatomical structures in the Totally Extra-Peritoneal (TEP) groin hernia repair.*

2.2.3 Postoperative complications

"Nothing so prevents the occurrence of complications as one's awareness and fear of them."

- *Robert Bendavid, A leading hernia suregon, Toronto, 1998-2019*

There are mainly two important outcomes following a groin hernia repair that could impair the patient's quality of life; recurrence and pain. When patients were asked to theoretically decide between recurrence or speed of recovery after their groin hernia surgery, most regarded lack of

recurrence. This was described back in 1995 and stated in an early report by E. Nilsson when discussing hernia registers[36].

One of the main aims of the establishment of The Swedish Hernia Register (SHR), was to study recurrence rates nationally and improve outcomes. Today, it is proven that both quality and cost-effectiveness of groin hernia repair have been improved in Sweden with a register participation[36,37]. However, by detangling one problem we might in turn have gained awareness of another, that there hence still remains concerns about. The challenge we face today, is finding a way to improve chronic pain after a groin hernia repair. If today's patients were asked the same question on recurrence and pain following hernia repair, their answer might be different than those in 1995. Indeed, for surgeons, chronic pain has today gained increased recognition and has perhaps become the most important outcome to assess and improve following a groin hernia repair.

Recurrence

There has been a remarkable reduction in recurrence rates following an open groin hernia repair since the introduction of the Lichtenstein method[18]. Data from earlier studies report recurrence rates as low as under 4 %[16]. This outcome has been necessary to demonstrate, since the inguinal hernia repair has been described as the very cornerstone of general surgery. An estimation of the true recurrence rates is gained by studying the reoperation rates for recurrences. The true recurrence rate has been said to exceed the reoperation rate for recurrences with approximately 40 %[38]. Risk factors for developing a recurrence after a groin hernia repair could be either patient-related, hernia-anatomical - or technical reasons. Patient-related risk factors are sparsely studied. However, some earlier studies reports that female gender, smoking, medical conditions, such as connective tissue diseases and positive family history were examples of factors that were associated with an increased risk of recurrence[39-41]. A large hernia defect, a direct hernia and a recurrent hernia are anatomical-related factors that have been reported earlier to increase the risk of a recurrence[42-45]. Moreover, the anatomical mesh position varies with the method of repair and may influence the outcome of recurrence following a groin hernia repair. The latter was investigated in this thesis and will be discussed further in detail.

Pain

In contrast to low recurrence rates following a groin hernia repair, persisting pain after surgery is still a concerning substantial complication. Varieties of ranges can occur within "post-herniorrhaphy pain", such as short-term postoperative pain, discomfort, foreign body sensation and chronic pain.

Chronic pain

Chronic pain has been described to have a rate somewhere in the range of 10-12 % after a groin hernia rerpair[46,47]. However, some studies have reported disturbing incidences up to 30-60 %, confirming that chronic pain is an unfortunate problem that impairs patients' quality of life[48,49].

There have been attempts to classify chronic pain as either neuropathic or nociceptive. Chronic post herniorrhaphy neuropathic pain could be defined as described by Alfieri et al;

"A pain arising as a direct consequence of a nerve lesion or a disease affecting the somatosensory system, in patients who did not have pain before the original hernia operation, or, if they did, the post-operative pain differs from the pre-operative pain."[50]

The underlying cause of chronic pain following groin hernia repair has often been described to be undoubtedly multifactorial. Associated risk factors have been listed as young age, operation for a recurrent hernia, presence of preoperative severe pain, severe pain directly after surgery, female gender and an open repair[46,51,52]. Type of mesh as a risk factor for chronic pain will be additionally discussed in this thesis. In contrast to neuropathy-related complaints (due to perioperative nerve damage or nerve entrapment in the sutures), some suggest that the onset of chronic pain, as a consequence of the foreign body reaction of the mesh, typically occurs more than one year after surgery[53].

Pain can be assessed with different measurements and tools. The Inguinal Pain Questionnaire (IPQ) is an example of a highly validated tool developed in 2002 by Kehlet et al[54,55]. It was specially developed to evaluate groin pain after a groin hernia repair.

2.3 MESH

"If we could artificially produce tissues of the density and toughness of fascia and tendon, the secret of the radical cure of hernia would be discovered."

- *Theodore Billroth, Surgeon, 1829-1894*

2.3.1 History

In 1958, Dr. Francis Usher's started to develop a woven mesh (Marlex)[56]. Despite the various benefits of the woven polyethylene mesh, he continued the work for a more superior one. It was not until the Nobel Prize winner Giulio Natta, together with Karl Ziegler, introduced the *woven* polypropylene (PP) as a potential mesh material, that the foreign material started to gain terrain in hernia surgery[57]. Usher found out very quickly that the *knitted* PP had way more benefits. The work of his development of the knitted PP mesh revolutionized the approach to the abdominal wall defects and drastically lowered the recurrence rates following hernia repairs[58]. Studies have later supported these results and demonstrated that hernia repairs performed by using meshes reduce recurrence rates compared to hernia reconstructions with other methods[18]. Today, PP is the most frequently used polymer for the manufactured surgical mesh in hernia repair[59].

2.3.2 Mesh properties

A mesh's ideal *biological* characteristic can be described as atoxic, non-immunological and infection-averse with a satisfactory biocompatibility, high tissue incorporation and low adhesions to visceral organs. Moreover, a mesh's ideal *physical* properties can be considered to be high strength, minor shrinkage, good handling characteristics, macroporosity, low weight/density, high elasticity and no long-term degradation. Factors that determine these properties are the mesh's manufacture of polymer, filament, construction, tensile strength, porosity and surface[53,60]. Selected properties are, in coming sections, further described and discussed.

Porosity

The pore size is perhaps described as the main determinant of all the properties of a mesh. It has an important effect on the biocompatibility of the foreign body reaction after implantation[61].

Pores need to be > 75 μm in order to allow for fibroblasts, blood vessels and collagen to integrate. The mesh's pores are the framework of these cells and fibers in order to enhance the incorporation of the in-growth in the tissue. When having large pores in a mesh, macrophages and granulocytes can additionally enter the mesh space, in the event of an infection, to combat with it along with the mesh; a process otherwise difficult in microporous meshes[62]. When the incorporation of the mesh with the tissue begins, granulomas normally form around the pores. The granulomas can merge with each other, so called bridging, and as a consequence encapsulate the entire mesh. This occurs in microporous meshes due to the small space between the pores and the granulomas[53]. Consequently, a stiff scar plate and a reduced flexibility can appear. A panel with hernia surgeons has discussed the search for the ideal mesh and has agreed that a monofilament mesh with a pore size between 3 and 6 mm is preferred[63].

Weight

In mesh hernia surgery, two competing mesh concepts often lead to debate between hernia-mesh interested surgeons; arguing the *heavyweight small porous* concept and the *lightweight large porous* idea. Hence, the nomenclature of describing a mesh as either heavyweight or lightweight can be misleading, since there are actually no official definitions. This is expressed and discussed by Bringman and colleagues, who refer to the terms as *"no more than a name alluding to the recent history of marketed meshes"*[63].

In the meantime, hernia researchers are still continuingly referring to meshes as either heavy or lightweight. The definition proposed by Coda et al, has been used widely, suggesting that an ultra-light mesh is < 35g/m^2, light mesh 35-70 g/m^2, standard mesh 70-140 g/m^2 and a heavy mesh > 140 g/m^2 [64]. According to this definition, one can interpret that "standard" and "heavy" meshes seem to have been used interchangeably as heavyweight meshes. Furthermore, Hollingsky et al, performed biomechanical studies on lightweight and heavyweight meshes. They used thickness and weight to distinguish lightweight (< 0.5 mm thick, < 1 g) from heavyweight meshes (> 0.5 mm thick, > 1 g), for mesh measuring 15 x 10 cm[65]. Subsequently, lightweight meshes are usually referred to as having a weight of < 50 g/m^2 and heavyweight meshes of > 50 g/m^2. Consequently, lightweight meshes usually consist of larger pores and a smaller surface area. Thereof, pore size seems to overlap between the two groups. The new composite lightweight meshes consist of a very low weight, some of them almost < 30 g/m^2 with very large pores. These provide the advantage of a low foreign body reaction[66]. There is however a lack of long-term studies on humans in clinical settings, assessing recurrence rates of these meshes compared

to classical heavyweight meshes with a higher tensile strength. Cobb W.S et al's argument for the lightweight polypropylene mesh in hernia repair can be summarized with the captivating statement;

How low can we go…? [66]

The Foreign Body Reaction

Inflammation is the primary biological reaction to implanted surgical meshes. It is presented into four steps; an acute inflammatory response, chronic inflammatory response, foreign body reaction (FBR) and wound healing[67]. The FBR is a complex defense reaction, and the extent of the FBR to mesh prosthetics depends on the amount of incorporated material[68,69]. The purpose of the prosthetic mesh can be described to create a scar net, rather than a scar plate. Pain due to FBR is described to typically present after one year[62]. It follows the theory that meshes with small pores and more PP material will induce a greater FBR. These so-called heavyweight meshes can therefore cause higher rates of chronic pain due to a rigid scar plate, stiffness and a reduced abdominal wall compliance[70]. Lightweight meshes could lower this inflammatory response due to less material[68]. A lower inflammatory response gives improved tissue incorporation, increased abdominal wall compliance and increased comfort[66]. In spite of this, the debate on whether lightweight meshes provide adequate strength to resists a hernia recurrence, continues.

2.3.3 Mesh types

Today there are several surgical meshes on the market for hernia repairs. They are frequently classified as first generation (table 1), second generation (table 2) and third generation meshes (biological prostheses)[53]. The first generation of surgical meshes is predominately based on PP heavyweight meshes (HWM) with small pores. However, the understanding about the prevention of recurrences when using materials of high tensile strength, began to be questioned. Due to intensive fibrotic reactions from such materials, so-called "lightweight meshes" (LWM) were manufactured in 1998, with the aim to minimize complications hopefully without the expense of recurrence[60]. These new first generation lightweight meshes had larger pores and smaller surface area. The second generation of meshes was developed to avoid infections, high scar tissue and adhesions. These meshes are therefore in an ingenious way a combination of

more than one polymer and/or with other totally absorbable materials and called composite prosthesis. Biological prostheses will not be discussed in this thesis.

Type of Mesh	Filament	Pore size	Absorbable	Weight	Mesh name	Comment
Polyester	Multifilament Multifilament	Large (1,0-2,0 mm) Small	No No	Mediumweight ~ 40 g/m2 Heavyweight ~ 80 g/m²	Mersilene® (Ethicon) Parietex™ (Covidien)	Shrinks. High stability. Infection risk. Dense fibrous ingrowth. Degradation risk.
Polypropylene (PP)	Monofilament Multifilament	Small to medium > 1,0 mm	No	Heavyweight ~ 80-100 g/m²	Marlex® (BARD) Polysoft® (BARD) Prolene® (Ethicon) Surgipro™ (Medtronic) Parietene™ (Covidien) Prolite™(Atrium) Premilene® (B-Braun)	Strong. Fibrosis. Strong foreign body reaction. Infection risk.
PP	Monofilament	Large 1,0-3,6 mm	No	Lightweight ~ 36-48g/m²	Parietene Light™ (Covidien) Optilene® (B-Baun) Soft Mesh® (BARD) Prolene soft® (Ethicon)	Greater flexibility. Less fibrosis. Lower infection risk.
PP Preformed	Monofilament	Small or large	No	Heavyweight Lightweight	3D Mesh®/3D Mesh light® (BARD)	Preformed, easy to place in TEP without fixation.
ePTFE	Foil	Very small 0,003 mm (3 µm)	No	"Heavyweight"	Goretex® (Gore)	Smooth and strong. Multilaminar patch. Microporous! Infection risk. Worse ingrowth. High costs.

***Table 1**. Some examples of the first generation meshes and their characteristics. ePTFE = expanded polytetrafluoretylene.*

Type of Mesh	Filament	Pore size	Absorbable	Weight	Mesh name	Comment
PP + Polyglactin-910	Monofilament Multifilament	Large >3mm	Partially 50/60 % (42 days)	UltraLightweight ~27/35 g/m2	Vypro® , Vypro II® (Ethicon)	Vicryl is polyclactin (PG910). First light-weight meshes with large pores. More PP and PG in Vypro II.
PP + Poliglecaprone-25	Monofilament	Large >3 mm	Partially 60 % (90 days)	UltraLightweight ~ 28 g/m²	Ultrapro® (Ethicon)	Stronger and less inflammatory response than Vypro. Adhesion risk. Low foreign body sensation.
PP + Poliglecaprone-25	Monofilament	Large >3 mm	Partially 50 % (90 days)	Lightweight ~39 g/m²	Ultrapro Advanced™ (Ethicon)	Stronger than Ultrapro. Hexagon structure.
PP + Titanium coated	Monofilament	Large >1 mm	No	UltraLightweight ~35/16 g/m²	Ti-mesh light® (GfE) Ti-mesh extra light®	Possibly has a reduced inflammatory response compared to other meshes. Low tensile strength.
PVDF	Monofilament	Large > 1-2 mm	No	Mediumweight ~ 60 g/m²	Dynamesh®	PVDF causes less foreign body reaction. Strong.

***Table 2**. Some examples of the second generation meshes and their characteristics. PVDF = Polyvinylidenefluoride.*

The trend of mesh used for groin hernia repairs in Sweden has shifted from mainly using HWM in 2005 to increasingly performing the repairs with LWM (Figure 3), particularly in the laparoscopic approach (Figure 4). In the thesis, three main mesh groups have been investigated for their effect on recurrence and chronic pain following a groin hernia repair. These are PP heavyweight meshes, regular PP lightweight meshes and two different composite PP lightweight meshes. The proportion of Preformed meshes used in TEP in Sweden has been increased (Figure 4). The meshes are pre-shaped to be placed easily in the groin without any fixation and can consist of PP material with either larger or smaller pores. However, within the SHR it is not possible to breakout the type of Preformed mesh. So, to speak, weather the Preform mesh was a small pore heavyweight mesh or a large pore lightweight mesh could not be ascertained from the registration in the SHR.

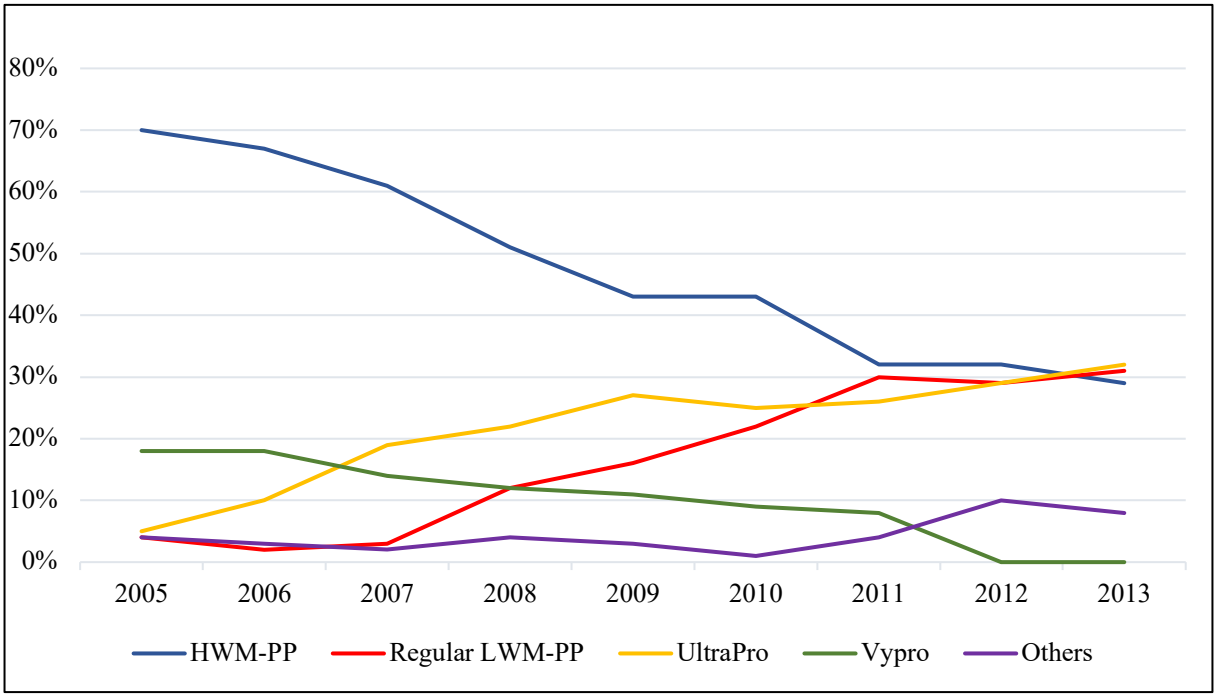

Figure 3. *Trends in mesh used in Sweden 2005-2013 for the* ***OAM*** *inguinal hernia repairs (n=94,601). Data from SHR. Others consist of; unknown (1173), polyester (967), another mesh (90), TiMesh (596), Progrip (175), ePTFE (117), Preformed (20).*

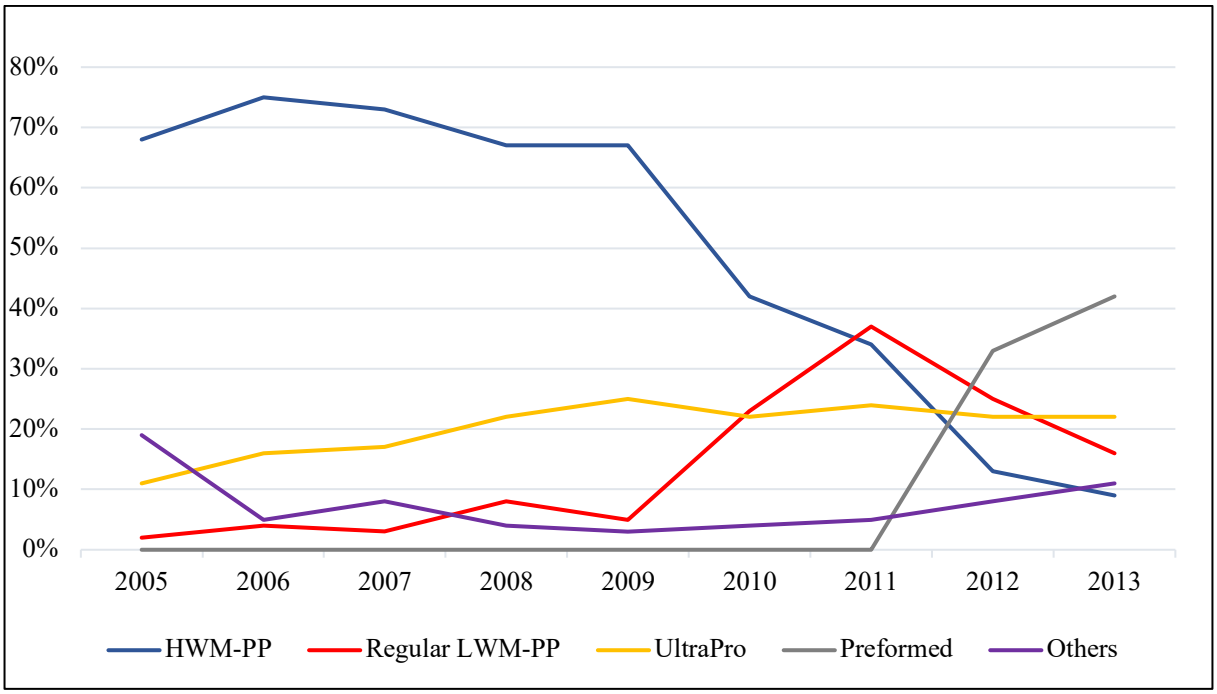

Figure 4. *Trends in mesh used in Sweden 2005-2013 for the* ***TEP*** *groin hernia repairs (n=17,348). Data from SHR. Others consist of; unknown (88), polyester (373), another mesh (333), TiMesh (298), Vypro (185), ePTFE (9), Progrip (2).*

PP Heavyweight and PP Regular lightweight meshes

In the SHR, the PP heavyweight meshes and the PP regular lightweight meshes (excluding LWM with an absorbable component) are summarized as groups referring to their weight, either over or below 50 g/m^2. Other mesh-properties apart from the weight have not been traditionally registered in the SHR. Composite PP lightweight meshes have been registered as a separate group, allowing to follow and evaluate outcome of that certain mesh.

Composite PP lightweight meshes

VYPRO®

VYPRO® was the first lightweight mesh to hit the market in 1998. It consists of 30 % PP and 70 % of polyglactin-910 (Vicryl). It is therefore constructed by both monofilament (PP) and multifilament components (Vicryl). The pore size is large > 3 mm and the estimated time for the absorbed component to reduce is eight weeks[71]. The mesh became a rapid favorite due to the long-term reduced inflammatory reaction and with better abdominal compliance, found in

animal experiments[72,73]. Considering the above-mentioned benefits of the composite mesh, VYPROII® was developed in order to gain more strength, temporary stiffness and hopefully to also avoid recurrences. It distinguishes from VYPRO® in the sense of consisting more of PP (50 %). The weight is therefore increased from 27 g/m^2 to 35 g/m^2 after absorption[74]. The SHR does not differentiate VYPRO® from VYPROII® in the registration.

UltraPro®

This composite PP lightweight mesh is one of the stiffest of the lightweight meshes during implantation due to the component poliglecaprone-25 (Monocryl). The mesh consists of 40 % PP and 60 % poliglecaprone-25. Poliglecaprone-25 resorbs within 90 days. The advantage compared to other lightweight meshes is the optimal handling during surgery, with its firmness that eventually reduces after implantation[75]. The inflammatory response is less than with VYPRO® and has a lower foreign body sensation[76]. The mesh consists of only monofilament structures with large pores > 3 mm and achieves a weight of 28 g/m^2 after absorption. This mesh was used for the onlay mesh repair in Paper IV.

UltraPro Advanced™

This mesh is new and developed from UltraPro®. Instead of a rhomboid braided structure of the pores, the mesh has a hexagon arrangement. It is described to have the same advantages as UltraPro®, but with higher tensile strength. It consists of more material of PP and polyglecaprone-25, but with a less amount of poliglecaprone-25 (50 %). The weight is initially 71 g/m^2 and 39 g/m^2 after absorption[77]. This mesh was used for the onlay mesh repair in paper IV and is currently being used in the randomized clinical trial of small umbilical hernia defects (Appendix A).

2.3.4 Lightweight or heavyweight meshes?

Although preclinical animal experiments are necessary to assess differences in mesh characteristics, the final main significant outcome of recurrence and pain needs to be studied on humans in clinical settings. This is mainly due to diseases and comorbidities that appear in humans, and that can influence the outcome.

The introduction to LWM in the OAM groin hernia repair has been promising. Several studies comparing LWM to HWM have reported advantages in terms of speeded recovery, less postoperative pain, earlier return to normal activity, increased patient comfort (with reduced mesh awareness), less chronic pain and crucially without necessarily increasing the risk of recurrence[78-84]. However, long-term differences between different meshes (with respect to recurrence rates) have been difficult to assess and results fail too fully please. Most of the conducted randomized clinical trials lack power in sufficient amount of hernia repairs to analyze recurrence as a primary endpoint. LWM appears to have advantages in TEP as well, in terms of less pain and early return to normal activity[80,85,86]. However, there are still concerns that the use of LWM may be associated with more hernia recurrences after TEP repair, especially for larger hernia defects[87-90].

The ideal in a hernia repair is to use a mesh that has a sufficient strength to prevent recurrence and simultaneously is associated with less side effects. Currently, the published data is conflicting regarding the outcome of pain following a TEP or an OAM groin hernia repair, in LWM compared to HWM. A meta-analysis[83] summarize the findings of six randomized trials comparing LWM to HWM in open groin hernia repair[79,82,91-94]. The results seem to be in favor of LWM in terms of less chronic pain (1 year postoperatively) and foreign body sensation[83]. However, one should mention that there is a difficulty in comparing the different studies since they have used different types of lightweight meshes. Sajid et al, reported similar results in a systematic review of OAM groin hernia repairs, demonstrating that LWM had better outcome on pain postoperatively[95]. However, there was a significant heterogeneity among the trials. The authors only included four trials[79,92,96,97] with reported data on follow up $\geq$ 1 year, and showed no difference in chronic pain between the meshes. Studies regarding pain in the use of LWM or HWM in TEP seem to result in no significant differences at one year follow up[78,89,98]. However, a recent randomized controlled trial of TEP groin hernia repairs showed not only a higher recurrence rate with the use of LWM, but also an increased rate of pain with the use of LWM compared to HWM[89]. The explanation for this could be due to the increased recurrences in the LWM group.

Most of the randomized clinical trials comparing recurrence rates and chronic pain between different meshes are reported by hernia experts. Studies about mesh in groin hernia repair reflecting the results from surgeons who are not specialized in hernia surgery nationally were lacking when I started the work of this thesis. Through the population-based SHR, this seemed favorable to study. The method consisted of a large amount of unselected hernia repairs with a

sufficient follow-up to assess differences in recurrence rates. Also, given that chronic pain after a groin hernia repair is still a concerning problem, there is a need for identifying risk factors for the condition. Therefore, we found it of great value to investigate, on a national population-basis, if the chronic pain rate was influenced by type of mesh used following an OAM inguinal hernia repair.

This was the rationale and background of the studies in paper I-III.

2.4 THE UMBILICAL HERNIA DISEASE

"Time for use of mesh repair for all umbilical hernias?" [99]

- *Fredrik Helgstrand, Thue Bisgaard, The Lancet, 2018*

2.4.1 Epidemiology

According to the EHS guidelines, an umbilical hernia is defined as a hernia present at the site of the umbilicus and 3 cm above or below the umbilicus[100]. The latter is usually also interchangeable called a "paraumbilical" hernia. Umbilical hernias in adults are relatively common with a global prevalence of 2 %[101-103]. Yet, the knowledge is limited and its underlying cause is still not fully understood. In contrary to the groin hernia disease, the umbilical hernia disease is still a disregarded subject in the area of hernia research.

Suggested risk factors for developing an umbilical hernia have included obesity, increased intra-abdominal pressure, liver cirrhosis with ascites, multiple pregnancies, previous abdominal surgery (incisional hernia in the umbilicus area) and long-term peritoneal dialysis from kidney failure[104,105].

Approximately 4,000 repairs are performed annually in Sweden, also including epigastric hernia defects[106]. The Swedish Ventral Hernia register in Sweden started in year 2007, but still only covers a minority of the ventral hernia repairs nationally[106]. Therefore, it is still difficult to study incidence, risk factors and recurrence rates of umbilical hernia repairs in Sweden via the register.

2.4.2 Surgical treatment

As for groin hernia defects, similar symptoms are presented for umbilical hernia defects, for which the definitive cure in adults is surgical treatment. Repair options include open primary suture repairs and mesh-based repairs. Mesh repairs can be performed either open or with a laparoscopic approach.

Suture repair

Small umbilical hernias have traditionally been repaired either with an open *Mayo's technique* or using an open *simple suture*. The Mayo umbilical hernia repair involves a double breasting of the linea alba, duplicating the aponeurosis in order to close the hernia defect[107]. One cannot help thinking that the main principle of the so-called "tension-free hernioplasty" becomes undoubtably violated here, and as such alternative surgical techniques have been used. A simple suture repair seems today be the most common method of repair in Sweden for small umbilical hernias[106]. However, the recurrence rates with a suture repair have not been negligible and have been described up to 20 %[108,109]. Consensus for which technique of repair should form the gold standard for small umbilical hernias is yet to be decided.

Mesh repair

The position of the mesh can be inserted in different anatomical spaces of the abdominal wall for the repair of the umbilical hernias (Figure 5). A *sublay, retro-muscular mesh repair* can be performed while placing the mesh below the rectus abdominis muscle, but above the posterior rectus sheath. Also, a *sublay, pre-peritoneal repair* can be achieved, where the mesh is placed above the peritoneum and below the entire abdominal wall. In addition, less complicated measures to achieve a tension-free hernioplasty, such as the use of *pre-peritoneal ventral patches* placed both intra and pre-peritoneal in the umbilical defect, have been performed. Furthermore, an *IPOM repair* can be done, inserting an intraabdominal coated mesh to prevent adhesions to the visceral organs. Finally, an *onlay mesh* can be placed above the hernia defect and the aponeurosis. The latter is adopted in the study of paper IV and also in the study protocol of the SUMMER Trial attached as Appendix A.

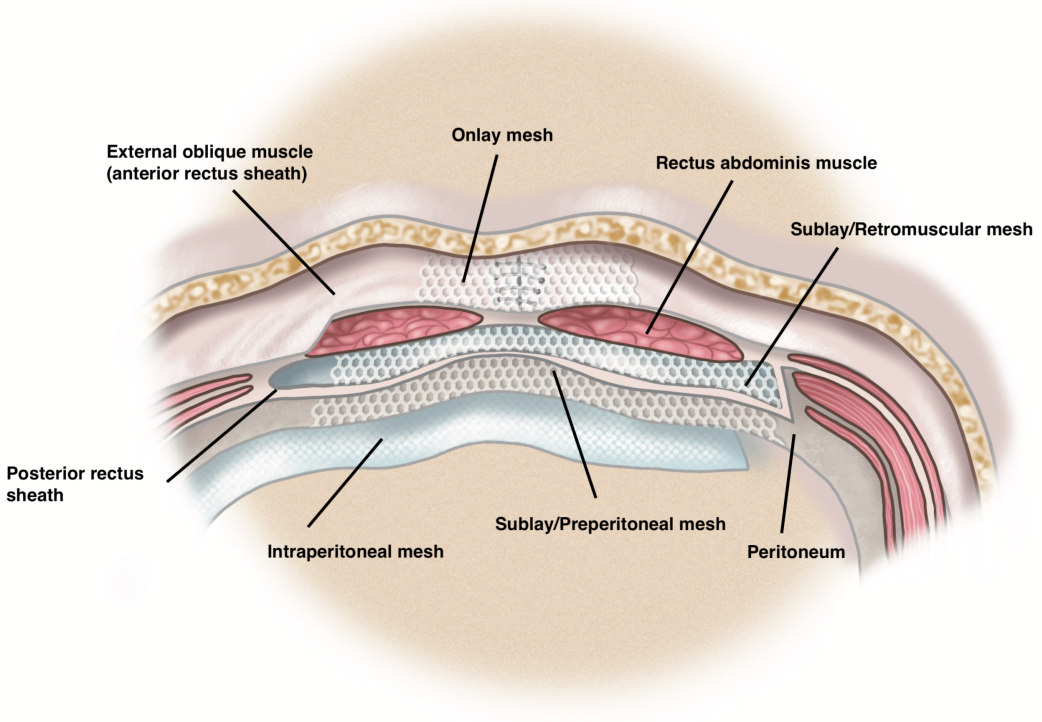

Figure 5. *Transverse section of the abdominal wall, illustrating the relevant anatomical structures of the abdominal wall and different mesh positions for hernia repairs.*

Mesh repair for umbilical hernias with by the above-mentioned methods seem to have been reserved and advocated for larger umbilical hernia defects. However, data from earlier studies have demonstrated lower recurrence rates with mesh reinforcement also in the open repair for small umbilical hernias[4,110-117]. These few published studies, report recurrence rates for suture repair between 4-15 % and much lower rates for mesh repair, between 0-5 %. Two randomized clinical trials are well known in this research field, but are unfortunately dated to almost 20 years at the time of this thesis. One of them involved only 50 patients with a mean follow up of 22 months[113]. The other consisted of 200 patients, where the authors also included hernias over 3 cm and with different mesh positioning[115]. The recurrence rate in this trial was ten times higher for suture repaired hernias than for mesh repaired ones. The differences in recurrences in this study were found associated to the technique (mesh versus suture repair) rather than the size of

the hernia[115]. These results support the hypothesis that the size of the defect may not singlehandedly play a decisive role in the risk of developing a hernia recurrence. Similar results have been published in a nationwide registry-based study with collected data from the Danish Ventral Hernia Database (DVHD) consisting of 4.786 hernia repairs[118]. The reoperation rate for recurrences in small umbilical and epigastric hernias less than 2 cm in defect size, were 2.2 % for mesh and 5.6 % for suture repair. The same authors also investigated the total true recurrence rate[109]. The total true recurrence rates were surprisingly high at 21 % for suture repairs and 10 % for mesh repair. This confirms that the reoperation for recurrences really underestimates the total recurrence rate and thus settles the need for clinical trials.

More recently, in 2018, a large, randomized, double-blind, controlled trial with 300 patients were published in *The Lancet*[119]. Kaufmann and colleagues compared suture to mesh repair in umbilical hernias of 1-4 cm[119]. The study is the first in modern literature with high level evidence for the treatment of small to medium umbilical hernias. The results demonstrated that mesh reinforcement had a significant reducing effect on recurrence rate compared to only a suture repair (4 % versus 12 %). A difficulty in this trial could be the optimal achievement of the pre-peritoneal flat mesh positioning in these small umbilical hernia defects. Indeed, we know from clinical experience of performing umbilical hernia repairs, that this dissection is not an easy job. Firstly, the peritoneum in the umbilical region is often thin and pre-ruptured. Secondly, the ligaments below can be difficult to blindly dissect free, for the creation of a suitable space for the inserted flat mesh. Also, the role of mesh in very small umbilical hernias of less than 1 cm still remains uncertain[120]. A small onlay mesh repair could be a safer and easier method of choice in these small defects.

Despite the above-mentioned advantages of a mesh repair, surgeons have still remained reluctant to use mesh in small ventral hernias. It could be due to the difficulty of placing a flat mesh in an optimal anatomical position in small defects, and also due to the fear of higher risk of postoperative complications after mesh repair. A meta-analysis found an increased risk for seroma and surgical site infections (SSI) in the mesh group compared to the suture repair group (7.3 % SSI rate and 7,7 % seroma rate in the mesh group compared to 6,6 % SSI rate and 3,8 % seroma rate in the sutured group)[116]. The other meta-analysis showed a clear preference for a mesh repair in reducing the recurrence rates without demonstrating any differences in complication rates between mesh and suture repairs[117]. Still, one should be observant of the fact that postoperative complications were doubled in the mesh group compared to the suture group

in the Kaufmann et al, trial[119]. The presence of seroma and SSI could seem slightly higher in the meta-analysis, for which the explanation could be the heterogeneity of studies with regard to hernia size, and other factors such as mesh positioning. For example, the risk of developing a seroma is theoretically higher in larger hernia repairs repaired with a retro-muscular technique, rather than in very small defects repaired with a small onlay mesh.

There are currently limited published studies of whether to use mesh in small umbilical hernia defects. The optimum anatomical position of the mesh in the repair of small ventral hernias ≤ 2 cm is also still debated. The decision to use mesh needs to balance the risk of surgical site complications against the previous demonstrated reports of lower recurrence rates. Since we hypothesized that a *small* onlay mesh does not necessarily have to be associated with increased rates of surgical site complications, we conducted a retrospective assessment (paper IV) of all the onlay mesh hernia repairs operated at our department at Södertälje Hospital. The study also became an important base for the ongoing larger national multicenter randomized clinical trial (SUMMER Trial) for the treatment of small umbilical hernias (Appendix A). A trial that compares suture repair to a repair with an onlay mesh above the sutured defect for small umbilical hernias is currently lacking in the present literature. Guidelines for umbilical hernia repairs have stressed the need for reliable and more strong data to instigate treatment recommendations[121].

3 AIMS OF THE THESIS

The overall aim of the thesis was to gain more knowledge about the main important postoperative complications following groin hernia repairs with different mesh types and to improve the surgical treatment of small umbilical hernias.

More specific aims were;

Paper I

To investigate and compare the long-term risk of reoperation for recurrence of different mesh types used in laparoscopic (TEP) groin hernia repair.

Paper II

To investigate and compare the long-term risk of reoperation for recurrence of different mesh types used in open anterior mesh inguinal hernia repair.

Paper III

To investigate and compare the chronic pain rate after surgery of different mesh types used in open anterior mesh inguinal hernia repair.

Paper IV

To investigate the treatment outcomes of a small onlay mesh repair for small umbilical hernias by assessing surgical site complications and recurrences after surgery.

4 MATERIALS AND METHODS

In addition to the description of the method in each published paper, I will in this section explain, motivate and give reasons to the chosen inclusion/exclusion criteria, selected variables for adjustments, definition of outcomes, type of meshes that were included and the statistical analyses that were performed. Furthermore, the ethical considerations of the study designs in this thesis will be emphasized.

4.1 THE SWEDISH HERNIA REGISTER

Paper I-III are large nationwide population-based cohort studies based on hernia repairs registered in the Swedish Hernia Register (SHR). In contrast to paper I and II, paper III is additionally a unique PROM study.

The SHR was established by Erik Nilsson in 1992 with only eight participating hospitals. It has been extensively developed over the years, currently covering close to 100 % of all groin hernia repairs performed in Sweden. At this present time, it is a world unique nationwide quality database of more than 320,000 registered groin hernia operations[3]. Procedures are recorded *prospectively* by the surgeon with the use of a standardized protocol without the knowledge of the exposure or the outcome. Patients are identified using their "personal identity number", a person-specific unique number given to each citizen in Sweden at birth. This allows registered patients to be followed from operation until reoperation or death. Recorded data includes details on patient- and hernia characteristics, along with reoperations and its indications.

It was not until 2004 that registrations of type of mesh used in the groin hernia repairs properly began. This is the reason for the chosen start-study period of 2005 in **Paper I and II.** The work on Paper I commenced in 2016 and required a minimum of a 2-years follow-up for adequate detection of hernia recurrences. Consequently, the most suited overall study period for Papers I and II was from 2005 to 2013.

Additionally, in 2012 a pain questionnaire assessing patient-reported outcome measures (PROMs) was sent out 1 year after surgery to all patients that had undergone a groin hernia repair from units participating in the SHR. This was done during a limited time period and ended in 2016. Thereof, the study period of **Paper III** is limited from 2012 to 2016. The distributed questions are extracted

from the Inguinal Pain Questionnaire[55]. This provided the unique opportunity to determine patient-reported pain rates through SHR, and not only reoperation rates for pain.

The SHR is highly validated and 10 % of the aligned units audited independently on a yearly basis by external evaluators. Moreover, it is linked with The Migration and Cause of Death Registry in Sweden, facilitating accurate follow-up times.

4.2 PAPER I

Study design

This is an observational comparative nationwide population – based cohort study analyzing all hernia repairs operated on with TEP (patients > 15 years old) and registered in the SHR, between 1st of January 2005 and 31st of December 2013. The follow-up time was until 30th of June 2016.

Study objectives

The primary outcome was to investigate and compare the difference in recurrence rate between LWM and HWM, used in these hernia repairs. We used reoperation for recurrence as a proxy measurement of the true recurrence rate. As such, this needs to be considered when interpretating the data and the concluded results. A recurrence (for which a re-operation was performed) was defined as a new hernia in the same groin as a previous TEP repair (the index operation), performed with a registration in the SHR. Our hypothesis was that LWM was not associated with an increase in reoperation rates for recurrences, compared to HWM.

Inclusion criteria and variables

Clinically important variables, that could affect both the exposure (type of mesh) and outcome (recurrence) were considered to be confounders. Age (divided into two categorical groups by the median), gender, ASA co-morbidity classification, hernia location in the groin (anatomy), primary/recurrent hernia, unilateral/bilateral hernia, size of the hernia defect, type of mesh (main variable) and mesh fixation were chosen variables to adjust for in the multivariable analysis. The

chosen variables are all different in Paper I-III. Applying a TEP repair (rather than an OAM repair) is more common for hernias in women and for simultaneously operated-on bilateral hernias. Also, the importance of *if* and *how* the mesh is fixated is an interesting question in the TEP repair procedure as it can affect the outcome of recurrence. We chose not to exclude the bilateral nor the recurrent hernia repairs, since they represented a significant amount of hernia repairs in the cohort. An adjustment was not made for the surgical degree of training, since 97 % of the TEP repairs in the cohort were performed by consultants. Initially, only surgical units that had performed a significant amount of TEP repairs, classified as "high-volume TEP centers", during this study period were considered to be included. However, the strength of demonstrating real-life nationwide data overweighed this decision, and thus all surgical units that performed TEP repairs were included. The type of defect is usually highly validated data, as it is based on anatomy and registered by the operating surgeon.

Selected meshes

The HWM group consisted of a variety of meshes that were registered in the SHR as a PP mesh with a weight > 50 g/m^2. These meshes cannot be separated by their specific name in the SHR. The LWM group consisted of registered meshes in the SHR with both PP LWM < 50 kg/m^2 and the composite PP LWM with an absorbable part of poliglecaprone-25 with a weight < 30 g/m^2 (UltraPro®, Ethicon). The reason for the grouped LWM meshes in Paper I was due to statistical reasons that will be further explained in the statistics section. Other meshes that were uncommon in Sweden during the study period, and used in only few hernia repairs in the cohort, were excluded. However, the so called Preformed meshes have gained great attention in the TEP repair and were frequently used during the study period. They accounted for 16 % of the data. After strong considerations we decided to exclude these from the included statistical analyses due to their particular group consisting of both LWM and HWM.

4.3 PAPER II

Study design

This is an observational comparative nationwide population – based cohort study analyzing all hernia repairs operated on with an open anterior mesh (OAM) repair (patients > 15 years old) and registered in the SHR, between 1st of January 2005 and 31st of December 2013. The follow-up time was until 30th of June 2016.

Study objectives

The same outcome and definition described in Paper I was also investigated in Paper II. To clarify, a reoperation for recurrence in Paper II was defined as a new hernia repair in the same groin as a previous OAM repair (the index operation), and performed with a registration in the SHR. The index OAM repair consisted only of registered repairs performed with a tension-free hernioplasty following a sutured flat mesh inserted over the entire inguinal floor to prevent both a direct and an indirect hernia recurrence. Our hypothesis was that LWMs was not associated with an increase in reoperation rate for recurrence compared to HWM.

Included criteria and variables

In contrast to Paper I, we had a lot more exclusion criteria in Paper II. We wanted to increase the quality of the interpretation of the results, and thus selected a study population to represent the target population that is today operated on with the so called "Swedish open anterior mesh hernia repair". Therefore, hernia repairs performed with non-suture affixed meshes and absorbable suture affixed meshes where excluded. Also, hernia repairs that is not commonly performed with an OAM repair today were excluded, such as femoral hernia repairs, bilateral hernia repairs and all women. Consequently, Paper II consisted of only elective inguinal hernia repairs on male patients. In the adjustments, we chose to additionally include the surgeon's seniority, since it is very common to perform an OAM hernia repair during residency. Other postoperative complications, such as seroma or hematoma can possibly affect the outcome of recurrence following an OAM hernia

repair. However, the true capture rate of these type of postoperative variables is questionable and suspected not to match the high capture rate of the other variables in the SHR.

Selected meshes

The selected meshes included in the statistical analyses were separated into four large groups; HWM-PP, regular LWM-PP, LWM-PP/PGC (Ultrapro®, Ethicon) and LWM-PP/PG (VYPRO® and VYPRO II®, Ethicon). In Paper II, we could keep the 3 different groups of LWM separated for the analysis of reoperation for recurrence. Hence, LWM-PP/PG was more commonly used in an OAM hernia repair than in a TEP hernia repair for the same study period.

4.4 PAPER III

Study design

This is an observational comparative nationwide population – based cohort study analyzing all hernia repairs operated on with an open anterior mesh (OAM) repair (patients > 15 years old) and registered in the SHR between 1st of September 2012 and 31st of October 2016, with a questionnaire assessing patient-reported-outcome-measures (PROMs). The follow-up time for all hernia repairs was 1 year after surgery.

Study objectives

The primary outcome was significant patient-reported chronic pain 1 year following an OAM inguinal hernia repair. The question put to the patient used for addressing chronic pain was item 2, extracted from the IPQ (Figure 6). The questionnaire was sent out one year after the index OAM hernia repair to all groin hernia operated patients registered in the SHR during the study period. Non-responders had a reminder sent out again within 30 days. In the analysis, level 1-3 (above the red line in Figure 6) was defined as no pain and level 4-7 (below the red line in Figure 6) as persistent significant pain. Our hypothesis was that LWMs was associated with a lower risk of developing chronic pain, 1 year following an OAM hernia repair compared to HWM.

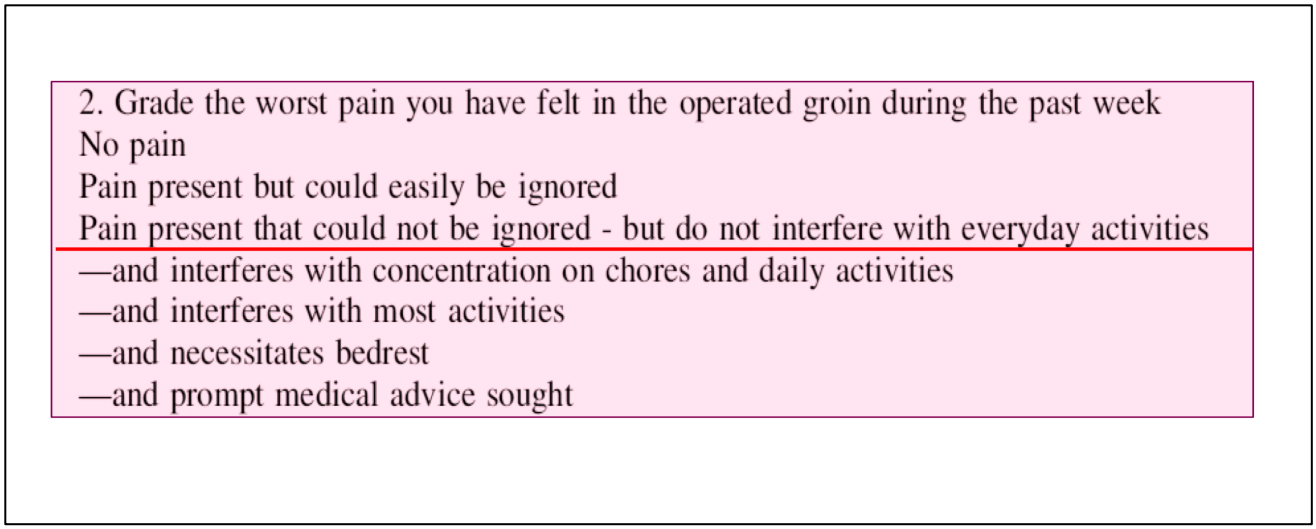

Figure 6. *Question number 2 from the IPQ that was put to the patient 1 year after the index OAM inguinal hernia repair.*

Included criteria and variables

The same definition of the included index OAM hernia repairs that was made in Paper II, was also generated for Paper III. Consequently, excluded hernia repairs and the included variables for adjustments in the statistical model were the same. In addition, the variable of nerve management during the operation was considered to be an important factor to adjust for in Paper III, since it was considered to be a variable that could affect the outcome. However, the nerve management was considered unlikely affect the exposure of choosing one mesh type over another in the repair of the hernia.

Selected meshes

The same definitions and mesh groups that were included in Paper II, was also included in Paper III, except for LWM-PP/PG. The study period of Paper III was subsequently compared to Paper I and II, finding the use of LWM-PP/PG generally rare during this period of time. However, it was still common to use HWM in the repair of the included hernias in Paper III.

4.5 PAPER IV

Study design

This is a descriptive, retrospective study investigating all small umbilical hernia repairs operated on with a small onlay mesh and registered in one single surgical center's medial database (Department of Surgery at Södertälje Hospital, in the region of Stockholm) between 28th of October 2015 and 31st of August 2019. Duration of follow-up was until 31th of December 2019, during which time all the patients were evaluated for treatment outcomes in the outpatient clinic documentation.

Study objectives

Since the decision to use mesh in small umbilical hernias needs to balance the risk of surgical site complications against the previous demonstrated reports of lower recurrence rates, our primary outcome was set to assess the presence of surgical site complications within 30 days after surgery. Hematomas, seromas and wound infections were investigated and the definition of the conditions were set before collecting the data. These were graded according to the Clavien-Dindo classification[122]. The secondary outcome assessed was the presence of recurrence until 31th of December 2019. The definition of a recurrence was bulging of a hernia in the earlier performed umbilical repair site. Patients were investigated for the treatment outcomes retrospectively via the hospital's outpatient clinic documentation. All patients were carefully informed to directly contact the outpatient clinic at the department of Surgery at Södertälje Hospital if any postoperative complication was suspected, but they were not regularly followed with a clinical examination after surgery.

Hence, the study demonstrated the frequency of the treatment outcomes of one single treatment without comparison to another method of repair. The explanation for the difficulty of comparing the onlay mesh repair to another repair within this study, was the local clinical routine that recommended all the small umbilical hernias between 2015 and 2019 be treated with a small onlay mesh.

Included criteria and variables

Clinically important variables that could affect the outcome of surgical site complications and recurrence was set to be investigated and collected from the hospital's medical records and the surgical database. Age, BMI, gender, ASA class, operation time and medical conditions were considered to be risk factors for the treatment outcomes. The surgeon's seniority was also collected and analyzed.

Exclusion criteria

The exclusion criteria were chosen to achieve an investigation of only *primary elective small umbilical hernias ≤ 2 cm*. This was an effort to ensure a homogenous group. For example, patients with a recurrent small umbilical hernia following a suture repair of an earlier primary hernia, that now had undergone a small onlay mesh repair, was considered to affect the treatment outcomes differently than a primary hernia. The argument was the same for an incisional small hernia in the umbilical tract following earlier surgery. Therefore, such conditions were excluded from the analyzed cohort.

The Onlay mesh repair

The surgical method of the onlay mesh repair is illustrated in Figure 7 and described in Appendix A - a study protocol of the SUMMER Trial. The figure illustrates the two different allocated surgical methods in the SUMMER trial; a continuous non-absorbable simple suture repair (Figure 7b) and 2) a continuous non-absorbable simple suture repair with a 4x4 cm onlay mesh applied to the defect, fixed by one suture in each corner and one suture in the middle (Figure 7c). The mesh repair used in the hernia repairs of paper IV consisted of the described method of Figure 7c, except for the mesh size and mesh type. In contrast to the SUMMER Trial, paper IV demonstrated an inconsistent use of mesh size in some cases between the surgeons. Therefore, the repairs included for the analysis in paper IV was performed with mesh sizes of 4x4 cm (± 1 cm). The mesh type used was either Ultrapro® or Ultrapro Advanced™ (Ethicon Inc).

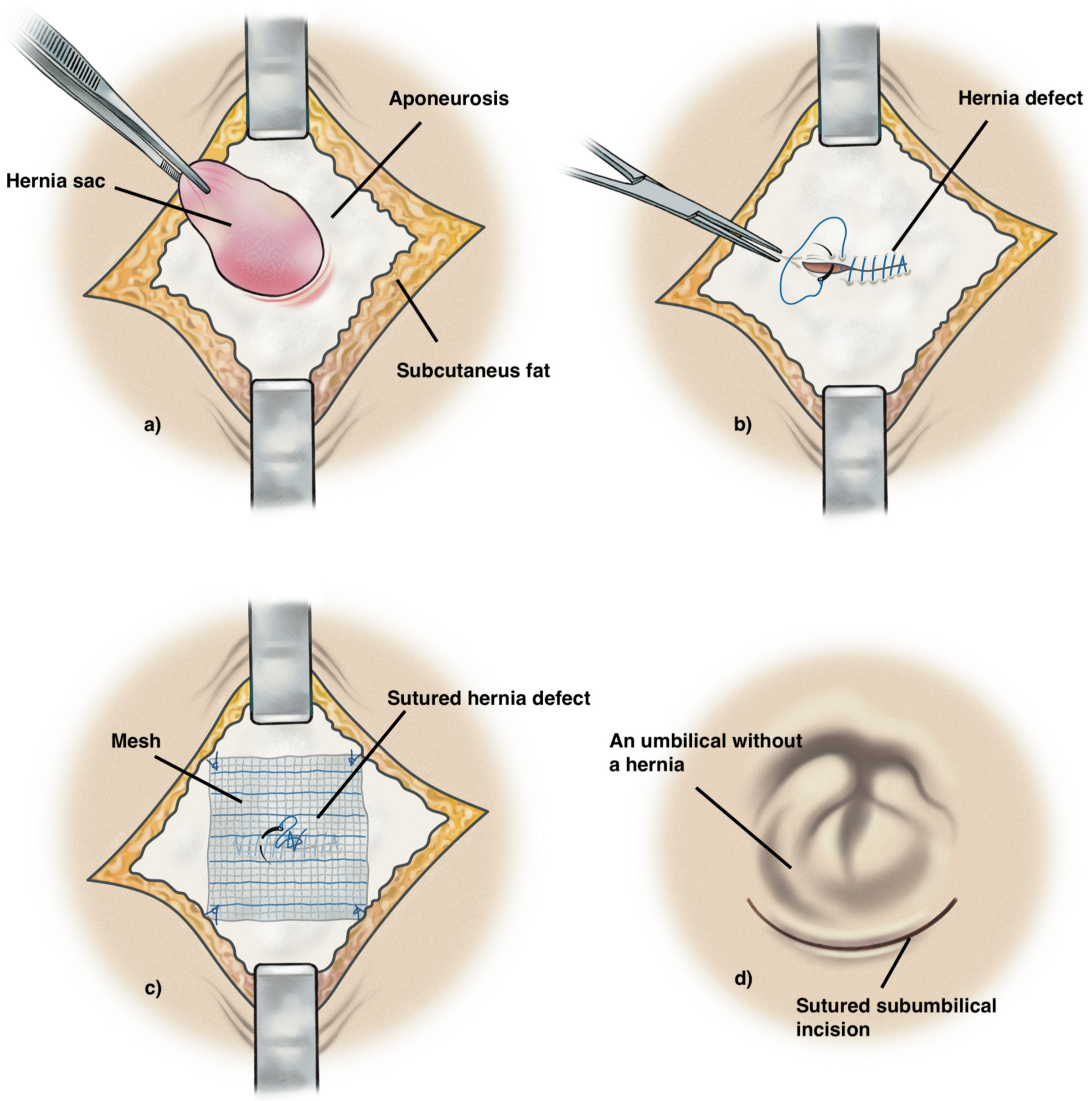

Figure 7. *Illustration of the two different allocated surgical methods in the SUMMER trial (Appendix A). c) presents the completed onlay mesh repair.*

4.6 APPENDIX A

In **Appendix A**, the method of the SUMMER trial (**S**ture**UM**bilical**ME**sh**R**epair); a prospective, national, multicenter, double-blinded, randomized clinical study comparing two different treatments for small umbilical hernias in adults > 18 years is described in a study protocol. The outcomes of a standardized 4x4 cm onlay mesh is being compared to a suture repair. 288 patients will be enrolled from 7 different Swedish surgical units and randomized to either a simple suture repair or to a

simple suture repair with an onlay-mesh (Figure 8). The randomization take place *intraoperatively* using a centralized web-based system, resulting in complete allocation concealment. Stratification is done by surgical site and by defect size. The primary outcome assessed is postoperative recurrence at 1 and 3 years. Secondary outcomes assessed are postoperative complications at 30 days, and pain at 1 year after surgery. Currently, approximately 180 participants are included, of which approximately 120 are randomized and operated on.

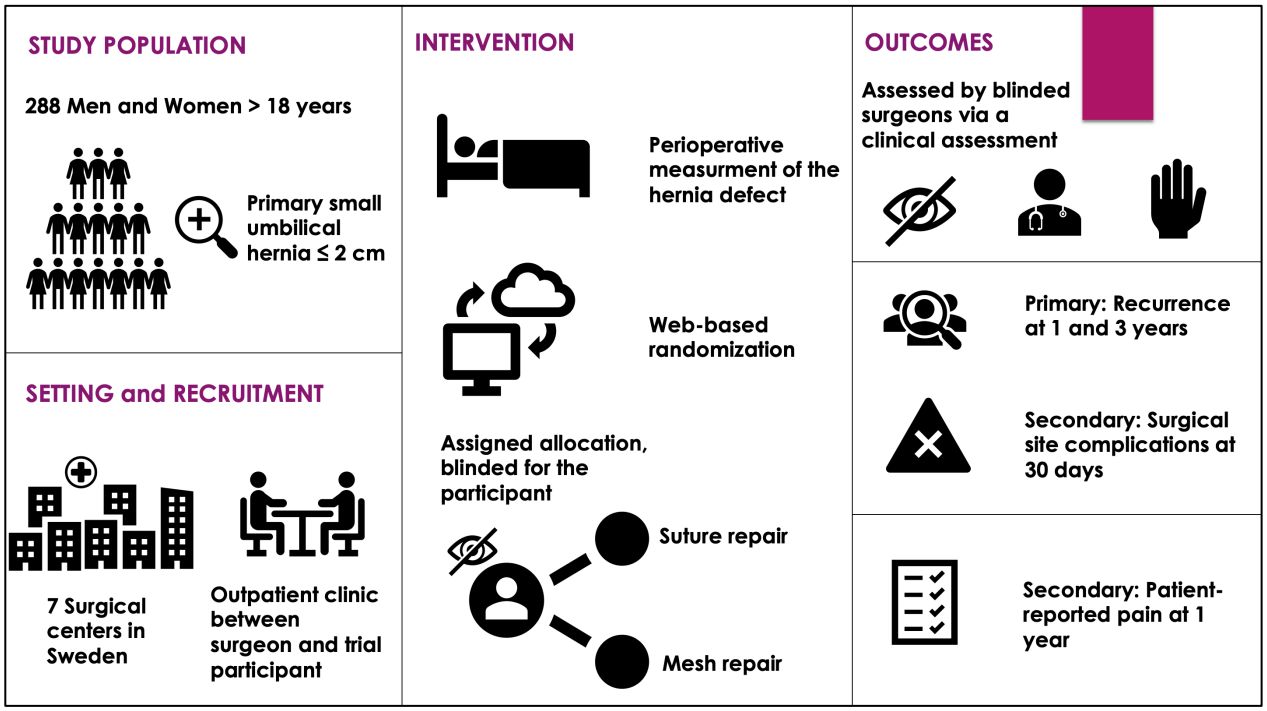

Figure 8. *Illustration of the study design for the SUMMER Trial.*

Table 3. *An epidemiological, summarizing overview of the thesis papers.*

	Paper I	Paper II	Paper III	Paper IV
Data source	SHR	SHR	SHR	1 Swedish surgical unit
Study design	Prospective population - based cohort studies + PROM design			Retrospective, descriptive study
Participants	> 13,000 elective groin hernia repairs in both sexes > 15 years.	> 70,000 elective inguinal hernia repairs on men > 15 years.	> 20,000 elective inguinal hernia repairs on men > 15 years with a response to pain questionnaire.	80 elective small umbilical hernia repairs of both sexes > 18 years.
Study period	2005 - 2013		2012 – 2016	2015 - 2019
Exposure	Type of mesh			Mesh repair
Outcome	Recurrence		Chronic pain	SSI, recurrence
Follow-up	Until 2016		1 year after surgery	30 days and until last of Dec 2019
Adjustments	Age, ASA class, sex, type of hernia, recurrent hernias, type of defect, size of defect, mesh fixation.	Age, ASA class, recurrent hernias, type of defect, size of defect, type of surgeon.	Age, ASA class, recurrent hernias, type of defect, size of defect, type of surgeon, nerve management.	None
Stratification	Sex (females)	None	None	None
Statistical analyses	Cox proportional hazards regression		Logistic regression	Descriptive analysis

4.7 STATISTICAL ANALYSES

Paper I and II

Hazard ratios (HR) and 95 % confidence intervals (CI) were estimated by a Cox proportional hazards regression model due to the time to event data. Each hernia repair contributed to person-time from the index-operation to recurrence, death, immigration or end of follow-up. The assumption in proportional hazard model for survival analysis or cumulative incidences is that the hazard in one group is a constant proportion of the hazard in the other group within the same variable. This proportion is the Hazard ratio. To interpretate this for the data in for example Paper I, one could say that the odds that the time to re-operation for recurrence for a hernia repair performed with LWM is more than for the hernia repairs performed with HWM. Initially we wanted to have three groups of meshes for the analyses in Paper I (HWM-PP, regular LWM-PP and LWM-PP/PGC), since it is interesting to estimate the recurrence rate for LWM-PP/PGC separately from regular LWM-PP. However, proportional hazards assumptions were tested for all the variables that were chosen to be included in the model. In Paper I we found that the variable of type of meshes, the gender variable and the type of hernia variable, did not conform the assumption and violated the proportionality of the model. Stratified analysis by gender and type of hernia was therefore performed in the multivariate model. However, this could not be achieved for the main variable: type of meshes. Either we could have chosen to present the data with three groups of meshes and use a multiple logistic regression model (with presented odds ratios (OR) for analyses without taking the different time to recurrence into consideration), or we could have performed the analyses as we have presented it in Paper I. We considered the different times to event to be more important, and the model therefore required us to combine the regular LWM-PP with the LWM-PP/PGC into one group in order to fit the proportionality of the Cox regression model. Even when the LWM group was separated in to a regular LWM-PP group and an LWM-PP/PGC group, both groups were associated with an increased reoperation rate for recurrence, compared to HWM in a multivariable logistic regression model.

The proportional hazards assumptions were also tested in Paper II for all the variables and the assumption of proportionality was confirmed.

We performed subgroup analyses in both Paper I and II due to its useful requirement in clinical practice. Questions such as;" what type of mesh to use in a large or a direct hernia" are typical. This was investigated with both unadjusted log-rank tests, presented in the Kaplan Meier curves, and

adjusted estimated risks from a Cox proportional regression model. The women in Paper I were excluded from the subgroup analysis due to their small number of events.

Paper III

Odds ratios (OR) and 95 % confidence intervals (CI) were estimated by a logistic regression model due to every hernia repair's identical time to event: assessing chronic pain *1 year* after surgery. The odds is an incidence calculating the events divided with the non-events in one group. An odds ratio is the incidence odds occurring in one group (could be the exposed group) divided by the incidence odds of occurring in the other group (could be the unexposed group). To translate this to Paper III, the odds (not the same as the chronic pain rate calculated) in the regular LWM-PP group was 0.188 and for the HWM group 0.193. The odds ratio is nearly 1, suggesting no differences between the two group's odds of the event to occur. Most of the variables in the logistic regression model in Paper III were by nature categorical variables from the SHR. However, the age variable was interesting, since we could either include the variable in its naturally continuous character or convert it to a categorical one, usually divided by the median. Age as a continuous variable against the binary outcome of chronic pain demonstrated a curved relationship, indicating that younger patients had a higher probability of pain following their repair. A categorical variable with three groups was set in order to assess if the youngest patients had an estimated increased risk of developing chronic pain compared to older patients.

Subgroup analysis was performed to investigate if the use of LWMs in the youngest age group, with an increased estimated risk of developing chronic pain compared to more elderly patients, was associated with a reduction in the risk of developing chronic pain compared to HWM.

Paper IV

Analysis was descriptive and variables were presented in numbers and frequency (%) for all the included umbilical hernia repairs. The continuous variables were described in median with range. Hence, the follow-up time in this study was presented as the median time in months after surgery where patients were followed in the outpatient clinic documentation.

Subgroup analysis was performed to investigate if the cases with surgical site complications stood out in case of other variables such as; BMI, age, gender or perhaps smoking in comparison to the group with no surgical site complications.

4.8 ETHICAL CONSIDERATIONS

The Paper's (I-IV) and Appendix A's study protocol in this thesis were all approved by the Regional Ethics Review Board in Stockholm, Sweden. Here, I present an ethical reflection and consideration of the various papers.

Paper I-III

In Paper I-III only aggregated data from the SHR were collected without any accesses to sensitive information. Oral informed contests are obtained from all participants for registration in the SHR. There were no special ethical considerations required to carry out the studies in Paper I-III. No individual patient data were analyzed, only at a group level. Furthermore, it is ethically very defensible to use already collected data from a validated register in order to conduct studies to improve outcomes. Since each Swedish citizens have unique social security number, registered patients can easily have their surgical journey tracked in any surgical unit participating in the SHR, until death or emigration. By combining this large amount of data from almost all surgical units in Sweden, we have great benefits to analyze the data and to interpret the results for a high external validity.

Nevertheless, one can discuss whether it is ethically justifiable to perform studies from the SHR with patient's information about their surgery and without each individual patient having been specifically informed about the exact use of their data? Patients who are operated on for their groin hernia at present time give their oral consent to participate in the register and can withdraw their consent at any time. Studies performed via the register are also briefly described on the website. Gathering written informed consent for a specific research issue from thousands of patients retrospectively would be nearly impossible and superfluous. All studies from the SHR aim to improve the care for the future groin hernia patients.

Paper IV

The study population in Paper IV are not recorded in a register. A data set of the collected variables were set up with uncoded personal information. Likewise in paper I-III, there were no special ethical considerations required to carry out the retrospective data collection. However, we performed the data collection from the patients' medical records without a consent from the patients. Again, gathering a written informed consent for a specific research issue from nearly 100 patients retrospectively is considered excessive. Sometimes, the retrospectively collected information can reveal significant data for the certain patient's future treatment outcomes. That situation can lead to an ethically difficult situation. However, in this certain research question, that was not considered an issue. Instead, the data collection that was presented on a group level can truly be beneficial for the future umbilical hernia patients.

Appendix A

I would also like to emphasize the different ethical reflections that have emerged regarding the intervention study described in Appendix A.

All procedures performed, involving intervention in human participants are in accordance with the ethical standards of the Helsinki declaration and Good Clinical Practice protocol. Oral and written informed constants are obtained by all participants prior to their inclusion and randomization.

Evaluating the *risks* versus the *benefits* of conducting an interventional study should be one of the central and most important ethical considerations to clarify. In my opinion, it forms the pillar of whether we should carry out a study or not.

The *benefits* of conducting the study described in Appendix A could prove substantial. If an onlay-mesh repair reduces the risk of recurrence following an umbilical hernia repair, without giving any increase in wound-related complications, this will be of great importance for future umbilical hernia patients. The patients will experience as good surgery as before, but with a lower risk of recurrence and re-operation. This directly contributes to better satisfaction and less suffering for the patient. It can also have a positive effect on health economics, in that some patients might be able to avoid a re-operation of a larger and more demanding scale. The idea of using a mesh for minor hernia defects may change in general surgeon's minds, contributing to a potential paradigm shift.

Two things have formed the basis of how I have assessed the *risks* with the study described in Appendix A; the *probability* of developing complications, *the severity* of the complications, and the two aspects in relation to each other. If the probability of developing a less serious complication is low, there will probably never be any problem with the evaluation of the risk versus benefit analysis. The difficulty, I would say, is when the probability of getting a serious complication is high or even when the probability is small, but the severity of the complication is high. We are probably all in line with the fact that trial participants must not be exposed to suffering and danger, for which if that is the case, the benefit must be defensible and strongly considered. This means that certain research should be excluded from being carried out by interventions, despite the fact that the increase in knowledge can be significant.

The polypropylene mesh presented in the study protocol has been routinely used in human hernia surgery for many years, and is well documented. The small umbilical hernia repair, regardless of method, involves the standard risks of complications. Both surgical methods presented in the study protocol are already well known and have previously been used without any reported serious risks to the patient. The complications following umbilical hernia surgery with small defects are considered to be few with a low frequency. Thus, both the probability of developing a complication and its severity is considered low. The usual complications are those commonly stated for any surgical procedure such as bleeding, infection, fluid accumulation; including other medical complications related to an operation/anesthesia. Unfortunately, these problems can also occur in those who are operated on without a mesh. The trial described in Appendix A aims to investigate and compare the rates of complications in both groups of the trial in a controlled manner.

The required informed consent of the trial participants prior to inclusion in the clinical trial is different from the other register studies. I devised the informed consent as such to ensure adequate and comprehensible information for the trial participants. The challenge was to give a balanced and neutral account of the two different surgical methods, despite our hypothesis of a mesh repair being superior to a simple suture for the risk of recurrence.

Finally, an obvious ethical situation has come to my knowledge when including trial participants in the study in a clinical outpatient setting. In some cases, the potential trial participants could meet the inclusion criteria, but could be considered to not present enough symptoms of their small umbilical hernia to benefit from a repair. This is where the boundaries of health care and research collide. The research mindset of focusing on including participants in clinical trials needs to follow the first priority of assessing good health care with correct indications for surgery.

5 RESULTS

5.1 PAPER I

In total, 17,349 hernia repairs were eligible from the SHR during the study period. After excluded meshes, 13,839 hernia repairs remained for statistical analysis. 7449 hernia repairs were repaired with HWM and 6390 with LWM. A total number of 491 of these were reoperated for recurrence. The median follow-up time was 88.2 months for the HWM-repairs and 56.8 months for the LWM-repairs. The cumulative overall reoperation rate for recurrence in the cohort was 3.5 %.

The main findings in Paper I was the associated increased risk of reoperation for recurrence for the age and type of mesh variable. (Table 3).

The hernia repairs in patients ≥ 59 years old were associated with an increased risk of recurrence compared to younger patients that had their hernias repaired during this study period (Table 3).

	Univariate	model		Multivariate	model	
Variables	**HR**	**CI (95 %)**	***P***	**HR**	**CI (95%)**	***P***
Age, years						
< 59	1(ref)			1		
≥ 59	1.41	1.18-1.69	**< 0.001**	1.33	1.10-1.60	**0.003**
Type of mesh						
HWM	1			1		
LWM	1.44	1.21-1.72	**< 0.001**	1.56	1.29-1.88	**< 0.001**
Size of defect						
< 1.5 cm	1			1		
1.5 – 3 cm	1.12	0.88-1.43	0.367	1.01	0.79-1.31	0.911
> 3 cm	1.40	1.06-1.86	**0.019**	1.27	0.94-1.71	0.124

Table 3. *Selected significant variables in the univariate and multivariate Cox's proportional hazard ratio model for the outcome of reoperation for recurrence*

Furthermore, the investigated main variable was shown to be a significant risk factor for reoperation for recurrence. More specifically, hernia repairs performed with LWM were associated with an increased risk of reoperation for recurrence, compared to those repaired with HWM (Table 3, Figure 9).

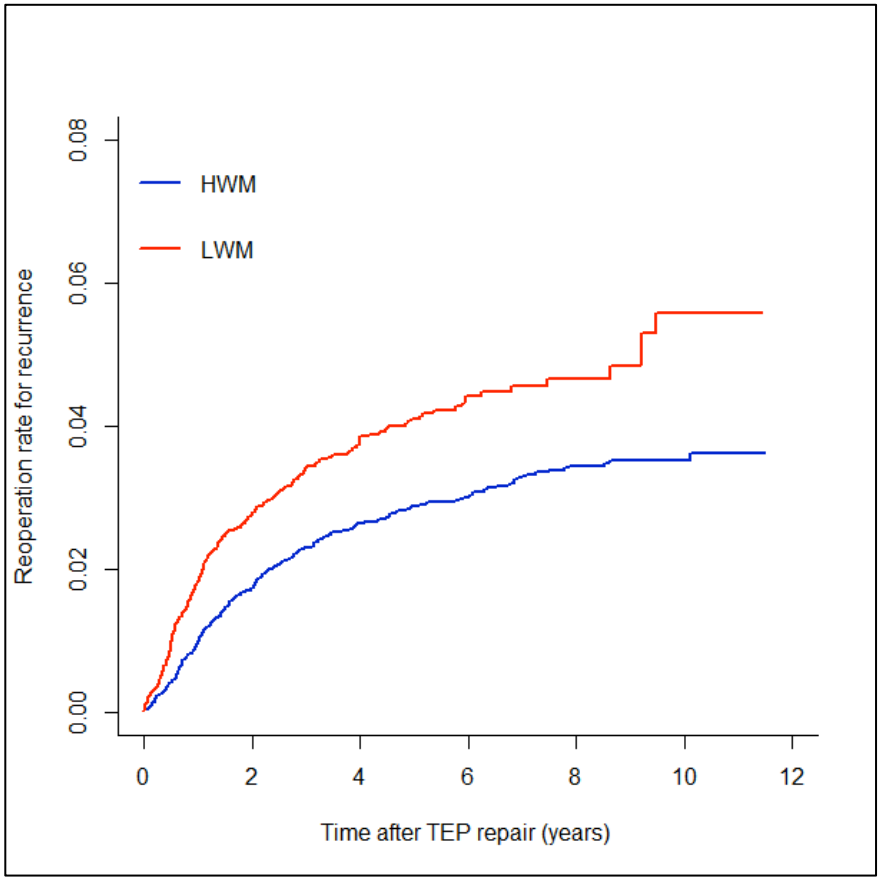

Figure 9. *Kaplan Meier curve illustrating the significant ($p < 0.001$) lower rate of reoperation for recurrence for HWM compared to LWM during the time following a TEP hernia repair on men..*

Hernia repairs with a defect > 3 cm appeared to be associated with an increased risk of recurrence, compared to smaller hernias that were repaired in the cohort. However, this result was not significant in the multivariate analysis (Table 3).

Subgroup analysis demonstrated that in smaller (HR 1.31, CI 0.83-2.11) and in indirect (HR 1.33, CI 1.01-1.76) hernia repairs, the risk of reoperation rate for recurrence with the use of LWM were more comparable to HWM.

5.2 PAPER II

A total of 94,601 hernia repairs were eligible from the SHR during the study period. After excluded meshes and other exclusion criteria, 76,495 hernia repairs remained for the statistical analysis, of which 1676 were reoperated on for recurrence. 38,729 hernia repairs were repaired with HWM, 13,002 with regular LWM-PP, 17,029 with LWM-PP/PGC and 7735 with LWM-PP/PG. The median follow-up time was 7.4 years for repairs with HWM, 4.8 years for regular LWM-PP, 5.5 years for LWM-PP/PGC and 8.2 years for LWM-PP/PG. The cumulative overall reoperation rate for recurrence in the cohort was only 1.2 %.

The main findings in Paper II were that regular-LWM-PP were not associated with an increased risk of reoperation for recurrence compared to HWM-PP (Figure 10, Figure 11). However, the other two LWM-groups, LWM-PP/PGC and LWM-PP/PG, were associated with a significant increased risk of reoperation for recurrence compared to HWM (Figure 10, Figure 11).

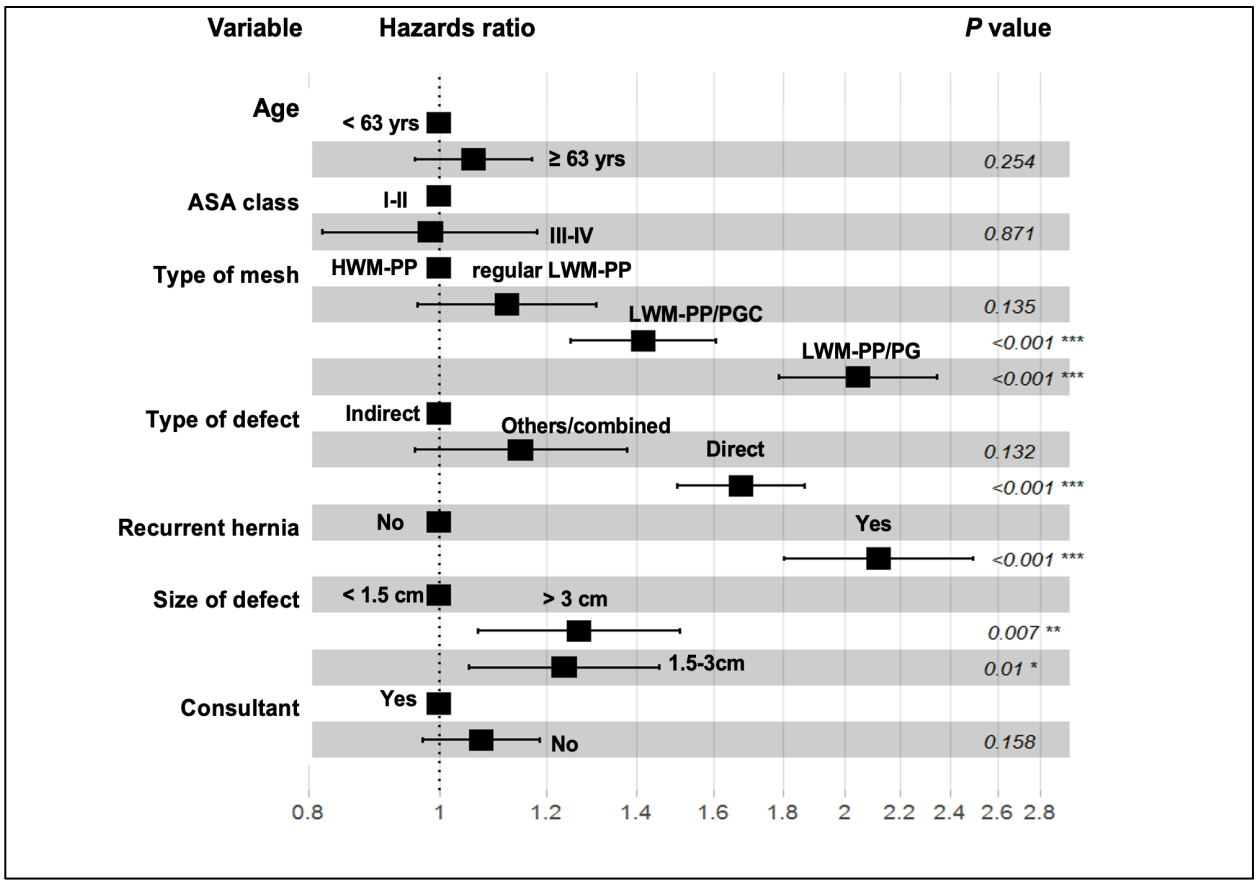

Figure 10. *Forrest plot illustrating hazard ratios and confidence intervals with p-values of the different variables in the multivariate Cox´s proportional analysis of the outcome of reoperation for recurrence. The reference variable of each variable group is presented in the plot with hazards ratio 1. * Stands for significant p-values.*

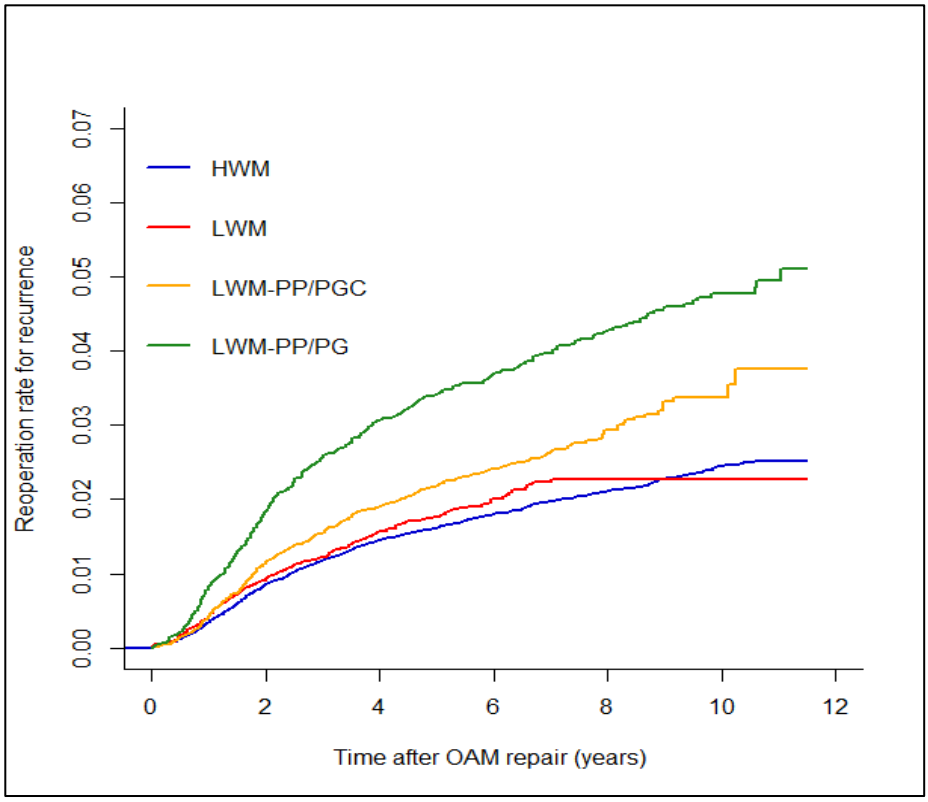

Figure 11. *Kaplan Meier curve illustrating the rate of reoperation for recurrence during the time after the OAM repair in male hernia repairs.*

Other variables that were shown to be associated with an increased risk of reoperation for recurrence were repairs for a direct or a larger hernia, and a recurrent hernia (Figure 10). The hernia repairs in older patients were in this cohort not associated with an increased risk of recurrence compared to younger patients that had their hernia repaired.

The subgroup analysis demonstrated no significant increased rate of reoperation for recurrence for LWM-PP/PGC and regular LWM compared to HWM in the repair of smaller hernia defects. (Figure 12).

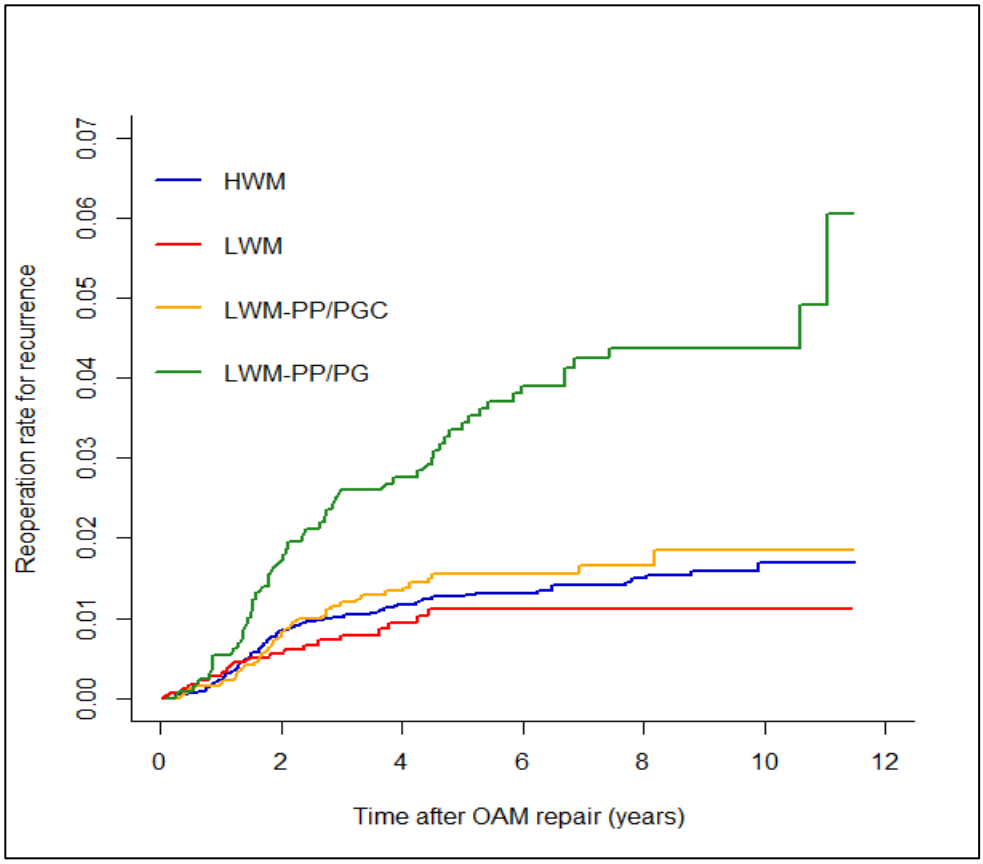

Figure 12. *Kaplan Meier curve illustrating the rate of reoperation for recurrence for the four mesh groups in the repair of smaller hernia defects following the OAM inguinal hernia repair on men.*

5.3 PAPER III

A total number of 43,303 hernia repairs were registered in the SHR during the study period of Paper III. Of these, 30,577 provided answers to the pain questionnaire with a response rate of 70.6 %. After exclusion, a total of 23,259 hernia repairs performed with three different mesh types (HWM-PP, regular LWM-PP and LWM-PP/PGC) remained for the statistical analysis.

The main finding in this study was the high chronic pain rate following an OAM inguinal hernia repair on men, particularly of young age. The significant persistent pain 1 year after surgery was reported as 15.9 % by the entire study population and 19.4 % among patients aged less than 50 years, making young age in this cohort the most evident risk factor for the assessed outcome (Figure 13).

Adjusted multiple logistic regression analyses demonstrated that the estimated risk of developing pain 1 year after an OAM hernia repair were similar for the three different mesh types (Figure 13).

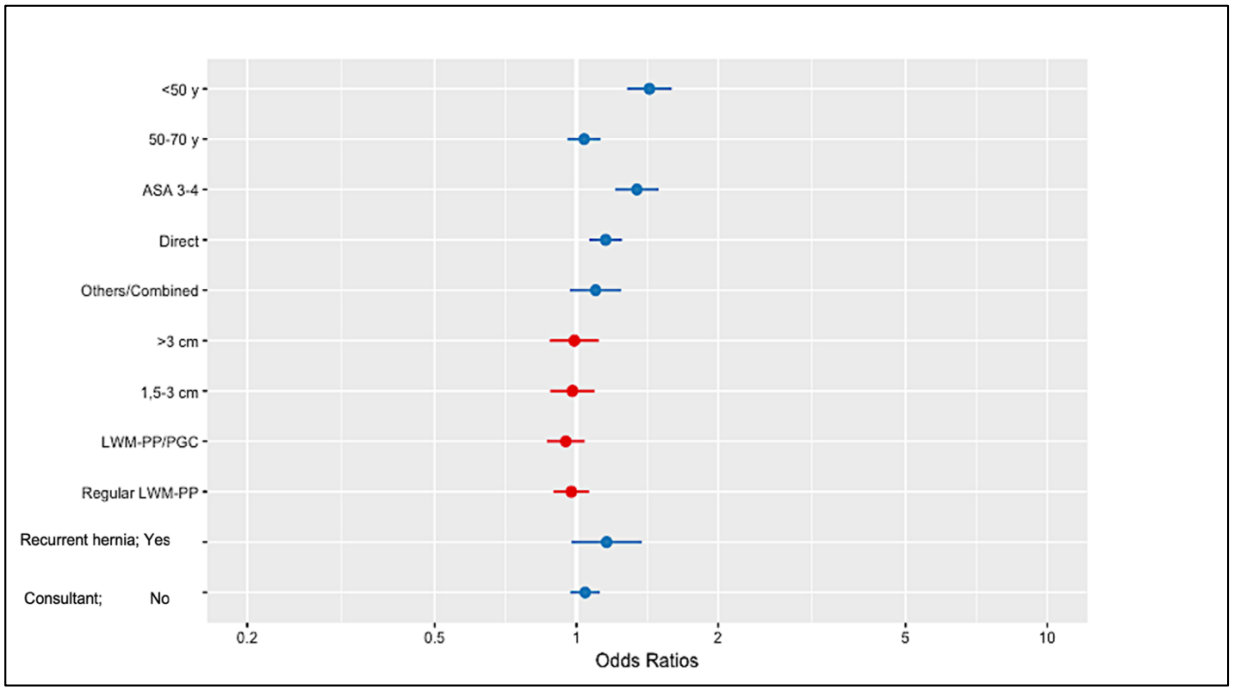

Figure 13. *Forrest plot of the adjusted multiple logistic regression analyses of the included variables for the outcome of pain 1 year after surgery with estimated odds ratios and confidence intervals. Hence, the reference variable of each variable group is not presented in the plot. The reference variables are; > 70 y, ASA 1-2, Indirect hernias, <1.5 cm hernias, HWM-PP, No recurrent hernia and Consultant (yes).*

The most interesting subgroup analysis was to investigate if the risk of developing pain 1 year after surgery in the younger age group (of less than 50 years old) were influenced by the type of mesh. The results showed no significant difference in the risk of chronic pain between the mesh groups (Figure 14).

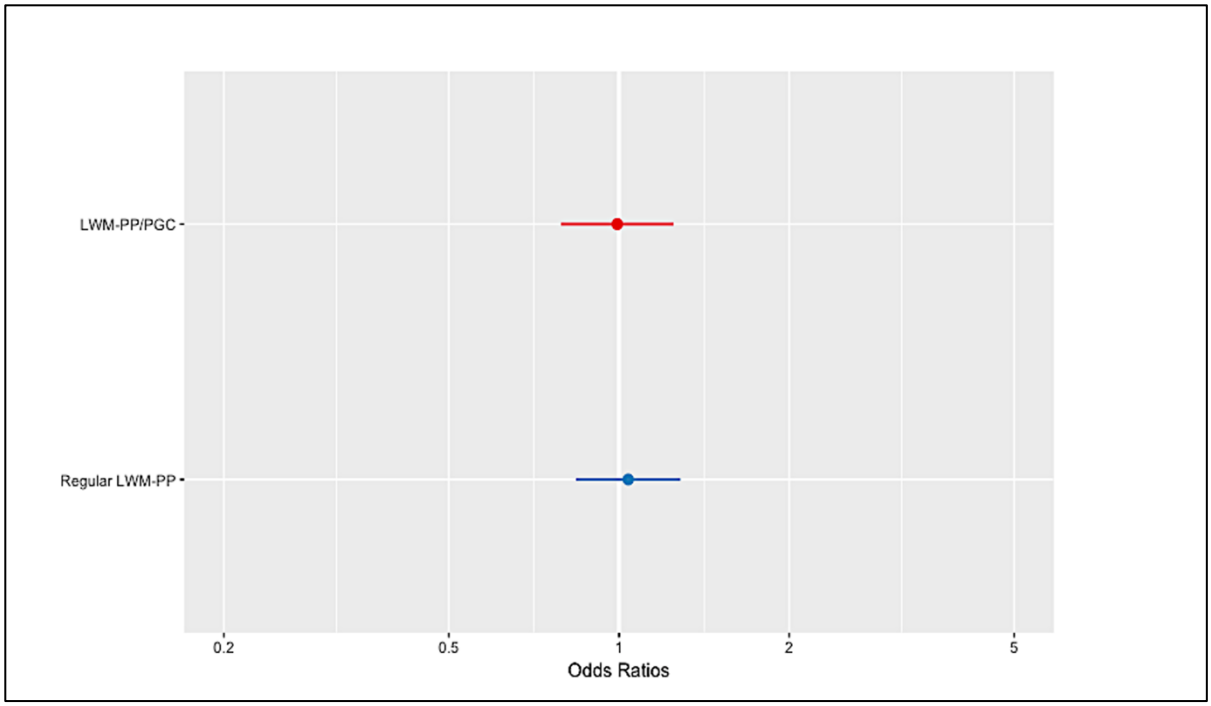

Figure 14. *Forrest plot of the subgroup analyses of the included meshes for the outcome of pain 1 year after surgery with estimated odds ratios and confidence intervals in the young ages group < 50 years old. Reference was HWM-PP and not presented in the plot.*

5.4 PAPER IV

In total, 253 umbilical hernia repairs were eligible from Södertälje Hospital's surgical database (using ICD codes) during the study period. After exclusion of suture repairs and mesh repairs with a sublay positioning and a laparoscopic approach, 115 hernia repairs remained for further investigation. Thereafter, a total of 80 small elective umbilical hernias ≤ 2 cm (Figure 15), repaired with a 4 x 4 cm (± 1 cm) onlay-mesh (Figure 16) remained for the final statistical analysis.

The follow-up of the patients (n = 80) in the outpatient clinic documentation after surgery was 29 (4.3-50.1) months in median (range). The patients were middle aged (46 years old in median) and predominantly males (67 %). Furthermore, the median (range) BMI was 28 kg/m^2 (19-38) and all the patients were mostly healthy (ASA I-II nearly 90 %). Among the registered risk factors, smoking was the most frequently observed in over 20 % of the patients.

The main findings in Paper IV were the low frequency of surgical site complications. Only 4 out of 80 (5 %) patients were found, from the outpatient clinic documentation, to have had a seroma (3 patients) and a superficial wound infection (1 patient). All the patients with a treatment outcome healed well within the follow-up without the need for a re-operation. There were no registered cases of recurrences during the follow-up period.

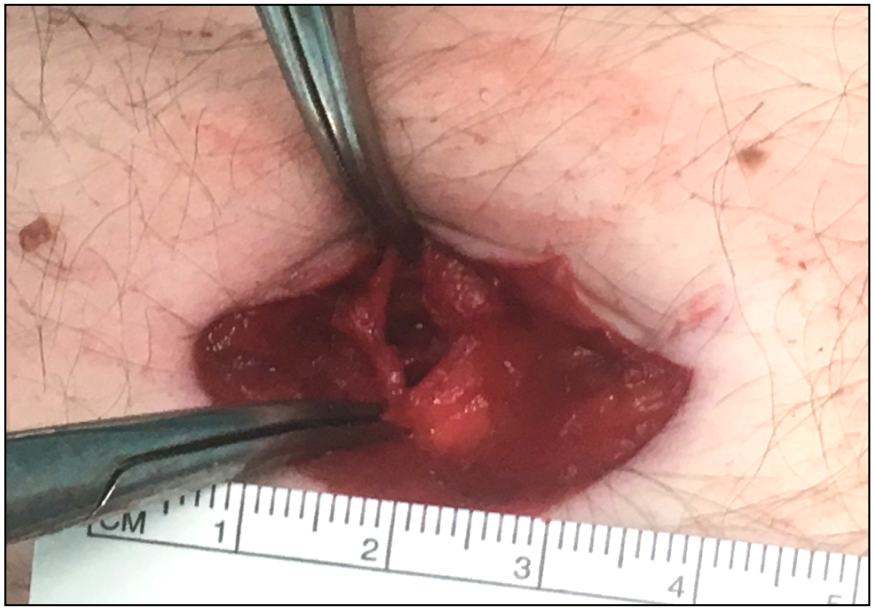

Figure 15. *A small umbilical hernia with a defect < 2 cm.*

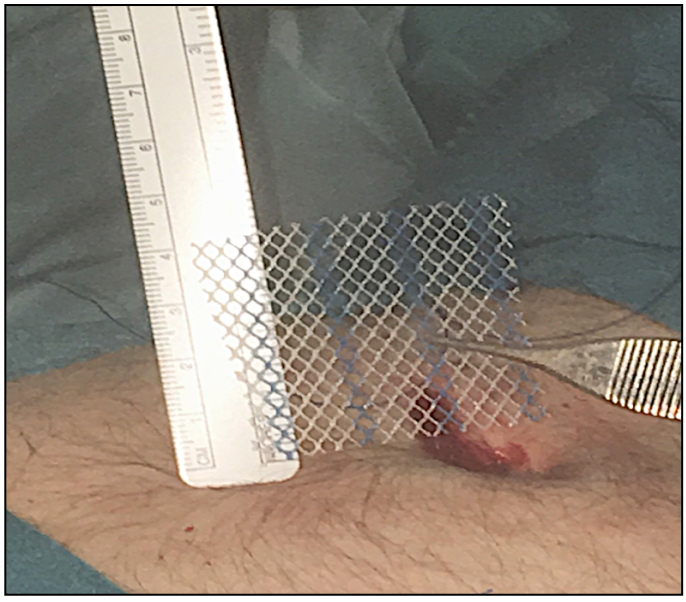

Figure 16. *A small 4x4 cm lightweight mesh was being prepared to be placed above the aponeurosis on the sutured hernia defect.*

6 DISCUSSION

6.1 INTERPRETATION OF MAIN FINDINGS

6.1.1 Lower recurrence rate with HWM in TEP groin hernia repair and clinical significance

Paper I is the largest population registry-based cohort study to investigate the concerns of increased recurrences with the use of LWM in TEP hernia repair. The results demonstrated an associated increased risk of recurrence with LWM compared to HWM following a TEP groin hernia repair. These findings are in line with earlier reported results from other authors[84,87], which was also confirmed in a recent large randomized controlled trial with 300 participants[89]. A lightweight mesh was compared to a standard heavyweight mesh for the primary outcome of recurrence. Both 2-years[90] and 5-years[89] follow-up demonstrated that the heavyweight mesh was superior to the lightweight mesh in respect to recurrence. The very same authors also summarized all the trials in the field in a systematic review and concluded that HWM should be used over LWM in a TEP repair to avoid increased recurrence rates[123]. The explanation for these results can be the less intrinsic weakness and less fibrosis achieved by LWM compared to HWM, consequently forming inadequate scar tissue with less ability to resists a hernia recurrence.

Moreover, one cannot continue the general discussion of our findings without emphasizing the clinical significance of the results. The study demonstrated an overall low and small difference in recurrence rate in absolute numbers between the mesh groups (4 % vs 3.2 %). The results translated into a number needed to treat (NNT) would be; 125 repairs that can be performed with LWM before an event of a recurrence occur. This needs to be taken into consideration along with LWM positive effects on discomfort, early recovery after surgery and short-term pain compared to HWM[92,95,124].

The strength with Paper I is the large population-based cohort with high national coverage and consequently a reflection of the general population and the clinical reality in our country. The data represents all the TEP-surgeons in the entire nation with long-term results, compared to TEP- experts that normally perform the repairs in clinical trials.

The specific limitations with Paper I was the difficulties to adjust for the surgeon's technical skills (despite nearly all being consultants) in performing the crucial preperitoneal dissection in the TEP repair for the optimal insertion of the mesh. The TEP repair became popular in Sweden in the middle of the study's time period. Potential learning curves affecting the cohorts' data and recurrence rate cannot be ruled out (Figure 17).

There are more overall strengths and limitations for Paper with regard to the methodology. These are similar for paper I-III and will be discussed in detail in further section.

6.1.2 Long-term results and LWM for the OAM inguinal hernia repair

In paper II, we did not find any significant differences between hernias who underwent a repair with regular LWM-PP (1.7 %) compared to with HWM-PP (1.9%) for the outcome of reoperation rate for recurrence. However, the two other lightweight mesh groups with an absorbable component added to polypropylene, LWM-PP/PGC (2.3 %) and LWM-PP/PG (4.1 %), were both associated with an increased risk of recurrence compared to HWM. In terms of NNT, one would need to repair 240 hernias with LWM-PP/PGC and 45 hernias with LWM-PP/PG for an event of a recurrence to occur. The NNT should therefore be put in relation to LWM-PP/PGC previously reported great advantages in lowering the rate of discomfort and short-term pain compared to HWM[92,95,124]. However, the recurrence rate for LWM-PP/PG is considered to be too high and the NNT is unacceptable low. Therefore, the risk of increased recurrence can certainly consider to outweigh the benefits of the softer lightweight PP-PG mesh.

Smietanski et al, have earlier compared one regular LWM-PP to a standard HWM and could not identify any difference in recurrence rates[92]. Similar results were reported from Nikkolo et al, using another regular LWM-PP to a standard HWM with a 3-year follow-up[125]. These reports correspond well to our findings that regular LWM-PP without a partially absorbable component seems to result in low recurrence rates without any significant difference compared to standard HWM following an OAM inguinal hernia repair.

Our results in Paper II reflect at least one of the main principles of trusting research – reproduceable results over time. The Dutch recently summarized the results from all the published clinical trials of using LWM compared to HWM following an OAM groin hernia repair and concluded that only LWM should be recommended for use in an open anterior mesh groin hernia repair[126].

A possible underlying mechanism of these results following an OAM repair, in contrast to why LWM demonstrates more recurrence cases compared to HWM in a TEP repair, can be that the method of inserting and fixating the mesh is different and that the lower amount of PP in LWM can still achieve a god support for the hernia in the open approach. The method of the OAM hernia repair is a standardized well-structed approach that stretches several years back, thus most likely having progressed through the learning curve (Figure 17). An explanation for the increased recurrence rate for the composite LWM-PP meshes could be that some surgeons have been fixing the mesh incorrectly, not knowing that the fixation of softer meshes usually need an increased number, and less spaced out, sutures.

The strengths with Paper II consist of the overall strengths with high coverage nationwide population-based cohorts. More specifically, the long-term follow-up gave reliable data for the outcome of reoperation for recurrence. Also, the multivariate analyses in the study tackles known confounders and factors affecting the outcome. The specific limitations with the study were the lack of the specific information about the meshes and other patient-related characteristics that could have affected the outcome. Although LWM-PP/PGC were specified as a group, the SHR cannot provide information that distinguishes VYPRO and VYPRO II from the LWM-PP/PG group. Also, data on other mesh properties apart from weight are limited within the SHR.

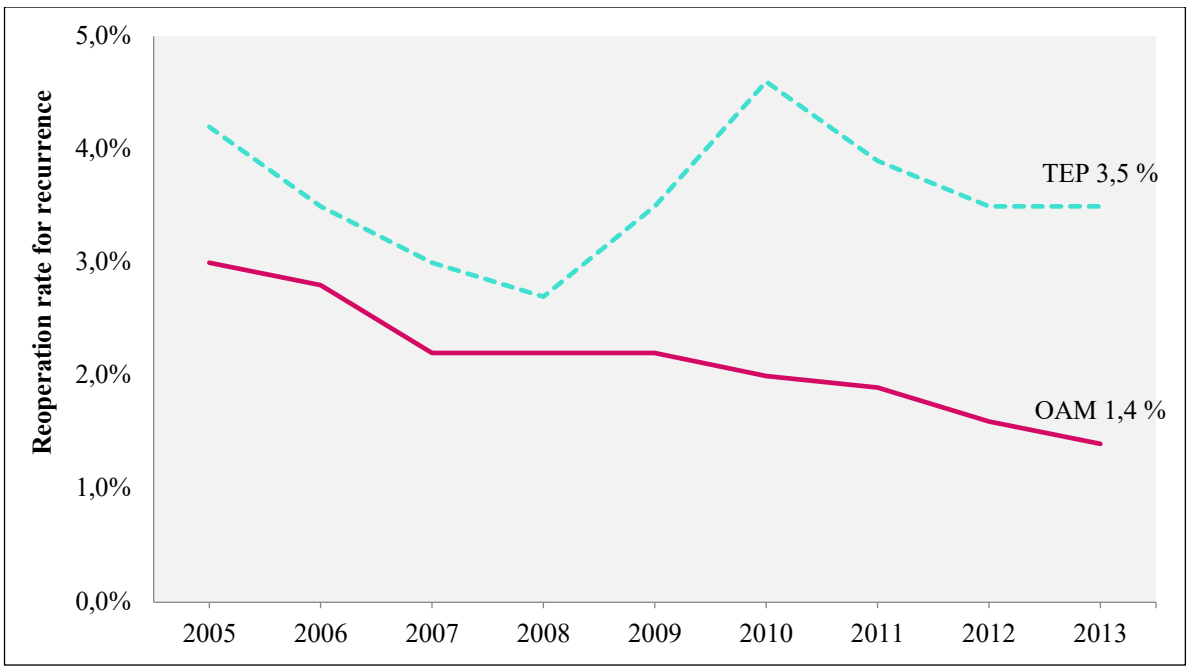

Figure 17. *Data extracted from the SHR. Reoperation rate for recurrence by each year for TEP - versus OAM groin hernia repair during the study period of paper I and II.*

6.1.3 Mesh type and chronic pain following OAM inguinal hernia repair

The scientific question of interest in Paper III is very pertinent in time. Investigating risk factors for chronic pain following hernia repair is substantial in order to improve its outcome. There is still conflicting data in the current literature whether lightweight meshes can reduce the risk of chronic pain compared to heavyweight meshes. The chronic pain rate in Paper III was undoubtedly unsatisfactorily high at a level of almost 16 % at 1 year after surgery. This is patient-reported significant pain that affects the patient's lives on a daily basis in varying degrees. For the younger patients having hernia repairs, the rate in the cohort was even higher, nearly 20 %. Being a surgeon with a special interest in hernia repair, and with several inguinal hernia repairs performed, this rate is a worrying discrepancy to the clinical setting. This number of patients with chronic pain has not been exposed to my knowledge yet in the outpatient clinic. Thereof, the importance of investigating PROMs after surgery.

Nevertheless, our analysis failed to show a particular mesh having an influence on developing chronic postoperative pain following an OAM inguinal hernia repair in men. When comparing our results with randomized clinical trials (RCTs), they differ both in rate and risk; whereas usually trials report lower chronic pain rates. The Swedish TEPLICH trial reported only a 9.8 % rate of chronic pain following an OAM groin hernia repair[127]. However, they did not include patients under the age of 30. The Dutch TULIP trial described a chronic pain rate of 12.9 % at 12 months after surgery[128].

Moreover, a meta-analysis[83] could assess a significant lower risk of chronic pain with lightweight meshes compared to heavyweight meshes when comparing several RCTs[79,82,92-94]. In contrast to that, a systematic review[95] found no difference in four homogeneous RCTs[79,92,96,97] with a follow-up of 1 year or more for the same outcome. Usually, the performing surgeons are experts in repairing hernias in clinical trials and this can certainly reduce the complication rate following the procedure[129]. Also, one can suspect that trial participants are scoring less pain if they are included in a trial with a well-organized follow-up. One limitation with these meta-analyses and systematic reviews is the usage of different types of meshes in the trials. This surely makes it difficult to compare studies and interpretate the results. Also, the definition of pain differs in time and in scale. We used a clear definition of chronic pain 1 year after surgery with a reduced short form of the IPQ[55]. The single items have been reported to be an interchangeable and a more user-friendly tool in daily practice than the complete IPQ[130].

Other previous studies with hernia repairs from the SHR have demonstrated similar rates of chronic pain, between 15-18 % following an OAM groin hernia repair[35,131]. Also, a recent

published Swedish randomized clinical trial in which the authors also used the short form of the IPQ, could interestingly reveal a clearly significant lower risk of chronic pain following an OAM inguinal hernia repair with lightweight mesh compared to heavyweight mesh after 9-12 years[132]. The most interesting in this trial is the much lower rate of chronic pain at a level of maximum 3 %. This indicates that chronic pain can fade away with time. This was also concluded from the TULIP trial's long-term data, which revealed a major decrease in chronic pain rate after 7 years following a groin hernia repair[133].

Despite paper III not being a randomized clinical trial, this study can emphatically present robust patient-reported data from the general population in Sweden. It also proves that postPROM:s can be successfully utilized via a register and distributed in large cohorts with good compliance. The acceptable response rate to the pain questionnaire and the availability of the data on the loss to follow-up repairs, allowing comparison of responders and non-responders to detect bias was a further strength. The validity of this is discussed under the section of bias, along with other limitations of the study.

However, the main specific limitation of the study was the lack of information regarding pain (prePROM) before surgery among the hernia patients. This could represent a central confounding factor and the lack of controlling for it may have influenced the results.

6.1.4 Onlay mesh for the repair of small umbilical hernias?

Despite earlier data showing support for mesh reinforcement in small umbilical hernia defects[110-118], surgeons in Sweden are at the time of writing still reluctant to use mesh in these cases. I believe it is due to difficulties relating to the anatomical placement of the mesh in these small defects and concerns of higher risk of post-operative surgical site complications with mesh. Considering that small umbilical hernias make up 90% of all umbilical hernia repairs in Sweden, and hernia repairs are the most common procedures performed by general surgeons[4], it is essential for surgeons to have a consensus on the least morbid and most effective technique of repair.

The report in paper IV can add important knowledge of the observed low surgical site complication rates of onlay-mesh repairs in small umbilical hernias. However, the results of the

assessed outcomes of recurrence were considered to be less sufficient data precluding robust conclusions to be drawn.

The presence of the few surgical site complications in paper IV was not entirely with accordance of other earlier studies that have demonstrated higher rates of surgical sites complications with mesh. Several explanations can be discussed with regard to this discrepancy. Firstly, in contrast to other studies, we investigated a homogenous group of *small* defects and only *umbilical* defects. Secondly, the subcutaneous dissections for the *small onlay mesh* were minimal. Different mesh positioning and hernia size can certainly affect the surgical site complication rate. The risk of developing a seroma is higher in larger hernia defects repaired with a retro-muscular technique, rather than in very small defects, repaired with a small onlay-mesh with a minimal undermining to facilitate placing the mesh above the aponeurosis. For example, a meta-analysis found an increased risk of seroma and surgical site infections in the mesh group (7.3 % and 7.7 %) compared to the suture repair group (6.6 % and 3.8 %), but with different methods of mesh positioning[116]. Kaufman et al. reported in their large randomized clinical trial, a surgical site complication rate for the mesh group that did not significantly differ from the sutured repair group, but was described in 6.8 % (10 out of 146) of the sublay/pre-peritoneal mesh repairs in 1-4 cm umbilical hernias[119]. Thirdly, high BMI can be one of the factors that can affect the outcome of postoperative complications following a ventral hernia repair[134,135]. The patients in our cohort, with a median BMI at 28 kg/m^2, could been considered to be close to normal weight. To delay surgery in patients with a high BMI until a normal BMI was undoubtedly a selection here. However, this simply reflects the reality in selecting patients to surgery in outpatient clinic setting in order to achieve a low rate of postoperative complications for the patient benefit.

Furthermore, the current study design of a retrospective analysis in paper IV comes with several limitations in interpretation of the results. The main point was to reflect on if the treatment outcome rate was either over- or underestimated? Underreported data, incomplete data, information from medical records, lack of confounder information and selection to surgery are some of the issues that has been identified as potential sources of bias. The study population is limited and, as an effect of it, the events of the assessed outcomes become rare. Therefore, the low surgical site complication rate can be an effect of a small sample size. The rare events also made it difficult to draw any conclusions regarding the potential cause or risk factors of the occurrence of the surgical site complications. Moreover, some of the adverse events of surgical

site complications could have been missed in patients who decided to seek for a complication following their hernia repair in another hospital or their family doctor. Finally, selection for surgery with the onlay mesh repair was certainly generated by the surgeons. The alternative was usually treatment with suture repair. However, both methods of repair are relative similar with comparable indications. Surgeons may have selected patients with defects that were considered to have a low risk of recurrence and surgical site complications (for example with a low BMI and a good fascia quality) to only be sutured. If these patients would have been included in the onlay mesh repair cohort as well, the surgical site complication proportion would probably have been even lower than 5 %. And in contrast, we also believe that patients that were considered to be at a higher risk of recurrence after surgery were certainly sometimes selected to be repaired with an open ventral patch mesh repair. Thereof, the cohort could have missed out some patients with a greater risk of postoperative complications.

Should we use the onlay mesh repair for small umbilical hernia repair? Well, we can, but we can still not say that we should. Such a conclusion calls for further studies comparing the method with other repairs in a prospective nature to assess whether an onlay-mesh can reduce recurrences in small umbilical hernia repairs without increasing the surgical site complication rate. However, the study can provide additional knowledge to surgeons considering using mesh in small umbilical hernia repairs, and thereof making the onlay-mesh repair a safe and easy alternative when choosing a mesh repair method for the treatment of small umbilical hernias.

6.2 METHODOLOGICAL CONSIDERATIONS

"It is the mark of an educated mind to rest satisfied with the degree of precision which the nature of the subject admits and not to seek exactness where only an approximation is possible."

- *Aristotle, philosopher, 384–322 BC*

The methodological considerations were once said to me to be the main chapter in the thesis. And perhaps, this is where I prove to demonstrate my awareness of the limitations associated with the paper's methodology and the interpretation of the obtained results.

6.2.1 Prospective population-based register cohorts

"Life can only be understood backwards, but it must be lived forwards."

- *Soren Kierkegaard, philosopher, 1813–1855.*

One of my all-time favorite quotes. Three epidemiological studies in this thesis can be referred to as population-based register cohorts. *Cohort studies* are usually defined as observational studies in which people are exposed to something and followed up over time for an outcome to appear at a particular time after the exposure. Cohort studies can either be descriptive or analytical, whereas two or more groups can be comparable of incidences and risk estimates. The great advantage of cohort studies is the episode of the exposure before the outcome has occurred, and consequently the important sources of introducing bias can be avoided. This forward in the time process is valuable for assessing a possible casual association. The studies are therefore usually elegantly called *prospective studies.* However, sometimes the distinction between prospective and retrospective cohort studies can be difficult. If the collected data of the exposed subjects appears after the follow-up time and the occurrence of the outcome, a retrospective analysis is made and bias is probably being introduced. This is the case for Paper IV and the different types of bias will be discussed furthermore. Since cohort studies requires observation of a large number of subjects over long time to obtain statistically significant results, they can be complex to carry out. Therefore, already prospectively collected data in long-term registers suits perfectly for assessing rare outcomes in a fervent way. All data of the exposure and the covariates in the SHR for Paper I, II and III are registered prospectively during the procedure of the hernia repairs. Still, the study design may present concerns of not properly addressing the scientific questions, inclusion and exclusion criteria and planned analysis prior to data entry. Consequently, so called "cherry picking" and serendipity can occur. In addition to the registration of clinical trials before the start of the study, one should also nowadays register observational register studies. This increases the transparency of what is to be analyzed before processing the already collected data.

Furthermore, the term *population-based* is another more valuable and prestigious expression, referring to a high national coverage of the repairs in the register. As a result of the close and accurate monitoring of the Swedish hernia population, the cohorts in paper I-III represents nearly the entire population that the studies intend to target. The strength in having such an

accurate representation of the study population, rather than just a sample, greatly improve the external validity of the results. Therefore, as a minor notice, I take the opportunity to address that we did not present p-values from variable-tests in paper I-III:s baseline tables. These tests are made to be tested on sample study population to prove if the chosen sample is representative of the population for which the study is intended to target, which in this case was considered superfluous.

Furthermore, in addition to being *prospective population-based register cohort studies*, paper I-III in this thesis has several overall strengths. Data quality on outcomes such as reoperation for recurrence and the registered hernia related variables is considered to be good and highly validated with few missing values. The allure is that the data represents the real clinical setting in the entire nation, with unselected repairs and unselected surgical centers.

6.2.2 Validity

"Consistency is more important than accuracy."

- *John M. Cowden, epidemiologist, 1953-*

The quote refers to surveillance research, whereas absolute accuracy (also known as validity) can be considered unachievable.

Nevertheless, either the scientific results of the study are true or there is a mistaken result – an error. *Random error* is a result of variation by chance that causes imprecise results with low accuracy without being reproducible. It will be discussed under the precision section. If it is not by chance, a *systematic error* (a recognizable, reproducible source) can be introduced in the study design and in the analysis.

The internal validity usually refers to the presence of systematic errors. In brief, systematic errors are those where an established exposure-outcome relationship in a study can be explained by other factors. In other words, when assessing internal validity, one can ask oneself if there is a

causal association between the exposure and the outcome, and if the exposure is the cause of the outcome.

Moreover, have we measured what we were intended to measure? We used a proxy outcome for recurrence in paper I and II; reoperation for recurrence. Even if the registered outcome of a re-operation for a recurrence is a very robust and valid measurement for the true recurrence, the overall recurrence rate is probably underestimated. And more importantly, is it suitable to only use mesh weight to detect an association with hernia recurrence? Also, are the increased recurrences in paper I and II due to the use of LWM? With our analysis in Paper III, can we rule out that the type of mesh did not affect chronic pain rate 1 year after an open inguinal hernia repair? And finally, several questions were raised when interpreting the results and the data in paper IV.

To determine the internal validity, systematic errors introduced by the investigators (namely bias and confounding) are being explored.

Almost all studies are prone to bias and confounding and they may have affected also this thesis studies in varying degrees.

Selection bias

I will never forget the statement about selection bias by the Head of the Research school at Karolinska Institutet;

"Selection bias is the heaviest one - stay away from it!"

I have come to an understanding that selection bias has many faces and you do not want to introduce it to your study. The overall general definition of the bias is sampling bias, meaning that the association between the exposure and the outcome in the sample study population differs from those not in the study. In other words, there have been some flaws in the sample design and the sample study population will accurately represent the target population. The studies in the thesis should not have been affected in a major way by this definition of bias, since the outcome has not yet taken place during the registration of the exposure. And the sample study population is in some way the target population. A perhaps stricter criteria of the included hernia repairs was applied to paper II and III. These studies were considered to have a selected study population at the cost of controlling for potential confounders. This was thanks to having

achieved a study population that represented the target population repaired with an open anterior mesh inguinal hernia repair in current times. As an effect, the results can easier and optimistically be applied in clinical settings for the target population.

However, in cohort studies, selection bias can also occur with loss to follow-up. In paper III, the response rate for the pain questionnaire was 70.6 % of the hernia repairs. Although this response rate would be considered acceptable, almost 30 % were lost to follow-up. If the reasons for this loss can be associated with the outcome and exposure, a selection bias could have been introduced. For example, if subjects with more pain from a particular type of mesh were more likely to not respond to the pain questionnaire, a concern of a selection bias should be raised. An analysis of variables related to the lost to follow-up hernia repairs, was made in paper III. They were certainly younger in age and this fact alone can explain the non-responding rate of the questionnaire (Figure 18). However, we have some proof that younger patients seemed to score higher in pain and therefore the chronic pain rate in paper III could have been even higher. To speculate, perhaps people tend not to bother answering questionnaires if they don't have issues from their operation. In that case, the chronic pain rate in the study is overestimated.

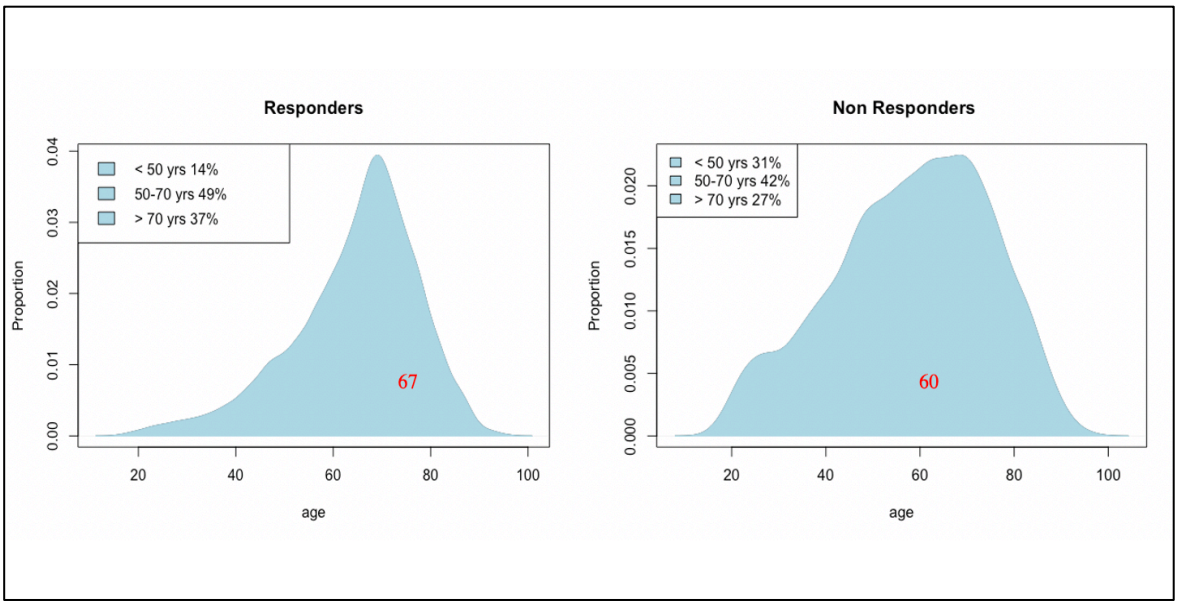

Figure 18. *Density histogram illustrating a different distribution of the responders and the non-responders. The lost to follow-up repairs were younger in age. The red numbers are the median age in each distributed population.*

In paper IV, the association between the exposure (the onlay mesh repair) and the outcomes in the sample study population can certainly differ from those not in the study. However, we did not have a control group in this study, which more usually can contribute to a selection bias for example in the case of case-control studies, as subjects from the control group can be selected from a population that did not produce the cases that were exposed.

Still, one can say for certain that surgeons have selected the cases to be repaired with an onlay mesh due to several factors and therefore the study population is selected and will not be correctly representative of the target population. This can create a bias in the treatment outcomes in both directions. We have investigated all the small umbilical hernias repaired with a small onlay mesh in a single center and our sample was also selected with some exclusion criterias. The single center investigation can represent a selection that certainly effects the generalizing of the results.

The clinical trial described in Appendix A, with its random allocation and stratification, will expectantly control for selection bias. Yet, if participants drop out of the trial with a non-random reason, concerns may arise that the remaining participants no longer represent the original sample population, irrespective of the size of the study population.

Information bias

This structural bias is usually referred to as incorrect or poor measurement of the variables and assessed outcomes, or poor collection of the data. This is not something unusual and it will happen. However, the estimates of the risks can be biased if a misclassification occurs that is different between the comparing groups. If not, it is based on chance in all groups with the same proportions and non-differential. One concern is if a misclassification of the mesh registration could have biased estimates in Paper I-III. More specifically, some surgeons in some surgical units could have registered some of the LWM as HWM, creating uncertainty in the classification of the exposure. This misclassification should not have impacted the outcome and is therefore considered a non-differential. The outcomes are considered to have been assessed and measured similarly in all groups in paper I-III. The measurement bias for the patient-reported outcome of pain following an OAM inguinal hernia repair in paper III should also be considered to be minimal, since the subjects could be considered blinded for the exposure of which type of mesh that was used.

Regarding Paper IV, a certain degree of information bias was introduced since the controlled variables were sometimes incomplete. Incomplete information about mesh size and umbilical defect size was sometimes missing in the medical records. This led to exclusion. However, the data of the robust baseline variables was considered correct without any missing values. This cannot be said regarding the treatment outcomes. The occurrences of surgical site complications and recurrences were not standardized in this study. It was up to the surgeon to considered it and also report it in the medical records. However, our measurements and registration of the treatment outcomes were standardized by for example using the Clavien-Dindo scale. Still, I believe that a Clavien-Dindo scale 1 was not considered to be of any clinical significance by the surgeon, and thus excluded from being reported in the medical record. Most likely, this can have created a bias and an underestimation in the rate of surgical site complications.

In the clinical trial, described in Appendix A, all the baseline variables are measured and registered in the same way at all the involved surgical units prospectively. The exposure of getting a mesh or not, I will say, is a strict definition and the study is stratified per center. However, the outcome is measured only through primary a clinical assessment. The investigators evaluating the outcome are thus blinded for the allocation (exposure). Hopefully this will achieve equal efforts for the centers to discover events equally in the groups to minimize the measurement bias. The measurement bias for the patient-reported outcome of pain following the operation of the umbilical hernia should also be minimized, since the subjects are blinded for the exposure.

Confounding

In contrast to bias that can create a false association, confounding describes an association that normally is true, but potentially misleading by another factor or factors. The multiple causes and mixed effects for the outcome of reoperation for recurrences and pain in paper I-III was a concern.

Dealing with confounders was a challenge in Paper I-III. The regression model is crucial in large cohort studies in order to obtain control for confounding. Although performing multivariate analyses on factors (confounders) that were considered to affect both exposure and outcome, no statistical model can calculate what kind of factors are confounders and what other factors are

more representative as mediators (to not adjust for) in the pathway between the exposure and the outcome. Apart from all the statistical challenges, these assumptions are made by the researcher, who also decides which factors are classified as confounders.

A general weakness of registers is the lack of patient-specific baseline information of medical conditions. The registration of these variables in the SHR has not always been in a comprehensive and compulsory way. This has, however, now been improved. Unquestionably, variables like for example smoking and BMI, could have affected the outcome assessed in Paper I-III. On the contrary, the question is whether these patient-specific variables are actually considered as true confounders with an association to the exposure i.e., which type of mesh to have been chosen in the hernia repair if you were a smoker or not?

A statistically significant correlation through cohort studies, without a randomization to exposure, can certainly not be stated as a causal relationship between the exposure and the outcome in one direction. There will always be unknown confounders that can potentially be associated with the exposure and the outcome.

In contrast, with a randomized clinical trial (such described in Appendix) one could ideally rely completely on the large sample size to achieve a randomly balanced distribution of the involved variables into the two trial arms, and as a result achieve a balanced random distribution of both unknown and known confounders. This way, the randomization only will affect the exposure, and only the exposure will cause the outcome. However, to gain more precision to achieve a causal relationship, the analyses will also be adjusted for fixed effects in a regression model.

We cannot be certain that the mesh was the reason for the surgical site complications in the cases of paper IV. The events were few (4 out of 80) and therefore no robust conclusions can be made of other factors that could have been involved in affecting the outcome.

Generalization

The external validity is usually referred to as generalization. It can be explained as an extension of a model to apply in broader context, i.e., enabling a conclusion of a study to be applied to other populations and circumstances. Hence, the external validity depends on the internal validity. Provided that the internal validity is considered acceptably high in paper I-III, the external validity should be high (at least moderate) since the studies include the general population in Sweden. The conclusions could be applied to future populations in Sweden undergoing hernia repairs. Whether the results can be applied to other populations in the world is a more complex question to answer.

Due to limited robust conclusions from paper IV, The SUMMER trial described in Appendix A was conducted to give us more valuable data. It is carried out as a multicenter study with a large number of participating surgeons. These factors are advantageous for achieving external validity. However, the method includes narrow inclusion criteria with several exclusion criteria and therefore the umbilical study population will probably achieve a high internal validity, but perhaps at the cost of a reduced generalizability.

6.2.3 Precision

Random errors reflect the studies' precision and itself usually corresponds statistically to the size of the confidence intervals and p-values. The precision can be improved by increasing the size of the sample in order to achieve an increased number of outcomes (events) of interest. It is also crucial to have necessary information on potential confounders. Unfortunately, these factors permeate paper IV.

A *type I error* can exist theoretically in both paper I and II, whereas an association between type of mesh and reoperation for recurrence appears statistically significant even though in fact no causal relationship exists. However, a *type II error* of not proving a statistical association that in fact exist, can be considered as a minor problem in the thesis' cohort studies. The overall power of the thesis studies must be considered to be high.

6.3 GENDER PERSPECTIVE

The described studies in the thesis differentiate in the inclusion of different genders. The anatomical circumstances are different for the female versus the male hernia and the choice of method for the repair reflects this.

Paper I includes both women and men. We controlled for the female gender in the multivariate analysis since the reoperation for recurrence rate was considered to be extremely low compared to men. Also, the rare events of the outcome in the subgroup analysis in paper I was the reason for the exclusion of the women. In the studies on the open anterior mesh inguinal hernia repairs (paper II and III), women were excluded as they are not to be operated on with an open anterior approach[17]. As a result, the analysis was restricted only to men. The group being studied was chosen to be representative of those patients who are operated on today with an OAM repair.

It is very interesting that the male patients represented almost 70 % of the cohort in paper IV. I don't believe it is a selection to surgery by gender. A concomitant rectus diastasis (that in certain cases can be found to be significant) can be more common in women than in men with small umbilical hernias. This could have been led to those women being selected to another surgical method of repair than a small onlay mesh repair. However, I more believe that the gender ratio presented in paper IV can be the true ratio for the umbilical disease by gender. Men usually have other anatomical circumstances with more intraabdominal fat that can be a risk factor for developing an umbilical hernia.

6.4 CHALLENGES IN SURGICAL INTERVENTION

" The randomized clinical trial is the epidemiologic centerpiece of clinical epidemiology"

- *Rothman KJ, epidemiologist, 1945-*

Or, depending on how the inclusion runs; "*An experiment which any damn fool can design and frequently does" – Anonymous.*

This section is dedicated to the many methodological and practical challenges that arose whilst conducting the randomized clinical trial described in Appendix A.

The strengths with a trial that consists of a prospective, multi-center, large sample size design with several surgeons involved and a random allocation with double-blinding will undoubtably be major and the bias will be minimized. I will leave out these recognizable epidemiological strengths, and instead I would like to emphasize some more "hidden" methodological obstacles that has appeared to me during the conduction of the SUMMER trial, that I could not fully expand in the study protocol.

Surgical intervention studies traditionally follow several years of surgical clinical experience. This is very different from, for example, drug trials. It may be considered strange and unscientific to practice a surgical method without having the underlying proven evidence for it. Like for example in paper IV. But there may also be a valuable point to it.

A respected professor of surgery (urology) once asked us younger unexperienced researchers,

"Can we separate the handicraft from the craftsman?"

As a surgeon with a surgical intervention involving a surgical procedure to carry out, he got my attention. Indeed, surgery is a complex intervention. I believe that observational non-randomized studies can have a struggle to cope with all the hidden confounders that can led to bias. However, there is a challenge in evaluating innovation in surgery even by randomized controlled trials.

The purpose of the SUMMER trial is to assess if the *onlay mesh* is better than just suturing the defect, in respect to recurrence. To separate the therapeutic effect of the mesh from the surgeons' skills can be difficult. But there are some ways to get around this. Stratification of centers (a sort of indirect control for surgeons' or a surgical unit's skills) and involving several surgeons of different seniority are adopted in the SUMMER trial. Additionally, this RCT is being conducted at a perfect time, in my opinion. It is not done in an early stage of the development of its methods. Surgeons has practiced the onlay-mesh method repair for several years and the comparator is well established. Consequently, the learning curve of the technique should not be a concerning bias in the trial. Also importantly, it is still not late in time for the trial. A preserved balance of interest to be treated by both methods between the groups is still considered to be high. The latter of course greatly facilitates the surgeon's interest in including patients in the trial and the study participants interest in participating.

Trial recruitment is another obstacle. Patients should theoretically be unlikely to be reluctant to participate in the SUMMER trial, since the trial involves surgical procedures that are fairly similar. In contrast, more substantially different surgical procedures can be more problematic for the recruitment. Again, the similarity in surgical procedures within the allocations also reduces the imbalance of varied surgical expertise and minimizes bias.

"Surgical randomization" by itself can be another difficulty. A surgeon's uncertainty of what treatment the patient will receive and its subsequent effect is usually not welcomed in the operating room. Undeniably, as surgeons we want to be in control of what is best for the patient, after we have controlled for the tissue and the anatomical conditions of the procedure. A randomization to an allocation prior to surgery can therefore be an advantage in these cases. The disadvantage is that it can lead to an increased risk of excluding trial participants during the procedure, due to surgical issues. The gold standard analysis of an intention to treat protocol can therefore be disturbed. The SUMMER trial has a randomization close to time to intervention with an assigned allocation in the operating room following the control of the hernia defect. A crossover of procedure after randomization is completely excluded and this maneuver will favor the principle of preserving the intention to treat analysis. Although, one cannot still avoid thinking that there may be a risk that surgeons decide to exclude the advanced cases from the trial before randomization, as they think that a mesh should be applied in those cases. For example; an umbilical hernia with a very thin aponeurosis with a 2 cm defect. This can lead to a reduction in the chance of detecting differences in recurrence rates between the groups.

Standardization is commonly considered a positive aspect and is the cornerstone of randomized controlled trials. However, a surgical procedure as part of an intervention has several interacting components that can challenge units' ability to differentiate and standardize aspects such as procedures before surgery, during surgery and the staff around the trial participant after surgery. I believe we have managed this in a balanced way for the SUMMER Trial. However, we have been very strict with general anesthesia and usage of the same mesh for all the trial subjects in the study protocol. The downside will be that some potential trial participants may not be included in the trial.

Blinding of the outcome investigator and the trial participants are crucial in the SUMMER trial to reduce bias, but can be a barrier for recruitment of patients. The uncontroversial harm-to-benefit profile of the surgical procedures in the trial can compensate for this. However, the benign small umbilical hernia repairs contribute to patients not being prone to return for the long-term follow-ups. It will be a challenge to achieve compliance for this, both from the trial subjects and

from the involved surgeons to track the patients. The trial design could have been modified better for the follow-up controls in order to reduce drop-outs.

7 CONCLUSIONS

- The reoperation rate for recurrences following a TEP groin hernia repair was affected by the type of mesh used. Lightweight meshes were associated with an increased risk of recurrence compared to heavyweight meshes.

- While heavyweight meshes were found to have advantages of avoiding increased recurrence rates, lightweight meshes can still be recommended for use in indirect and smaller hernia defects in TEP groin hernia repairs, where the reoperation rate for recurrence were more comparable to heavyweight meshes.

- Elective open anterior mesh inguinal hernia repairs in men had a low cumulative reoperation rate for recurrence, but an unsatisfactorly high rate of chronic pain one year after surgery.

- There is no benefit of using heavyweight meshes in elective open anterior mesh inguinal hernia repairs on men, since regular lightweight meshes were not associated with an increased risk of reoperation for recurrence, irrespective of the size or the type of the hernia.

- Type of mesh did neither influence the rate nor the risk of developing chronic pain one year following an elective open anterior mesh inguinal hernia repair on men.

- The best surgical treatment for small umbilical hernias is still undetermined. Reparing small umbilical hernias with a small onlay mesh can be a safe alternative with low rates of surgical site complications. Randomized controlled trials are warranted to assess whether onlay mesh can reduce recurrences in comparison to a simple suture repair for the repair of small umbilical hernias.

8 FUTURE PERSPECTIVES

The studies in this thesis have provided both expected and unexpected results. They have also clearly demonstrated the need for further knowledge and research in some particular areas.

Firstly, the main direction for future research I find most important and essential through this thesis is the improvement of surgical treatments for small umbilical hernias. Secondly, clinical registers have become very close to my heart as I have understood how important they are for quality improvement, as some areas for future development have been identified.

Improving treatments for small umbilical hernias – A paradigm shift?

The research of small umbilical hernias has started to gain precedence, but is still under development. And change of clinical practice requires feedback to surgeons with good data quality. It would be of a great value in the future to nationally study the umbilical hernia repairs demographic characteristics and choice of repair method in Sweden. The study in paper IV only scratched the surface regarding mesh use in small umbilical hernias. Therefore, we conducted The SUMMER Trial (in Appendix X) in effort to hopefully contribute well to the current literature on how small umbilical hernias can be repaired in a good and safe way to avoid high recurrence rates. We expect that results from the SUMMER trial will have a direct effect on small umbilical hernia repair standard protocols both nationally and internationally, and give us valuable knowledge for future treatment recommendations. The patient benefit will be significant.

The future goal is to achieve a standardized method (similar to the OAM inguinal hernia repair) that is described as *structured, reproducible, easy* and *safe* with low recurrences whilst in the hands of all general surgeons performing the technique. If mesh repair compared to a simple suture repair influences the recurrence rates by significantly lowering them, a paradigm shift to use mesh in all abdominal wall hernias, irrespective of location, type and size, will probably be reached. When then mesh becomes adopted in small umbilical hernia repairs in the future, it is interesting to compare different mesh positioning; sublay or onlay mesh placement? There are no data from clinical trials that directly has addressed this question.

Or perhaps, will a simple suture repair still be suitable for small umbilical hernia repairs? At least we have made an effort to investigate the scientific question properly.

Registry-based randomized clinical trials (rRCT) and PROMs

The role of observational cohort studies from prospective nationwide populations-based registers have lately been emphasized as particularly appreciated in research. Precisely for the reason that they represent "the real-world" with a large amount of data that is already collected. However, randomized clinical trials still seem to be the cornerstone to achieve level 1 evidence, However, their clinical difficulties can truly be significant. The goal seems to always minimize the known and unknown confounders and to reduce the selection bias by a randomly assigned allocation. Consequently, the natural way of heading to the future of achieving high-level evidence with robust-cost-effective research with less obstacles along the way would be to conduct registry-based randomized clinical trials (rRCT).

rRCT have already been developed through other highly validated Swedish nationwide registers. The SHR can be suitable for this study design. The registration of preoperative variables of interest and randomization via the register would be less problematic to achieve. The challenge would be to define what outcomes to assess. A conflict may arise with the clinical outcome measures conducted in a classical RCT compared to the registered variables in a register. For example, we can still only use the reoperation for recurrence to study recurrence through the SHR. The assessment of the *clinical*-reported outcomes of the true recurrence rate would be an issue here. However, the SHR has done some great progress with postPROMs, which aims to study *patient*-reported outcomes after surgery. Clinical trials with PROMs are becoming more efficient and also, probably much more relevant. I am confident that in some way, we can also manage in the future to systematically register patient-reported outcomes measures (prePROMs) prior to surgery in SHR in a feasible and effective way. And finally, the ideal improvement would be to align the *clinical*-reported outcomes and the *patient*-reported outcomes in the framework of a national register.

Improvement of mesh registration in the SHR

This thesis with mesh hernia repair as a focus has highlighted some concerns with the mesh registration within the SHR. Even though we prefer to categorize variables and mesh groups to seek some order in the overall system, one should be aware that this grouping can additionally lead to bias in the analysis and affect the results. In the future, I would rather see that the surgeons only register the mesh's name in the SHR without the need to reflect on and choose what type of mesh it is. I believe that this can minimize the misclassification and increase the possibility to investigate a certain mesh of interest.

Swedish Ventral Hernia Register

The registry-based study design is a centerpiece of this thesis and therefore it is difficult to avoid writing about the important future perspectives related to the registers in Sweden regarding hernia repairs. The excellent development of SHR can be a good example for how to manage to progress the Swedish Ventral Hernia register in right direction. It is expected that it will take some time for the Swedish Ventral Hernia registry to achieve great national coverage and high validity. In order to achieve this, it is crucial to minimize the degree of difficulty of the standardized collected data that needs to be registered. This will minimize bias and workload for the surgeon. Also, a maintenance of a great enthusiasm within the surgical units to register data for the achievement of quality improvement must be kept regularly. Not until great coverage and highly validated data, can registry-based studies address clinical important issues through the Sweden Ventral Hernia register.

Lowering recurrence rates in TEP hernia repair

LWM seem to have advantages in the short-term follow-up of pain, discomfort and early recovery to work compared to HWM following a TEP groin hernia repair, but perhaps at the expense of more recurrences. Earlier trials and our cohort study in Paper I seem to confirm this association; and some of other authors extend the recommendations to only use HWM in a TEP repair, regardless of the hernia defect. It is always somewhat concerning when conclusions peak towards a way that can be nonbeneficial for the patients in another perspective. This depends in some way on how you look at the most important aspect valued by the patient, and which outcome measure should be prioritized. I am therefore not yet convinced that this is the truthful knowledge to accept in the TEP repair regarding the recommendations of what type of mesh to

use. In the near future, I am interested to see studies that can focus on investigating if certain fixation of lightweight meshes in the TEP repair can possibly reduce the recurrence rates. The issue would be effortlessly suitable to be addressed by a rRCT via the SHR.

Reducing chronic pain following groin hernia repair

The aim is to gain further knowledge about chronic pain following OAM inguinal hernia repair, especially in younger patients. A reviewer asked me if we should consider to reflect on the method of how we are suturing the inserted mesh in Sweden, since the study in Paper III demonstrated a concerning high chronic pain rate. Should we instead suture the mesh with a slow resorbable suture? Whilst all aspects are valuable, I believe it is more complicated than that. The issue of pain has been addressed in several epidemiological studies by other authors with data from the SHR, considering risk factors and different methods. For example, a laparoscopic approach may reduce this risk of chronic pain compared to an open approach. Perhaps we should set up more standard protocols in the clinical setting regarding method of choice for hernia repairs in younger patients?

Furthermore, long-term results from other studies demonstrate that the time itself seem to reduce chronic pain. Perhaps it can help us motivate patients in the clinical setting to be more patient with their condition? The aspiration is that more data can in a clearer way contribute to a foundation of how to handle these patients in the clinical setting.

9 SUMMARY IN SWEDISH

Bråck är en försvagning av bukväggens lager med en åtföljande öppning som kallas för en defekt eller bråckport. På så sätt kan innehåll från bukhålan bukta ut. Det finns olika bukväggsbråck, varav åtgärdande av ljumsk- och navelbråck tillhör våra absolut vanligaste operationer inom allmänkirurgi. Ljumskbråck är den vanligaste åkomman av dessa och det utförs ca 16,000 operationer årligen i Sverige, varav över 95 % av alla ingrepp är registrerade i det Svenska Bråckregistret (SBR). Registret ger information om olika operations- och patientrelaterade faktorer, inklusive information om operation för återfall och död då varje patient är registrerad med sitt personnummer. SBR har visat sig ha en mycket hög kvalitet på den insamlade datan.

Bråck kan medföra besvär i form av smärta och nedsatt livskvalitet och i svårare fall kan inklämning av bukinnehåll kräva en akut operation. Att ständigt förbättra utfallet efter dessa operationer är således avgörande för att denna patientgrupp ska få bra livskvalitet. Recidiv (återfall av bråcket) och smärta är de två främsta postoperativa komplikationer som kan ge patientlidelse med risk för en om-operation. Recidivrisken efter en ljumskbråcksoperation har minskat betydligt efter införandet av nätplastiken jämfört med enbart suturering av bråckdefekten. Syftet med nät vid operation av bråck är att bindväv ska växa in i nätet och bilda en armerad ärrvävnad som förstärker bukväggen. De senaste 30 åren har operationer för ljumskbråck med syntetiska nät (polypropylen) som ej tas upp av kroppen använts som standard för att förhindra och minska återfallsrisken. Detta har inte varit och är ännu inte idag lika självklart att använda för andra bråcktyper, såsom exempelvis vid små navelbråck. Kunskapen om rutinmässig nätinläggning vid små navelbråck är otillräcklig idag. Frågan är om nät även i detta sammanhang kan minska återfallsrisken jämfört med enbart suturering av bråckdefekten, utan att då eventuellt öka risken för sårrelaterade komplikationer? Och hur ska man placera nätet i förhållande till bråckdefekten?

Den så kallade öppna tensionsfria nätplastiken vid en ljumskbråcksoperation har även reducerat risken för kronisk smärta efter operation. Dock kan nätet i sig ändå ge besvär i form av obehag och främmandekroppskänsla. Det ideala vore att använda ett nät som är tillräckligt starkt för att förhindra recidiv (exempelvis ett fullviktsnät) men som samtidigt är tillräckligt ”lätt” (exempelvis ett så kallat lättvikstnät) för att ge en mjukare ärrvävnad och således mindre smärta. Att kunna skräddarsy för vilket nät man ska använda utifrån både ljumskbråcksanatomiska - och patientrelaterade faktorer vore önskvärt.

Denna avhandling har syftat till att undersöka recidivrisken och smärta för olika nättyper som har använts genom åren på patienter som har opererats för ljumskbråck i Sverige med hänsyn till både patientrelaterade- och ljumskbråcksanatomiska faktorer. Avhandlingen har även syftat till att kunna komma närmare en strukturerad behandlingsrekommendation för vilken operationsmetod som kan lämpa sig bäst vid operation av små navelbråck hos vuxna individer.

Detta har studerats via tre stora populationsbaserade registerstudier med prospektiv insamlad data från SBR samt via en svensk retrospektiv studie.

I **Delarbete I**, var syftet att studera risken för reoperation för recidiv med lättviktsnät jämfört med fullviktsnät vid en titthålsoperation (laparoskopisk – TEP operation) av ljumskbråck.

Den specifika frågeställningen av intresse var: *Ökar risken för recidiv av ljumskbråcket vid användning av lättviktsnät jämfört med fullviktsnät efter en titthålsoperation?*

13, 839 ljumskbråcksplastiker mellan år 2005 och 2013 samlades in från SBR och analyserades med minst två års uppföljning. 491 (3,5%) bråckplastiker hade opererats för recidiv och resultaten var associerade med en signifikant ökad risk för operation för recidiv vid reparationer där man hade använt lättviktsnät jämfört med fullviktsnät.

I **Delarbete II**, var syftet att studera risken för reoperation för recidiv för olika lättviktsnät jämfört med fullviktsnät vid en öppen operation av ljumskbråck.

Den specifika frågeställningen av intresse var: *Ökar risken för recidiv av ljumskbråcket vid användning av lättviktsnät jämfört med fullviktsnät efter en öppen operation?*

Data från 76, 495 bråckplastiker på enbart män som hade genomgått en öppen ljumskbråcksoperation mellan år 2005 och 2013 samlades in från SBR och analyserades med minst två års uppföljning. 1676 (2,1%) bråckplastiker opererades för recidiv och resultaten visade att vanliga lättviktsnät inte var förknippade med en ökad risk för operation för recidiv jämfört med fullviktsnät.

I **Delarbete III**, var syftet att jämföra den kroniska smärtrisken för olika lättviktsnät med fullviktsnät 1 år efter en öppen operation av ljumskbråck.

Den specifika frågeställningen av intresse var: *Minskar risken för kronisk smärta vid användning av lättviktsnät jämfört med fullviktsnät efter en öppen ljumskbråcksoperation?*

23, 259 män som var opererade och registrerade i SBR (svarsfrekvens på 70,6%) gav svar på smärtfrågeformuläret och således kunde patientrapporterade resultatmått analyseras. Kronisk signifikant smärta rapporterades av 15,8 % respektive 15,6 % för de som hade blivit åtgärdade

med två olika typer av lättviktsnät. Risken för att utveckla kronisk smärta 1 år efter operationen skilde sig dock inte signifikant från bråckplastikerna som hade utförts med fullviktsnät (16,2%). Yngre manliga patienter under 50 år hade en signifikant ökad risk för att utveckla kronisk smärta jämfört med de äldre patienterna i studien.

I **Delarbete IV**, var syftet att utvärdera hur många som hade drabbats av en sårrelaterad komplikation och recidiv efter att ha genomgått en så kallad onlay nätplastik (där nätet hade opererats in ovanför den suturerade bråckdefekten) för ett litet navelbråck ≤ 2 cm.

Den specifika frågeställningen av intresse var: *Ger operation av små navelbråck med ett litet onlay nät många fall av sårrelaterade komplikationer?*

Data från 80 patienter som hade genomgått en sådan operation analyserades. 4 stycken bedömdes ha drabbats av en sårrelaterad komplikation som bestod av en vätskeansamling (3 stycken) eller en sårinfektion (1 stycken) inom operationsområdet. Samtliga patienters komplikationer läkte ut och ingen behövde om-opereras.

I denna studie ingick enbart en liten grupp av patienter, varav några kloka slutsatser inför en behandlingsrekommendation var svårt att dra. Därför har vi startat en stor klinisk studie (SUMMER studien – Appendix A) med 7 olika svenska kirurgiska enheter som kommer att undersöka denna fråga närmare. 288 patienter kommer att lottas till antingen en enkel suturreparation eller till en enkel suturreparation med ett litet onlay nät på ovansidan av bråckdefekten. De utvärderade utfallsmåtten är recidiv 1 och 3 år efter operation och sekundärt; 30 dagars komplikationer och smärta 1 år efter operation. Ca 180 stycken studiedeltagare är redan inkluderade, varav ca 120 stycken är opererade och randomiserade.

Sammanfattningsvis har denna avhandling visat att användning av fullviktsnät kan ha fördelar för att undvika ökade fall av recidiv vid en titthålsoperation av ett ljumskbråck. Men vid operation av ljumskbråck hos män med en öppen teknik verkar det inte finnas någon anledning att använda fullviktsnät, då vanliga lättviktsnät inte visade sig vara förknippade med en ökad recidivrisk. Medan recidiv var ovanligt efter en öppen ljumskbråcksoperation på män, var den kroniska smärtfrekvensen efter en sådan operation otillfredsställande hög, särskilt hos yngre män. Typ av nät verkade dock inte påverka risken att utveckla kronisk smärta 1 år efter en öppen ljumskbråcksoperation. En god kirurgisk teknik för behandling av små navelbråck för att undvika recidiv undersöks fortfarande och vi kan förvänta oss att resultaten från SUMMER studien kommer att ge tillförlitliga data för framtida behandlingsrekommendationer för små navelbråck. Vi kan dock redan nu se i vår mindre studie att det var få fall av sårrelaterade komplikationer vid operation av små navelbråck med ett litet onlay nät.

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