ABDOMINAL WALL SURGERY

Management of frail patients

Barry de Goede

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Management of frail patients

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CHAPTER 1

Introduction

An abdominal wall hernia is an acquired defect or a weakening of an existing opening in the abdominal wall with an intermittent or continuous protrusion of abdominal contents through the opening. The word “hernia” is a Latin word, which means a “tear” or “rupture”.

An abdominal wall hernia occurs in humans far more frequent than in any other mammal. It has left an indelible mark throughout our earliest recorded history and is probably the penalty we pay in evolution due to the ability to distinguish ourselves from other mammals by walking in an erect position. The Egyptians (1500 BC), Phoenicians (900 BC) and ancient Greeks (400 BC) already described abdominal wall hernias and its (surgical) treatments through paintings, sculptures and ancient writings on papyrus. In history, various surgical and non-surgical treatments for (inguinal) hernia repair were used with a total ignorance of the anatomy of the groin, including castration, cauterization, bloodletting and tabacco enemas. It was because of publications by great anatomists and surgeons named Petit (1674 – 1750), Pott (1714 – 1788), Camper (1722 – 1789), Gimbernat (1734 – 1816), Richter (1742 – 1812), Hesselbach (1759 –1816), Bogros (1786 – 1823) and Fruchaud (1894 – 1960) which helped us to untangle and understand the complexity of the anatomy of the abdominal wall and groin.[1,2] At the end of the 19th century, the Italian surgeon Bassini developed a novel technique for inguinal hernia repair. He reconstructed the weakened transversalis fascia by suturing the autologous fascial, muscular and aponeurotic layers together, but under significant tension.[3,4] In the mid-forties, the Canadian surgeon Shouldice further improved this technique by suturing these layers separately. Unfortunately, other surgeons who used this technique could never match the low recurrence rates reported by both Bassini and Shouldice.[5,6] Even before Shouldice was born, experiments were performed using different woven grafts as reinforcement material in an attempt to reduce recurrence rates after inguinal hernia repair. A real breakthrough was the arrival of the polypropylene mesh; it was strong, biocompatible, could be sterilized and had a low price. By the end of the 1960s an American surgeon named Newman had already successfully used the polypropylene mesh in over 1600 procedures.[7] Despite this success, it took his colleague Irving Lichtenstein until the eighties to convince the surgical world of a “tension-free” repair using a polypropylene mesh to reinforce the transversalis fascia without approximating the defect.[8] To date the Lichtenstein repair is still considered the gold standard in open inguinal hernia surgery with recurrence rates of less than 5%, even when performed by non-experts hands. Over the past decades the minimally invasive laparoscopic techniques have made their entrance using a totally extra-peritoneal (TEP) or a trans abdominal preperitoneal (TAPP) approach. These techniques are increasingly used and associated with less postoperative pain compared to open inguinal hernia repair.[9]

OUTLINE OF THE THESIS

Abdominal wall surgery comprises the spectrum of procedures used in the treatment of abdominal wall hernias, including inguinal, umbilical and incisional hernias. As a group these are one of the more frequently performed operations worldwide and considered the ideal teaching surgical procedure for young trainees due to the diversity of technical aspects, challenging anatomy, and its relatively low risk of serious complications. This is particularly true for the relatively healthy general population in which abdominal wall hernias are commonly found. However, there are groups of frail individuals prone to an abdominal wall hernia due to their age or underlying disease such as elderly men, premature born infants and patients with liver cirrhosis. In these patients, a surgical procedure should be carefully planned or sometimes even avoided. Both surgery and watchful waiting can lead to serious complications. In the following chapters groups of elderly patients, premature born infants and patients with liver cirrhosis – prior, during and after liver transplantation, are discussed with regard to the incidence of abdominal wall hernias, risk factors associated with it and the (surgical) management of the most common hernias in these specific groups.

Over the last 20 years, the number of general surgical procedures being performed on elderly patients has increased rapidly. Despite more advanced surgical, anesthetic and medical techniques, older patients still continue to suffer more from postoperative complications compared to their younger counterparts.[10,11] The incidence of inguinal hernias and its repair also appears to increase with age.[12] Literature on this topic is sparse, especially in the middle-aged and elderly population. In **Chapter 2** the data of the Rotterdam Study – a prospective cohort study that started in 1990 in a district of Rotterdam, are analyzed in order to determine the incidence of inguinal hernias over time in men aged 45 years and older, and to gain insight into potential risk factors of inguinal hernia in these men.

To date, there is general consensus that preventing an inguinal hernia from an incarceration per se is not a proper indication to perform inguinal hernia repair. Interestingly, more than one-third of inguinal hernias are not even symptomatic at first presentation. Two randomized trials were performed comparing a watchful waiting strategy and surgical approach in the treatment of mildly symptomatic and asymptomatic inguinal hernia.[13,14] Both trials reported that no superiority could be found for elective repair over watchful waiting with regard to pain/discomfort. They concluded that watchful waiting is an acceptable strategy for men with minimally symptomatic hernia. However, long-term results showed extremely high crossover rates, especially in older men.[15,16] In **Chapter 3** the results of a multicenter randomized clinical trial

are described. The value of watchful waiting compared to elective repair in men aged 50 years and older with mildly symptomatic or asymptomatic inguinal hernia will be investigated.

The risk of inguinal hernia repair is not only increased in elderly men, but also in very young patients. Approximately 10 percent of prematurely born infants will undergo inguinal hernia repair before the age of 7, of whom more than half in the first year of life.[17,18] The most important factor that contributes to the increased risk of inguinal hernias in premature born infants is a persistent processus vaginalis, representing an embryological protrusion of peritoneum that precedes the descent of the testes during the second trimester of pregnancy. Normally it will obliterate immediately after birth. If this process fails, the result is a patent processus vaginalis and birth of a potential congenital or indirect inguinal hernias.[19,20] In these patients inguinal hernia repair is often postponed until a certain weight or age is reached. Surgery in premature born infants can be technically challenging due to comorbidities and risk of potential anaesthetic complications, especially in prematurely born infants with a very low birth weight (birth weight of 1,500g or less).[21,22] Postponing surgery however could not only increase the risk of incarceration of contents of the hernia sac, but it might also lead to an even more challenging repair due to a more thickened hernia sac and fibrous adhesions.[18,22,23] In **Chapter 4** risk factors of emergency surgery in order to optimize inguinal hernia management and timing of repair in prematurely born infants are identified.

Another group of frail individuals, who are generally advised to refrain from surgery unless it is absolutely necessary, are patients with liver cirrhosis and particularly those who suffer from concommittent ascites. Overall morbidity rates are reported as high as 70 percent for patients with cirrhosis undergoing non-hepatic surgery.[24,25] Although literature on this topic is abundant, it varies highly in quality and is full of individual, not necessarily evidence-based opinions and similarly valued underlying assumptions. **Chapter 5** includes a systematic review to give an overview of which procedures are most hazardous in patients with liver cirrhosis undergoing non-hepatic surgery.

Patients with liver cirrhosis and refractory ascites have a 20 percent risk of developing an umbilical hernia in the course of their disease.[26] Despite the high incidence, optimal management of an umbilical hernia in patients with liver cirrhosis remains controversial. It is often advised not to perform umbilical hernia repair in these patients, because of the presumed high peri- and postoperative risk of complications such as bacterial contamination of ascites, worsening of liver function, and high recurrence rates after elective repair.[27-29] A watchful waiting strategy, however, can

be complicated by incarceration or spontaneous rupture and evisceration following necrosis of the overlying skin. This could lead to an emergency procedure, which puts patients at an even greater risk for serious complications than after elective surgery.[30,31] In **Chapter 6** the postoperative outcomes of 30 consecutively performed umbilical hernia repairs in patients with liver cirrhosis and ascites with an expected time to liver transplantation of over 3 months are reported.

Based on the results of the prospective cohort study outlined in the previous chapter, in **Chapter 7** the study protocol of a randomized controlled trial is presented. This trial will compare watchful waiting with elective repair of umbilical hernias in patients with liver cirrhosis and ascites.

Umbilical hernias that are not corrected during liver transplantation are still at risk for incarceration of the bowel which can result in serious morbidity or even death.[30] Therefore, umbilical hernia repair seems to be warranted in all candidates for liver transplantation in which umbilical hernia repair is not already performed prior to the transplantation. Two approaches for umbilical hernia repair during liver transplantation can be used, either through a separate, umbilical incision or from within the abdominal cavity through the laparotomy wound used to perform the liver transplantation. In **Chapter 8** both approaches are compared in a retrospective study.

As mentioned previously, abdominal wall hernias such as inguinal and umbilical hernias can be congenital, acquired during life, or the result of an underlying disease. In contrast, an incisional hernia is considered a postoperative complication after abdominal surgery. In the general population incidences range between 11 and 20 percent.[32,33] In patients operated upon for an abdominal aortic aneurysm and in obese patients undergoing abdominal surgery through a midline laparotomy incidences of incisional hernias of more than 30 percent have been reported.[34] With improved long-term survival after liver transplantation, incisional hernias have also become an increasingly diagnosed and clinically relevant complication in patients after liver transplantation.[35,36] In **Chapter 9** the incidence of incisional hernias after liver transplantation with the use of a right subcostal (J-shaped) incision is reported, potential risk factors for incisional hernias are identified and its impact on health-related quality of life is determined.

In **Chapter 10** the (surgical) management issues of abdominal wall hernias in elderly patients, premature born infants and patients with liver cirrhosis are discussed additionally providing perspectives for further research.

Finally, in **Chapter 11** and **Chapter 12** (Dutch summary) the main findings of this thesis are summarized.

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CHAPTER 2

Risk factors for inguinal hernia in middle-aged and elderly men: Results from the Rotterdam Study

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ABSTRACT

Background: Prospective data on risk factors and the incidence of inguinal hernia are sparse, especially in an elderly population. The aim of this study was to determine the incidence of and risk factors for inguinal hernia.

Methods: We analyzed data from the Rotterdam Study, a prospective cohort study that observed the general population aged ≥45 years of Ommoord, a district in Rotterdam, from baseline (1990) over a period of >20 years. Diagnoses of inguinal hernia were obtained from hospital discharge records and records from general practitioners. Multivariate regression analysis was performed to determine risk factors for inguinal hernia development.

Results: Among 5,780 men, with a total of 50,802 person-years, who did not have a hernia at baseline, 416 cases of inguinal hernia occurred (7.2%). The 20-year cumulative incidence was 14%. Age-adjusted hazard ratio (HR) for inguinal hernia for men relative to women was 12.4 (95% CI, 9.5 – 16.3; P < .001). On multivariate analysis, the risk of inguinal hernia increased with advancing age (HR per 1-year increase in age, 1.03; 95% CI, 1.02 – 1.04; P < .001). Participants with a body mass index (BMI) of 25 – 30 kg/m^2 had an HR of 0.72 (95% CI, 0.58 – 0.89; P = .003) compared with a BMI <25; a BMI >30 had an associated HR of 0.63 (95% CI, 0.42 – 0.94; P = .025).

Conclusion: Inguinal hernia is common in the middle-aged and elderly male population and its incidence increases with advancing age. Overweight or obese patients have a lower risk of developing an inguinal hernia.

INTRODUCTION

Inguinal hernia repair is the most frequently performed operation in general surgery. In 2003, approximately 770,000 inguinal hernia repairs were performed in the United States.[1-4] The lifetime risk of undergoing inguinal hernia repair is as great as 42.5% for men and 5.8% for women.[5-8]

Etiological factors for the development of a primary inguinal hernia include not only the presence of a patent processus vaginalis and altered metabolism of collagen connective tissue and the extracellular matrix, but seems also to result from increased intra-abdominal pressure.[9,10] Patient-related factors that are thought to be associated with the development of inguinal hernia are aging, male sex, smoking, diabetes, physical activities, and family history.[7,9-16]

The incidence of inguinal hernia appears to increase with age, especially in men through the fifth to seventh decade of life.[12,15] Excess body weight has also been considered to be a risk factor for the development of inguinal hernia, because it is believed, among other factors, to affect the intra-abdominal pressure.[9] However, the association of obesity with inguinal hernia is still not well established. Several studies provided conflicting data, and some even suggest a protective effect for the development of inguinal hernia.[7,9,12,15-17]

In the United States, the prevalence of obesity increased from 27.5% in 1999 to 37.2% in 2010 among men between the age of 40 and 59.[18,19] It is likely that both the incidence and prevalence of inguinal hernia will increase globally as a result of our aging population, but possibly also because of increasing prevalence of obesity. Therefore, inguinal hernia constitutes a very relevant public health issue. Despite this public health issue, data from large, prospective cohort studies that evaluate the relationship between the incidence of inguinal hernia and risk factors are sparse, and few studies have focussed on the more elderly male population.[12,15]

The aim of our study was to analyse data within the Rotterdam Study, a prospective cohort study ongoing since 1990 in the city of Rotterdam in The Netherlands, to determine the incidence of inguinal hernia among middle-aged and elderly men and to create insight into the association of inguinal hernia with potential risk factors.

MATERIALS AND METHODS

The Rotterdam Study is a prospective cohort study that included individuals from the district of Ommoord in Rotterdam, The Netherlands, from January 1990 onwards. Initially, 7,983 participants out of 10,215 invitees (78%) of the Ommoord district were recruited (RS-I). In 2000, 3,011 participants of 4,472 invitees who had become 55 years of age or moved into the study district since the start of the study were added to the cohort (RS-II). In 2006, a further extension of the cohort was initiated in which 3,932 subjects of 6,057 invitees between the ages of 45 to 54 were included (RS-III). By the end of 2008, the Rotterdam Study, therefore, comprised 14,926 subjects aged ≥45 years with an overall response at baseline of 72.0% (14,926/20,744) for all 3 cycles (RS-I, RS-II, and RS-III).

The participants were all examined in detail at baseline. They were interviewed at home (2 hours) followed by an extensive set of examinations (a total of 5 hours) in a research facility in the center of their district. These examinations focused on possible causes of invalidating diseases in participants aged ≥45 years and were repeated every 3–4 years in the participant characteristics that could change over time. The study design, objectives, and major findings of the Rotterdam Study have been described extensively elsewhere.[20] The medical ethics committee at Erasmus University of Rotterdam approved the study, and written informed consent was obtained from all participants.

Participants in the Rotterdam Study are followed for a variety of diseases, including the presence of an inguinal hernia. The participants of the first cohort (RS-I) were interviewed at baseline and asked if they were ever diagnosed or admitted to the hospital owing to the presence of an inguinal hernia. In the second (RS-II) and third (RS-III) cohorts, questions with regard to inguinal hernia were not incorporated in the baseline interview. To identify all incident events of inguinal hernia since the start of the Rotterdam Study, International Classification of Primary Care (ICPC) codes for diagnosis of inguinal hernia (D89) or other hernia (incisional- and/or umbilical hernia, D91) were retrieved from general practitioners in the Ommoord district. In addition, hospital discharge records of the participants of cohort RS-I, RS-II, and RS-III with regard to the diagnosis of inguinal hernia were obtained using the Landelijke Medische Registratie (LMR) codes, the national medical register used in The Netherlands. For all participants, these records were checked for cases of inguinal hernia including the period (far) before the point of entrance into the Rotterdam study to avoid potential bias in prevalent cases of inguinal hernia. Being added after the original design of the Rotterdam Study, the current analysis is thus classified as post-hoc. Data on body

mass index (BMI, kg/m^2), age, sex, diagnosis of diabetes mellitus, smoking, and use of corticosteroid medication were collected at baseline and extracted from the cohort database, because they were considered relevant determinants in relation to incidence of inguinal hernia. The presence of type 2 diabetes mellitus was defined by the use of antidiabetic medication or by a non-fasting or post-load plasma glucose level >11.1 mmol/L (200 mg/dL). The use of medication was determined by questionnaire at baseline. Drug exposure (classified by ATC code [http://www.whocc.no/atc_ddd_index/]) is monitored continuously since the initiation of the Rotterdam Study in 1991 by using computerized pharmacy records of the pharmacies in the Ommoord district. Both the ICPC and the LMR codes are standardized, and validity was checked by the data management team of the Rotterdam Study.

Statistical analysis

Prospective analyses were performed using the Cox proportional hazards (CPH) regression model to identify risk factors related to the proportion of incident cases of primary inguinal hernia in men. Participants with a prevalent (pre-existing) inguinal hernia at baseline or participants who developed a recurrent/contralateral hernia during the study period were excluded from the analysis. Time at risk was calculated from the date a participant entered the Rotterdam Study to the first date a primary inguinal hernia was diagnosed, date of last contact, or the date of death. We used 5-, 10-, 15-, and 20-year Kaplan-Meier estimates to infer the cumulative incidences of inguinal hernia over time.

Univariate regression analyses were performed to determine the relationship of incident cases of primary inguinal hernia with risk factors by analyzing each potential risk factor adjusted for age as a continuous variable. BMI was entered as an ordinal variable and was modelled using 3 categories for BMI: < 25.0, 25.0 – 30.0, and >30 kg/m^2. Age was modelled using 3 categories: <65, 65 – 75, and >75 years. Other baseline factors that were adjusted for age and entered in the model were: diabetes mellitus (yes/no), steroid use (yes/no), smoking (never/former/current), and presence of other hernia (yes/no).

Multivariate regression analysis was performed using a CPH model to control for effects of multiple potential risk factors. Potential risk factors that were related to incident cases of primary inguinal hernia after univariate regression analyses (P <0.10) were included in the CPH model. All factors met the proportional hazards assumption of a relatively constant risk ratio through examination of -log (-log) survival curves. All analyses were performed using the Statistical Package for the Social Sciences version 17.0 (SPSS Inc, Chicago, IL). Continuous data are presented as mean ± standard deviation.

RESULTS

In the Rotterdam Study, after exclusion of participants with an inguinal hernia at baseline (348/14,926), the overall proportion of incident cases of primary inguinal hernia was 3.2% (477 cases among 14,568 participants). There were 5,870 men and 8,788 women without a prevalent (pre-existing) inguinal hernia at baseline. The proportion of incident cases among male participants was 7.2% (416 cases among 5,780 participants) compared with 0.7% of primary inguinal hernia (61 cases among 8,788) among female participants. In the 5,870 men, the 5-year cumulative incidence of developing inguinal hernia was 4.3% compared with 0.3% in women. The mean age in men was 64.7 ± 9.5 and 68.1 ± 8.6 years in women. The 10-year cumulative incidence was 7.9% compared with 0.7%, and for 15 years it was 11.6% compared with 1.0%, and for 20 years it was 14.0% versus 1.8%. Adjusted for age, the hazard ratio (HR) for inguinal hernia for men relative to women was 12.4 (95% CI, 9.5 – 16.3; P < .001). Therefore, further analyses were conducted only on the 5,870 men of the Rotterdam Study. Baseline characteristics of the 5,870 male participants are shown in Table 1.

Table 1. *Baseline characteristics for inguinal hernia among men in the Rotterdam Study, The Netherlands (n = 5,780), 1990 – 2008.*

Characteristic	*Diagnosis of inguinal hernia (n = 416)*	*No inguinal hernia (n = 5,364)*	*P - value*
Follow-up (y)	13.0 (5.2)	9.0 (5.8)	<.001
Age (y)	66.6 (8.2)	64.5 (9.5)	<.001
Height (cm)	175.1 (6.6)	175.9 (7.1)	.025
Weight (kg)	78.5 (11.1)	82.6 (13.0)	<.001
Body mass index*	25.6 (3.1)	26.7 (3.6)	<.001
Cigarette smoking, n (%)			.199
Never	56 (13.5)	848 (15.8)	
Former	243 (58.4)	2941 (54.8)	
Current	89 (21.4)	1280 (23.9)	
Corticosteroid use, n (%)	2 (0.5)	85 (1.6)	.091
Diabetes Mellitus, n (%)	27 (6.5)	438 (8.2)	.004
Other hernia, n (%)	1 (0.2)	38 (0.7)	.525

**BMI was calculated as weight (kg)/length (m^2).*
Data are mean (SD) values unless otherwise specified.

The 5-, 10-, 15-, and 20-year cumulative incidence of developing an inguinal hernia and its association with increasing age was unadjusted; all other potential risk factors

and the cumulative incidence of the development of an inguinal hernia over 20 years were adjusted for age (Fig. 1; Table 2). The HRs for development of an inguinal hernia were greater for participants between the age of 65 and 75 years (HR, 1.4; 95% CI, 1.11 – 1.70; P < .001) and for participants >75 years of age (HR, 1.9; 95% CI, 1.46 – 2.51; P < .001) in comparison with the reference group of participants <65 years of age.

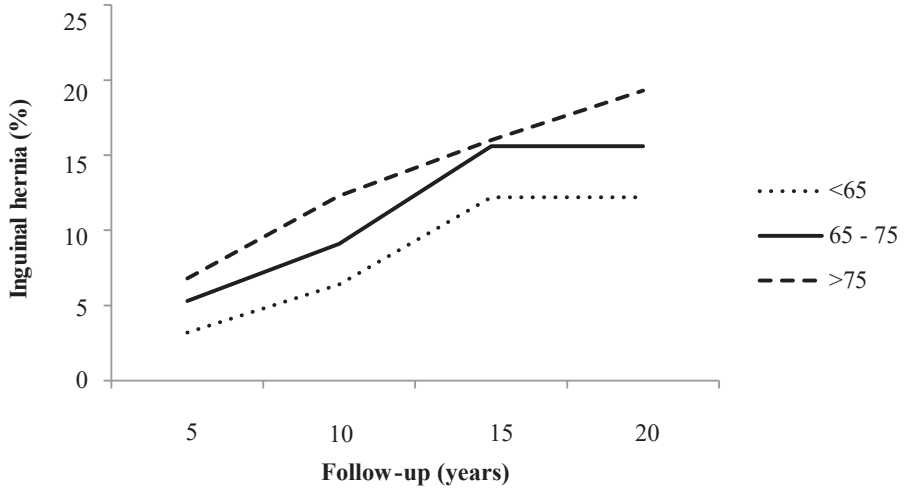

Figure 1. *Risk of inguinal hernia by age among men in the Rotterdam Study, The Netherlands, 1990 – 2008.*

The cumulative incidence the development of an inguinal hernia among men decreased with baseline BMI. The 20-year cumulative incidence was 17.2% in participants with a BMI of <25 kg/m^2 and 12.3% in participants with both BMI of 25 – 30 kg/m^2, and participants with a BMI >30 kg/m^2. The HRs for the development of an inguinal hernia were less for participants with a BMI of 25 – 30 kg/m^2 (HR, 0.71; 95% CI, 0.58 – 0.87; P < .001) and for participants with a BMI >30 kg/m^2 (HR, 0.53: 95% CI, 0.36 – 0.79; P < .001) in comparison with the reference group of participants with a BMI <25 kg/m^2.

The presence of diabetes mellitus at baseline showed a cumulative incidence of 15.3% over 20 years for the development of inguinal hernia among men. The HR for the development of an inguinal hernia showed a protective effect in the presence of diabetes mellitus, which was of borderline significance (HR, 0.68; 95% CI, 0.46 – 1.00; P = .05). Cigarette smoking, corticosteroid use, or the presence of another hernia at baseline were not associated with the development of inguinal hernia in the middle-aged and elderly male population of the Rotterdam Study.

Table 2. *Risk of inguinal hernia (unadjusted) over 20 years and age-adjusted hazard ratio for inguinal hernia among men in the Rotterdam Study, The Netherlands (n = 5,780), 1990 – 2008.*

Risk factor	*No. of participants*	*No. with inguinal hernia*	*Risk of inguinal hernia (%)*	*Age-adjusted hazard ratio**	*95% CI*	*P - value*
Age (y)						<.001
<65	3,377	204	12.2	1.0		
65 – 75	1,485	141	15.6	1.4	1.1 – 1.70	
>75	918	71	19.3	1.9	1.46 – 2.51	
Body mass index						<.001
<25	1,793	176	17.2	1.0		
25 – 30	2,727	187	12.3	0.71	0.58 – 0.87	
>30	747	30	12.3	0.53	0.36 – 0.79	
Cigarette smoking						.609
Never	904	56	17.4	1.0		
Former	3,184	243	14.3	0.86	0.65 – 1.16	
Current	1,369	89	12.7	0.87	0.62 – 1.21	
Corticosteroid use						.156
No	5,665	412	14.1	1.0		
Yes	87	2	3.9	0.37	0.09 – 1.47	
Diabetes Mellitus						.050
No	3,581	353	14.8	1.0		
Yes	465	27	15.3	0.68	0.46 – 1.00	
Other hernia						.593
No	5,741	415	14.0	1.0		
Yes	39	1	2.6	0.59	0.08 – 4.17	

**Estimated using Cox Proportional Hazards regression analysis, adjusted for age a continuous factor; the factor age was unadjusted.*

The final CPH model for multivariate regression analysis included age, BMI and diabetes mellitus (Table 3). Increased baseline age remained associated with a greater risk of inguinal hernia development (HR, 1.3; 95% CI, 1.02 – 1.04; P < .001). Increased baseline BMI had still a protective effect for inguinal hernia among middle-aged and elderly men; participants with a BMI of 25 – 30 kg/m^2 had a HR of 0.72 (95% CI, 0.58 – 0.89; P = .003), and participants with a BMI >30 kg/m^2 had a HR of 0.63 (95% CI, 0.42 – 0.94; P = .025) in comparison with the reference group of participants with a BMI <25 kg/m^2. Increased baseline BMI remained protective when included in the model as a continuous variable (HR, 0.93; 95% CI, 0.90 – 0.97; P < .001). Although diabetes mellitus seemed to show a protective effect in univariate analysis, this result did not remain significant after adjustment for age and BMI in the final CPH model (HR, 0.70; 95% CI, 0.47 – 1.05; P = .086).

Table 3. *Multivariate-adjusted hazard ratio for inguinal hernia among men in the Rotterdam Study, The Netherlands (n = 5,780), 1990 – 2008.*

Risk factor	*Multi - adjusted hazard ratio*[*]	*95% CI*	*P value*
Age (y)	1.03	1.02, 1.04	<0.001
Body mass index			
<25	1.0	(Referent)	-
25 – 30	0.72	0.58, 0.89	.003
>30	0.63	0.42, 0.94	.025
Diabetes Mellitus			
No	1.0	(Referent)	-
Yes	0.7	0.47, 1.05	.086

DISCUSSION

This study showed a 20-year cumulative incidence of inguinal hernia in 5,870 middle-aged and elderly men of the Rotterdam Study of 14.0%. The age-adjusted HR for the development of inguinal hernia was 12 times greater among men. This study also demonstrated that being overweight or obese was associated with decreased incidence of inguinal hernia. Advancing age was a significant risk factor for development of an inguinal hernia in middle-aged and elderly men, but no relationship could be determined between diabetes mellitus and inguinal hernia development.

These are relevant findings, because inguinal hernia repair is the most performed procedure in general surgery. In 2003, approximately 777,000 inguinal hernia repairs were performed in the United States.[1-4] Others have reported that the lifetime risk of undergoing inguinal hernia repair is greatest for the adult male population, especially in the final decades of life.[5-8,12,15] Obesity is also considered to be a risk factor for inguinal hernia.[9] In the United States, the prevalence of obesity increased from 27.5% in 1999 to 37.2% in 2010 among men between the age of 40 and 59.[18,19] Surprisingly, the relationship between obesity and inguinal hernia is still not well established; even a protective effect has been suggested.[7,9,12,15-17] Therefore, it can be argued that owing to ageing of the population and increasing prevalence of obesity, inguinal hernia constitutes a relevant public health issue.

The theory that collagen quality of collagen and collagen metabolism are important in the development of (direct) inguinal hernia is widely accepted.[21] In the elderly population, the balance between the formation and degradation of collagen seems to be shifted, favouring a decrease in connective tissues, resulting in less collagen

cross-linking and, therefore, less strength and stability of the collagen fibres.[22,23] In addition, data on skin biopsies of elderly patients have demonstrated an increase in matrix metalloproteases 2 and 9 (MMP) and a decrease in the tissue inhibitors of metalloproteinases 1 and 2 (TIMP), which play a role in this collagen degeneration.[24,25] These changes may increase the risk of developing an inguinal hernia with advancing age.[26] The current study provides data on the 5-, 10-, 15-, and 20-year cumulative incidence of development of an inguinal hernia in middle-aged and elderly men and the association of inguinal hernia with increasing baseline age. The HR in male participants aged >75 years almost doubled in comparison with participants <65 years, supporting the theory described herein.

The hypothesis that individuals who are overweight or obese are more likely to develop inguinal hernia has been questioned by several studies.[7,9,12,15-17] Our study contributes to these previous findings and provides data on the 20-year cumulative incidence of development of an inguinal hernia among middle-aged and elderly and an association with decreasing baseline BMI; the HR of the development of an inguinal hernia was decreased by almost half in men with a BMI >30 kg/m^2 compared with men with a BMI <25 kg/m^2.

To date, only two prospective cohort studies have been performed that evaluate the relationship between inguinal hernia and potential risk factors.[12,15] Both studies demonstrated an "unexpected" relationship between overweight or obese male participants and a decreased risk of inguinal hernia. It was hypothesized in these studies that the lesser incidence of inguinal hernia in participants with increased body weight could be explained by a decreased chance of diagnosis of inguinal hernia in these participants on physical examination.

In 2007, Ruhl et al[15] examined risk factors for inguinal hernia among US adults aged 25 – 74 years who participated in the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study (1971 -1975) and were followed through 1992 – 1993. They demonstrated in multivariate analysis that a greater incidence of inguinal hernia among men was associated with increasing baseline age and the presence of concomitant hiatal hernia, whereas black race, being overweight and obesity were associated with a lesser incidence. Although the conclusions drawn from that study support our data with respect to age and BMI, the National Health and Nutrition Examination Survey I study focused only on the adult US population aged 25 – 74 years, whereas the present study focused more on the elderly male population. Furthermore, as mentioned by the authors, the follow-up occurred only 10 and 20 years after the baseline examination. Two recently published papers based on a retrospective review

of all inguinal hernia performed on adult US residents of Olmsted County, Minnesota, supported these findings.[8,17]

In 2008, Rosemar et al examined risk factors for inguinal hernia in a community-based sample of middle-aged Swedish men who were followed-up from baseline (1970 – 1973) until 2004. The conclusion drawn from that study was that middle-aged Swedish men who are overweight or obese also had a lesser incidence of inguinal hernia. A decreased risk was noted with advancing age and among heavy smokers. Although this study supports the results of both the study by Ruhl et al and the current study, this Swedish study only analyzed middle-aged men and only allowed identification of participants who were hospitalized for inguinal hernia, whereas the current study included middle-aged and elderly men and diagnoses of inguinal hernia not only from hospital discharge records, but also from the medical files of general practitioners.

Although our study confirms the previous findings of the 2 earlier mentioned cohort studies, our study provides insight into the association of inguinal hernia with potential risk factors of a middle-aged and elderly male population in Western Europe. Our study has limitations. The Rotterdam Study contains data of 3 cohorts (RS I, RS II, and RS III); in the first cohort it was asked explicitly if participants had a known inguinal hernia, which was not the case for the other 2 cohorts, which may have led to potential differences in prevalent cases of inguinal hernia between the cohorts. In an attempt to compensate for this potentially huge bias, all 3 cohorts were checked for a diagnosis of inguinal hernia through records of hospitals and general practitioners, including the period (far) before entrance into the Rotterdam Study. Therefore, this possibility should have biased the results only minimally. Because case definition was based on records of hospitals and general practitioners, and a questionnaire was only used for the first cohort, participants with asymptomatic inguinal hernia could have been missed and case ascertainment may have been incomplete; confirmation of hernia diagnoses by physical examination or ultrasonography within the Rotterdam Study was not possible. These limitations also played a role in the other 2 mentioned cohort studies. Another limitation is that the protective effect of BMI in relation to inguinal hernia development could also be attributable to the fact that diagnosing an inguinal hernia can be more difficult in overweight or obese patients owing to their obesity.[12,15] Therefore, imaging should be incorporated in future studies.

In conclusion, this large prospective cohort study that provides evidence for risk factors of inguinal hernia in middle-aged and elderly West-European males by confirming previous findings of an increased risk of developing an inguinal hernia with advancing age and lesser risk of inguinal hernia in overweight and obese male participants.

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CHAPTER 3

Watchful waiting versus surgery of mildly symptomatic or asymptomatic inguinal hernia in men aged 50 years and older: A randomized controlled trial

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ABSTRACT

Objective: To compare if watchful waiting is non-inferior to elective repair in men aged 50 years and older with mildly symptomatic or asymptomatic inguinal hernia.

Background: The role of watchful waiting in elderly male patients with mildly symptomatic or asymptomatic inguinal hernia is still not well established.

Methods: In this non-inferiority trial we randomly assigned men aged 50 years and older with mildly symptomatic or asymptomatic inguinal hernia to either elective inguinal hernia repair or watchful waiting. Primary endpoint was the mean difference in a 4-point pain/discomfort score at 24 months of follow-up. Using a 0.20-point difference as a clinically relevant margin, it was hypothesized that watchful waiting was non-inferior to elective repair. Secondary endpoints included quality of life, event-free survival and crossover rates.

Results: Between January 2006 and August 2012, 528 patients were enrolled of whom 496 met the inclusion criteria: 234 were assigned to elective repair and 262 to watchful waiting. The mean pain/discomfort score at 24 months was 0.35 (95% CI 0.28 to 0.41) in the elective repair group and 0.58 (95% CI 0.52 to 0.64) in the watchful waiting group. The difference of these means (MD) was -0.23 (95% CI -0.32 to -0.14). In the watchful waiting group 93 patients (35.4%) eventually underwent elective surgery and 6 patients (2.3%) received emergent surgery for strangulation/incarceration. Postoperative complication rates and recurrence rates in these 99 operated individuals were comparable to individuals originally assigned to the elective repair group (8.1% vs. 15.0%; P = 0.106; 7.1% vs. 8.9%; P = 0.668, respectively).

Conclusions: Our data could not rule out a relevant difference in favor of elective repair with regard to the primary endpoint. Nevertheless, in view of all other findings, we feel that our results justify watchful waiting as a reasonable alternative compared to surgery in men aged 50 years and older.

INTRODUCTION

Inguinal hernia repair is one of the most frequently performed surgical procedures worldwide constituting a major economic burden on the healthcare sector.[1,2] The incidence of inguinal hernia increases with age, especially in men from the fifth to the seventh decade of life.[3,4] Interestingly, in this population more than one-third of inguinal hernia is reported to be mildly symptomatic or asymptomatic at first presentation.[5-7]

Surgical tradition advocated that inguinal hernia should be repaired to prevent a hernia complication, even if presented as asymptomatic.[5,8] To date, the general consensus states that prevention of incarceration of inguinal hernia per se is not a proper indication to perform surgery. Chronic postoperative inguinal pain has become an increasingly important issue after inguinal hernia repair with reported incidences of approximately 12% after open tension-free repair.[9,10]

Until now 2 randomized clinical trials have been published, comparing a watchful waiting strategy and surgical approach in treatment of mildly symptomatic and asymptomatic inguinal hernia. Both trials reported that no superiority could be found for elective repair over watchful waiting with regard to pain/discomfort, concluding that watchful waiting is an acceptable strategy for men with minimally symptomatic hernia.[11,12] The long-term results, however, showed crossover rates to 72% in patients who were initially treated conservatively, even rising to 79% in patients over 65 years old.[5,13] The authors concluded that most patients will develop symptoms over time and recommend surgical repair for medically fit patients with a painless inguinal hernia.

The objective of this study was to determine the non-inferiority of watchful waiting to elective repair in men aged 50 years and older with mildly symptomatic or asymptomatic inguinal hernia.

METHODS

Eligibility criteria

Men aged 50 years and older with a mildly symptomatic or asymptomatic inguinal hernia (pain/discomfort score 1 or 0) were eligible for inclusion. We utilized a 4-point pain/discomfort score that was also used in the trial by Fitzgibbons et al.[11] The level of pain/discomfort was determined by the selection of one of the following 4 options:

0) no pain or discomfort due to the hernia when working, exercising or performing any of a patient's usual activities;

1) mild pain or discomfort due to the hernia when working and exercising that does not prevent a patient from performing his usual activities;

2) moderate pain or discomfort due to the hernia when working, exercising, and performing any of a patient's usual activities;

3) severe pain or discomfort due to the hernia when working, exercising, and performing any of a patient's usual activities.

Excluded were those with a bilateral, scrotal or femoral hernia or those classified as American Society of Anaesthesiologist (ASA) class 4. We have only included men in the present study because the incidence of inguinal hernia exceeds that of women by far. Men with a first recurrent inguinal hernia were not excluded. An inguinal hernia was confirmed on physical examination. Confirmation of the diagnosis with the use of ultrasonography was optional, not mandatory. Patients were recruited from 29 community and academic centers in the Netherlands and two Belgian centers. Study enrolment commenced on January 1, 2006. The last patients were included on August 31, 2012. All included patients provided written informed consent. Detailed information on the randomization procedure, data collected during follow-up, and ethical considerations and monitoring can be found in the Supplementary Appendix II.

Follow-up

Patients assigned to surgery underwent repair as soon as possible after randomization (preferably within 4 to 8 weeks). Patients in both treatment groups were invited for follow-up at 3, 12, 24, and 36 months at the outpatient clinic of each participating center. During these follow-up visits patients underwent physical examination. Independent trial coordinators conducted the follow-up visits at 3, 12, 24, and 36 months. Surgery was performed at the surgical department of the involved center. In consultation of the patient, the surgeon determined the operation technique used for inguinal hernia repair. Patients who were randomly assigned to watchful waiting were given written instructions to recognize a hernia complication (incarceration or strangulation) after randomization.

Primary and secondary endpoints

The primary endpoint was the mean difference in the 4-point pain/discomfort score between patients assigned to watchful waiting and elective repair after a follow-up

period of 24 months. Secondary endpoints were: 1) health-related quality of life measured at baseline, 3, 12, 24 and 36 months, 2) the overall 3-year crossover rate in patients assigned to watchful waiting and 3) the overall 3-year event-free survival between the two treatment groups, defined as survival free from moderate or severe pain (pain/discomfort score of 2 or higher), hernia complication (incarceration or strangulation), ischemic orchitis and recurrent hernia. Health-related quality of life was assessed by the Short-Form 36 (SF-36) questionnaire, from which we have used the mean physical component scores (PCS) and the mean mental component scores (MCS) between the treatment groups at the different points in time; the EuroQol-5D (EQ-5D) questionnaire was also assessed at baseline, 3, 12, 24, and 36 months of follow-up.[14,15] The EQ-5D included a visual analogue scale (VAS) to rate overall health status on a scale of 0 (worst imaginable health state) to 100 (best imaginable health state).

Sample size calculation and statistical analysis

The power calculation was based on the difference in mean pain/discomfort score between groups after a 24-month follow-up period. To show non-inferiority, the lower limit of the two-sided 95% CI for the difference (elective repair minus watchful waiting) should not exceed the pre-specified non-inferiority margin. The determination of the non-inferiority margin was based on clinical and statistical considerations, for which a margin of 0.20 points after 24 months was chosen. This required the accrual of 528 patients (2x220 + 20%) at a power of 80% to take into account a potential loss to follow-up of 20%.

Percentages were compared between groups using the chi-square test or Fisher's exact test. Comparison of continuous data was done with use of the Mann–Whitney test. Time to event was calculated from the date of randomization until an event occurred; patients were considered censored if they died, were lost to follow-up or completed follow-up without any event with a maximum of 36 months (length of the study period). Overall 3-year event-free survival was calculated and compared with the use of Kaplan-Meier curves. The Kaplan-Meier method was also used to estimate the overall 3-year crossover rate among patients assigned to watchful waiting. The log-rank test was used for the univariate comparisons. For the differences in the 4-point pain/discomfort score a mixed model with an unstructured covariance matrix was used to allow for correlations within individuals over time. In addition, the analysis for the primary endpoint was stratified for men aged 50 to 65 years and 65 years and older, participating centers, and duration of inguinal hernia present at baseline. Statistical analysis was performed with SPSS software, version 20.0 (IBM Corp. 2011, Armonk, NY) and SAS software (PROC MIXED), version 9.3 (SAS Institute Inc, Cary, NC).

RESULTS

Study population

From January 2006 through August 2012, 528 patients were enrolled in the study of whom 258 were assigned to elective repair and 270 to watchful waiting. Study follow-up ended in August 2014. A total of 24 patients who were assigned to surgery were not included in the analysis: 21 patients withdrew consent immediately after randomization and 3 patients did not meet the inclusion criteria including 1 patient with a femoral hernia, 1 with a bilateral hernia, and 1 patient with a lipoma. A total of 8 patients who were assigned to watchful waiting were not included in the analysis: 4 patients withdrew consent and 4 patients did not meet the inclusion criteria including 1 patient with a femoral hernia, 1 with a lipoma, and 2 patients were excluded because they were younger than 50 years of age (Figure 1).

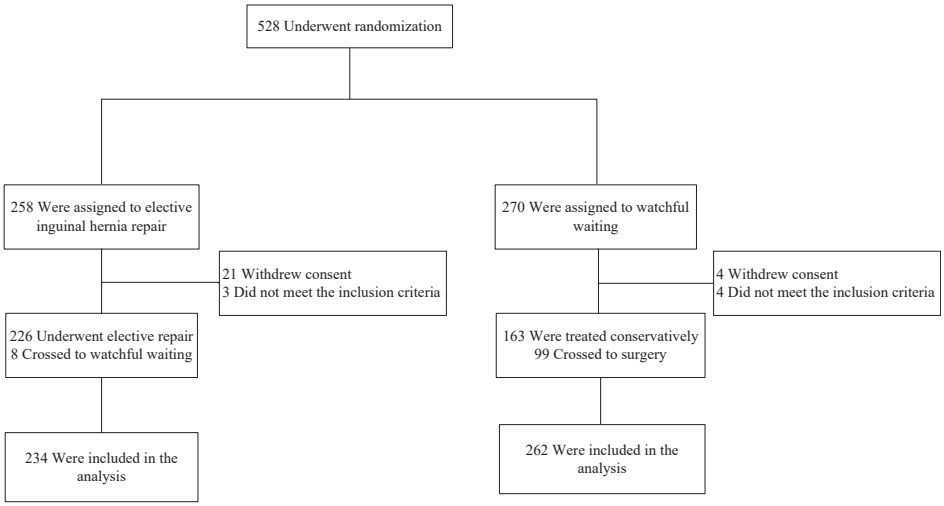


Figure 1. *Study enrollment.*[18]

Baseline characteristics and hernia details were balanced between the two groups (Table 1, 2). The mean age of the population was 65.1 years (SD 8.3) and the mean BMI was 24.9 kg/m^2 (SD 2.7). A total of 463 out of 496 men (93.3%) with mildly symptomatic or asymptomatic inguinal hernia were referred to the hospital by their general practitioner; 473 of 496 men (95.4%) presented with a primary inguinal hernia and 23 men (4.6%) had a first recurrence. An ultrasound was performed in 267 of 496 (53.8%) of the study population, and a radiologist was able to confirm the diagnosis in 241 (90.3%) of ultrasonographies.

Table 1. *Baseline characteristics of patients aged 50 years and older with mildly symptomatic or asymptomatic inguinal hernia, according to treatment group.*

Characteristic	*Watchful waiting (n = 262)*	*Elective repair (n = 234)*
Age – yr (mean, SD)	65.2 (8.3)	65.0 (8.2)
BMI* – kg/m^2 (mean, SD)	24.8 (2.7)	25.0 (2.7)
Smoking – n (%)		
Current	50 (19.1)	47 (20.1)
Former	112 (42.7)	104 (44.4)
None	83 (31.7)	73 (31.2)
Not reported	17 (6.5)	10 (4.3)
Packyears – yr (median, range)	5.0 (90.0)	7.3 (90.0)
ASA* classification – n (%)		
1	152 (58.0)	139 (59.4)
2	92 (35.1)	79 (33.8)
3	15 (5.7)	12 (5.1)
Not reported	3 (1.2)	4 (1.7)
Cardiovascular system – n (%)		
Angina	4 (1.5)	4 (1.7)
Hypertension	47 (17.9)	38 (16.2)
*MI**	8 (3.1)	8 (3.4)
Cardiac arrhythmia	12 (4.6)	10 (4.3)
Other	5 (1.9)	7 (3.0)
Not reported	2 (0.8)	3 (1.3)
TIA* or stroke – n (%)	10 (3.8)	5 (2.1)
Not reported	2 (0.8)	3 (1.3)
Diabetes Mellitus – n (%)	16 (6.1)	17 (7.3)
Not reported	2 (0.8)	3 (1.3)
Medication – n (%)		
Aspirin	33 (12.6)	28 (12.0)
Anticoagulants	33 (12.6)	22 (9.4)
Not reported	3 (1.2)	6 (2.7)
Pulmonary system – n (%)		
*COPD**	13 (5.0)	9 (3.8)
Chronic cough	2 (0.8)	2 (0.9)
Other	3 (1.2)	5 (2.1)
Not reported	2 (0.8)	3 (1.3)
Gastro-intestinal system – n (%)		
Liver cirrhosis	2 (0.8)	-
Constipation	4 (1.5)	1 (0.4)
Not reported	2 (0.8)	3 (1.3)
Back problems – n (%)	12 (4.6)	16 (6.8)
Not reported	2 (0.8)	3 (1.3)
Urinary tract – n (%)		
Prostate cancer	5 (1.9)	3 (1.3)
*BPH**	15 (5.7)	17 (7.3)
Urinary complaints	6 (2.3)	2 (0.9)
Other	2 (0.8)	2 (0.9)
Not reported	2 (0.8)	3 (1.3)

Table 1. *Baseline characteristics of patients aged 50 years and older with mildly symptomatic or asymptomatic inguinal hernia, according to treatment group. (continued)*

Characteristic	*Watchful waiting (n = 262)*	*Elective repair (n = 234)*
Health status – n (%)		
Independent	252 (96.2)	228 (97.4)
Partly dependent	4 (1.5)	2 (0.9)
Totally dependent	2 (0.8)	-
Not reported	4 (1.5)	4 (1.7)
Education – n (%)	245 (93.5)	220
Not reported	15 (5.7)	13 (5.6)
Employment – n (%)		
Paid work	93 (35.5)	82 (35.0)
Retirement	143 (54.6)	123 (52.6)
Unemployed	1 (0.4)	4 (1.7)
Unfit for work	8 (3.1)	5 (2.1)
Volunteer work	6 (2.3)	3 (1.3)
Domestic chores	5 (1.9)	4 (1.7)
Not reported	6 (2.3)	13 (5.6)

**BMI = body mass index, ASA = American Society of Anesthesiologists, MI = myocardial infarction, TIA = transient ischemic attack, COPD = chronic obstructive pulmonary disease, BPH = benign prostate hyperplasia.*

Primary and secondary endpoints

The mean 4-point scale pain/discomfort scores at baseline, 3, 12, 24, and 36 months for the two treatment groups are presented in Figure 2; the changes from baseline are shown in table 3. The mean pain/discomfort score at months 3, 12 and 24, i.e. the primary endpoint according to the protocol, was 0.35 (95% CI 0.28 to 0.41) in the elective repair group and 0.58 (95% CI 0.52 to 0.64) in the watchful waiting group. The difference of these means (MD) was -0.23 (95% CI -0.32 to -0.14). Similar results were found after adjustment for the stratification factors at randomization (men aged 50 to 65 years or 65 years and older, participating centers, duration of inguinal hernia present at baseline), 0.29 vs 0.51 (MD -0.22, 95%CI -0.31 to -0.13). The widths of these 95% CIs indicate that a difference of means greater than 0.20 in favor of elective repair cannot be excluded.

In the subgroups of men aged 50 to 65 years and men aged 65 years and older similar results were found: in men aged 50 to 65 years the mean 4-point pain/discomfort score was 0.57 for patients assigned to watchful waiting and 0.34 for patients assigned to elective repair (MD, -0.23; 95% CI, -0.36 to -0.11); in men aged 65 years and older the adjusted mean 4-point pain/discomfort score was 0.58 for patients assigned to watchful waiting and 0.36 for patients assigned to elective repair (MD, -0.22; 95% CI, -0.36 to -0.09).

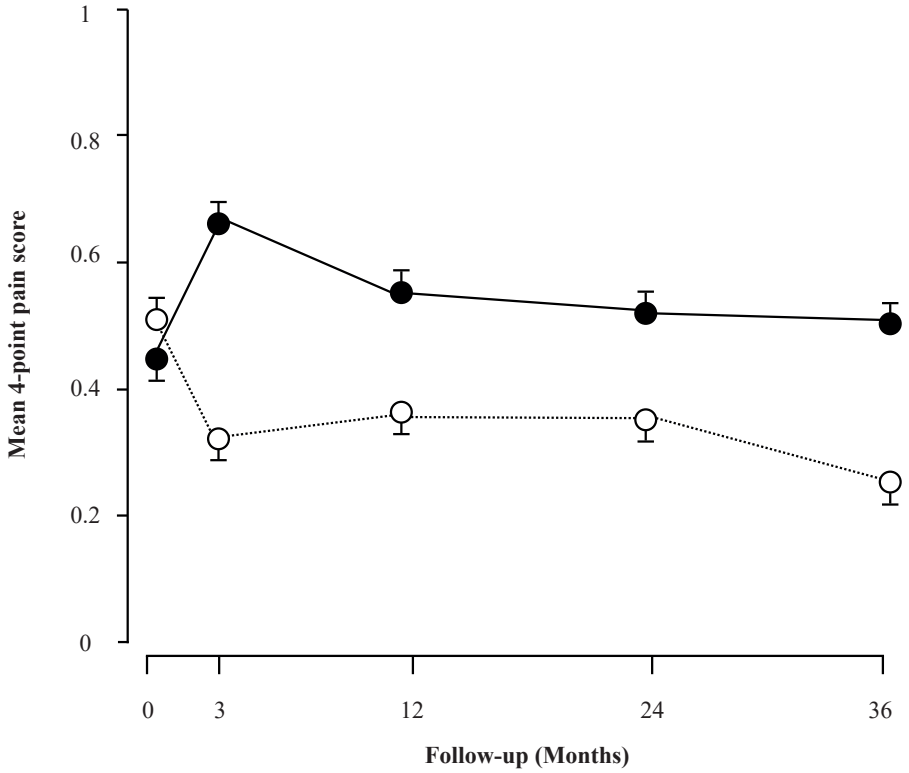


Figure 2. *Mean 4-point pain score (error bars represent standard error of the mean) at various time points after inclusion according to treatment arm (closed circles: watchful waiting, open circles: elective hernia repair).*

For the secondary endpoints, mean changes compared to baseline and mean differences between treatment groups for different measures of quality of life are presented in Table 3. At 3 months of follow-up the mean PCS score showed better results in the group assigned to watchful waiting compared with the group assigned to surgery (51.37 vs. 49.05; P < 0.001). However, at 12 and 24 months the mean difference in PCS scores of the SF-36 were in favor of the elective repair group.

The mean EQ5D scores at 24 months were slightly higher in patients assigned to elective repair compared with patients assigned to watchful waiting (0.91 vs. 0.90; MD, 0.04, 95% CI; 0.01 to 0.07; P = 0.009). At 3 months the mean VAS score rating overall health status was 87.02 in the elective repair group and 80.97 in the group assigned to watchful waiting (MD, 5.59, 95% CI; 3.78 to 7.40; P <0.001).

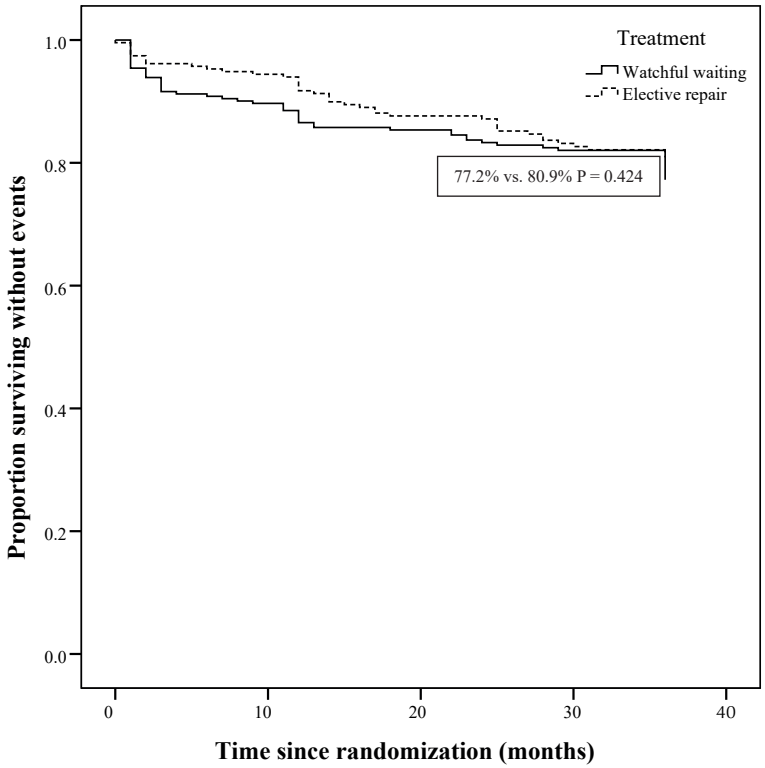
Table 2. *Hernia details of patients aged 50 years and older with mildly symptomatic or asymptomatic inguinal hernia, according to treatment group.*

Characteristic	*Watchful waiting (n = 262)*	*Elective repair (n = 234)*
Referral – n (%)		
General practitioner	244 (93.1)	219 (93.6)
Other specialist	9 (3.4)	8 (3.4)
No referral	-	1 (0.4)
Not reported	9 (3.4)	6 (2.7)
Time of presence at inclusion – n (%)		
≤ 3 months	133 (50.8)	118 (50.4)
> 3 months	129 (49.2)	116 (49.6)
Inguinal hernia – n (%)		
Primary	249 (95.0)	224 (95.7)
1st Recurrence	13 (5.0)	10 (4.3)
Side – n (%)		
Left	123 (46.9)	108 (46.2)
Right	138 (52.7)	126 (53.8)
Not reported	1 (0.4)	-
Enlargement – n (%)	47 (17.9)	42 (17.9)
Not reported	14 (5.3)	10 (4.3)
Reducibility – n (%)		
Spontaneously	171 (65.3)	159 (67.9)
Easy	82 (31.3)	67 (28.6)
With difficulty	3 (1.2)	2 (0.9)
Not reported	6 (2.3)	6 (2.7)
Positive family history* – n (%)	26 (9.9)	25 (10.7)
Not reported	2 (0.8)	3 (1.3)
Ultrasonography – n (%)	150 (57.3)	117 (50.0)
Diagnosis confirmed – n (%)	134/150 (89.3)	107/117 (91.5%)
Type – n (%)		
Medial	72/150 (48.0)	58/117 (49.6)
Lateral	43/150 (28.7)	29/117 (24.8)
Unclear	22/150 (14.7)	23/117 (19.7)
Not reported	13/150 (8.7)	7/117 (6.0)
Diameter – mm (mean, SD)		
Sagittal	17.9 (11.4)	18.9 (11.7)
Transverse	19.2 (9.4)	20.5 (11.3)

* *Positive family history of abdominal wall hernia (i.e. inguinal, umbilical and epigastric hernia).*

Intention-to-treat analysis showed a mean follow-up of 32.5 months (SD 7.5) for the elective repair group and 32.9 months (SD 6.7) for the group assigned to watchful waiting (P = 0.558). The 3-year cumulative incidence of patients with 1 or more event was 17.5% (41/234) in the elective repair group (25 individuals reported moderate or severe pain, 1 hernia complication, 1 ischemic orchitis, 20 recurrent hernias) compared with 20.6% (54/262) in the group assigned to watchful waiting (69 individuals reported moderate or severe pain, 7 hernia complications occurred in 6 individuals, 7 recurrent hernias);

the overall 3-year Kaplan Meier (KM) event-free survival was 80.9% after elective repair compared to 77.2% after watchful waiting (hazard ratio (HR), 1.20; 95% CI, 0.80 to 1.80; P = 0.377), which is presented in Supplementary Figure 3. The 3-year cumulative (KM estimate of 39.5%) crossover rate to hernia repair in patients who were initially assigned to watchful waiting was 37.8% (99/262); The crossover rate did not differ between the groups stratified for men aged 50 to 65 years or men aged 65 years and older (38.2% vs. 37.0%). The 3-year cumulative incidence (KM of estimates 9.9% and 7.8%; HR, 1.25; 95% CI, 0.53 to 2.96; P = 0.610) of a recurrent inguinal hernia was 8.9% (20/226) in the elective repair group compared with 7.1% (7 out of 99) in the group assigned to watchful waiting and crossed to surgery (P = 0.668). Recurrence rates were comparable between different surgical techniques, type of mesh, and participating centers.



No. at risk				
WW	262	225	203	137
ER	234	210	180	133

Figure 3. *The estimated overall 3-year event-free survival among patients aged ≥50 years with mildly symptomatic or asymptomatic inguinal hernia assigned to watchful waiting (WW) and elective repair (ER), according to intension-to-treat analysis.*

Table 3. *Mean baseline values and mean changes from baseline according to treatment group for measures of quality of life.*

Measure of Pain/ Quality of Life		*Watchful waiting (n = 262)*	*Elective repair (n = 234)*	*Mean Difference*	*P Value*[a]
4-point pain/discomfort score[c]					
	Baseline	*0.44 (0.38 ; 0.50)*	*0.51 (0.44 ; 0.58)*		
	3 months	+0.21 (0.11; 0.31)[b]	-0.19 (-0.30 ; -0.09)[b]	-0.41 (-0.55 ; -0.26)	<0.001
	12 months	+0.11 (0.01 ; 0.21)[b]	-0.15 (-0.24 ; -0.06)[b]	-0.26 (-0.40 ; -0.13)	<0.001
	24 months	+0.07 (-0.03 ; 0.17)	-0.16 (-0.26 ; -0.06)[b]	-0.23 (-0.37 ; -0.09)	0.001
	36 months	+0.06 (-0.04 ; 0.16)	-0.26 (-0.36 ; -0.16)[b]	-0.33 (-0.47 ; -0.18)	<0.001
EQ-5D[d]					
	Baseline	*0.92 (0.89 ; 0.94)*	*0.90 (0.87 ; 0.93)*		
	3 months	-0.02 (-0.03 ; 0.00)	0.04 (0.03 ; 0.07)[b]	0.06 (0.04 ; 0.09)	<0.001
	12 months	-0.02 (-0.04 ; 0.00)[b]	0.03 (0.01 ; 0.05)[b]	0.05 (0.02 ; 0.08)	<0.001
	24 months	-0.02 (-0.04 ; 0.00)	0.01 (0.00 ; 0.04)	0.04 (0.01 ; 0.07)	0.009
	36 months	-0.01 (-0.03 ; 0.00)	0.01 (0.00 ; 0.04)	0.03 (0.00 ; 0.05)	0.055
VAS[e]					
	Baseline	*83.52 (81.34 ; 85.70)*	*83.98 (81.95 ; 86.01)*		
	3 months	-2.55 (-3.76 ; -1.34)[b]	3.04 (1.65 ; 4.43)[b]	5.59 (3.78 ; 7.40)	<0.001
	12 months	-2.36 (-4.89 ; -1.05)[b]	-0.36 (-1.95 ; 1.22)	1.99 (-0.16 ; 4.14)	0.069
	24 months	-2.25 (-4.92 ; -0.75)[b]	-0.82 (-2.49 ; 0.85)	1.43 (-1.78 ; 3.63)	0.203
	36 months	-1.72 (-4.69 ; -0.23)[b]	-0.67 (-2.28 ; 0.94)	1.05 (-1.10; 3.19)	0.339
SF-36 PCS[e]					
	Baseline	*51.28 (50.06 ; 52.50)*	*51.27 (50.16 ; 52.38)*		
	3 months	0.09 (-0.79 ; 0.97)	-2.22 (-3.27 ; -1.18)[b]	-2.31 (-3.66 ; -0.96)	<0.001
	12 months	-0.86 (-1.58 ; -0.15)[b]	1.44 (0.62 ; 2.25)[b]	2.29 (1.24 ; 3.36)	<0.001
	24 months	-0.98 (-1.85 ; -0.12)[b]	0.79 (-0.12 ; 1.71)	1.77 (0.53 ; 3.02)	0.005
	36 months	-0.43 (-1.31 ; 0.45)	-0.05 (-0.99 ; 0.90)	0.38 (-0.89 ; 1065)	0.555
SF-36 MCS[e]					
	Baseline	*55.96 (54.79 ; 57.13)*	*56.56 (55.37 ; 57.75)*		
	3 months	0.17 (-0.68 ; 1.02)	-0.10 (-1.10 ; 0.89)	-0.27 (-1.56 ; 1.02)	0.679
	12 months	0.03 (-0.77 ; 0.84)	-0.22 (-1.15 ; 0.70)	-0.26 (-1.47 ; 0.96)	0.676
	24 months	-0.17 (-0.99 ; 0.64)	-1.15 (-2.01 ; -0.29)[b]	-0.98 (-2.16 ; 0.21)	0.106
	36 months	-1.16 (-1.99; -0.33)[b]	-0.02 (-0.92 ; 0.87)	1.14 (-0.08 ; 2.35)	0.067

Abbreviations: EQ-5D, the EuroQol-5D questionnaire; VAS, Visual Analogue Scale; SF-36, the 36-item short form health survey score; PCS, physical component score; MCS, mental component score.
Values between parentheses represent 95% CIs.
a: P values represent the difference between the two treatment groups for pain or measures of quality of life;
b: Mean change compared to baseline is statistically significant (P <0.05);
c: Expressed on a 0 (no pain) to 3 (severe pain) point scale;
d: Expressed on a 0 (worst) to 1 (best) point scale;
e: Expressed on a 0 (worst) to 100 (best) point scale.

The 3-year cumulative incidence of death was comparable between the two treatment groups; 3.0% (7/234) of patients died who were assigned to elective repair and 3.1% (8/262) of patients who were assigned to watchful waiting (P = 1.000). None of the deaths was hernia-related.

Inguinal hernia repair

In men assigned to elective repair 8 out of 234 patients (3.4%) did not undergo surgery; 7 patients decided immediately after randomization that they did not want to be operated on, and 1 patient was considered to be medically unfit for surgery due to progression of his comorbidities prior to the operation. In men assigned to watchful waiting 99 out of 262 patients (37.8%) crossed to hernia repair during the 36-month study period; 90 because of some degree of pain or discomfort, 6 because of a hernia complication, 1 because of cosmetic reasons and 2 for reasons unknown. Of the 6 patients who had a hernia complication, 5 men (1.9%) had an acutely painful groin without bowel obstruction due to an incarcerated hernia for which they underwent emergency surgery. In 1 patient (0.4%) an acute repair was performed because of a strangulated hernia. In none of those patients a resection of the bowel had to be performed. The median time between randomization and surgery was 7.0 weeks (range 67.0) for patients assigned to elective repair and 41.0 weeks (range 158.0) for patients assigned to watchful waiting and crossed to surgery.

Perioperative data of patients assigned to elective repair and patients assigned to watchful waiting who crossed to surgery were comparable and are provided in Table 4. The mean operation time was 45.7 minutes (SD 15.3) in the elective repair group, as compared to 47.4 minutes (SD 20.2) in the crossover group. Most surgeons performed Lichtenstein open tension-free repairs: 176 out of 226 repairs (77.9%) in patients who were assigned to elective repair and 69 out of 99 repairs (69.7%) in patients assigned to watchful waiting and crossed to surgery. In both groups more than half of patients were treated in day-care; one morbidly obese patient of the crossover group was admitted for observation at the intensive care unit due to respiratory distress and was discharged from the hospital after two days.

The total number of peri- and postoperative complications that occurred within one month are summarized in Table 5. A total of 66 peri- and postoperative complications were reported in 42 patients; the total number of patients with 1 or more postoperative complications was 34 out of 226 patients (15.0%) assigned to elective repair compared with 8 out of 99 patients (8.1%) assigned to watchful waiting and crossed to hernia repair ($P = 0.106$). In the elective repair group 1 patient was converted during surgery from laparoscopic to open repair and one patient needed a reoperation because of testicular ischemia; in the crossover group 1 patient had a cardiac arrest before surgery during the anaesthetic induction. During follow-up a reoperation was performed in 7 out of 226 patients (3.1%) assigned to elective repair: 2 because of continuing pain/

discomfort, 1 because of ischemic orchitis and 4 because of a recurrent hernia of which 1 patient underwent emergency surgery because of incarceration. In the cross-over group 5 out of 99 patients (5.0%) underwent a reoperation because of a recurrent hernia of which one was preceded by incarceration necessitating emergency repair.

Table 4. *Perioperative data of patients aged 50 years and older assigned to elective repair and patients who crossed to surgery after initial watchful waiting strategy.*

	Crossed to surgery (n = 99)	*Elective repair (n = 226)*
Operation time – min (mean, SD)	47.4 (20.2)	45.7 (15.3)
Operation technique – n (%)		
Lichtenstein	69 (69.7)	176 (77.9)
TEP[*]	11 (11.1)	24 (10.6)
TAPP[*]	2 (2.0)	9 (4.0)
Plug and Patch	4 (4.0)	3 (1.3)
PHS	1 (1.0)	3 (1.3)
Pre-peritoneal mesh repair	9 (9.1)	10 (4.4)
Type of repair not reported	3 (3.0)	1 (0.4)
Type of mesh – n (%)		
Flat mesh	64 (64.6)	180 (79.6)
Three-dimensional mesh	9 (9.1)	14 (6.2)
Mesh type not reported	26 (26.3)	32 (14.2)
Experience, procedures – n (%)		
<10	3 (3.0)	16 (7.1)
10-25	3 (3.0)	18 (8.0)
>25	40 (40.4)	116 (51.3)
Not reported	53 (53.5)	76 (33.6)
Type of anesthesia – n (%)		
Local	13 (13.1)	20 (8.8)
Spinal	36 (36.4)	107 (47.3)
General	30 (30.3)	91 (40.3)
Not reported	20 (20.2)	8 (3.5)
Nyhus classification[*] – n (%)		
Type I	8 (8.1)	38 (16.8)
Type II	14 (14.1)	46 (20.4)
Type III	38 (38.4)	111 (49.1)
Type IV	4 (4.0)	10 (4.4)
No hernia (lipoma)	1 (1.0)	1 (0.4)
Not reported	34 (34.3)	20 (8.8)
Nerve identification – n (%)		
No identification	7 (7.1)	8 (3.5)
1) Ilioinguinal nerve	20 (20.2)	59 (26.1)
2) Iliohypogastric nerve	1 (1.0)	2 (0.9)
3) Branch of genitofemoral nerve	-	2 (0.9)
Nerve 1 & 2	6 (6.1)	21 (9.3)
Nerve 1 & 3	6 (6.1)	14 (6.2)
Nerve 2 & 3	-	2 (0.9)
Nerve 1, 2 & 3	6 (6.1)	34 (15.0)
Not reported	46 (46.5)	76 (33.6)

Table 4. *Perioperative data of patients aged 50 years and older assigned to elective repair and patients who crossed to surgery after initial watchful waiting strategy. (continued)*

	Crossed to surgery (n = 99)	*Elective repair (n = 226)*
Transsection of the nerve – n (%)		
No transsection	35 (35.4)	126 (48.1)
1) Ilioinguinal nerve	12 (12.1)	19 (8.4)
2) Iliohypogastric nerve	2 (2.0)	4 (1.8)
3) Branch of genitofemoral nerve	-	3 (1.3)
Nerve 1 & 2	4 (4.0)	2 (0.9)
Nerve 1 & 3	-	2 (0.9)
Nerve 2 & 3	-	1 (0.4)
Nerve 1, 2 & 3	-	1 (0.4)
Not reported	46 (46.5)	68 (30.1)
Closure of subcutis – n (%)	70 (70.7)	163 (72.1)
Not reported	19 (19.2)	32 (14.2)
Closure of skin – n (%)		
Staples	-	5 (2.2)
Intra-cutaneous	81 (81.8)	180 (79.6)
Continuous	2 (2.0)	11 (4.7)
Interrupted	-	2 (0.9)
Continuous, intra-cutaneous	1 (1.0)	11 (4.9)
Strips	-	1 (0.4)
Not reported	15 (15.2)	16 (7.1)
Level of operation difficulty – n (%)		
Easy	31 (31.3)	94 (41.6)
Moderate	50 (50.5)	111 (49.1)
Hard	4 (4.0)	5 (2.2)
Not reported	14 (14.1)	16 (7.1)
Hospital admission – n (%)		
None	57 (57.6)	150 (66.4)
Surgical department	10 (10.1)	33 (14.6)
Intensive care unit	1 (1.0)	-
Not reported	31 (31.3)	43 (19.0)
Peri-operative antibiotics – n (%)	12 (12.1)	42 (18.6)
Not reported	51 (51.5)	53 (23.5)

**TEP = total extra-peritoneal repair, TAPP = trans-abdominal pre-peritoneal repair, PHS = prolene hernia system, Nyhus classification[19] : I) indirect inguinal hernia with normal internal ring, II) indirect inguinal hernia with dilated internal ring, III) direct inguinal hernia/posterior wall defect, and IV) recurrent hernia.*

Table 5. *Total number of perioperative complications in patients aged 50 years and older assigned to elective repair and patients who crossed to surgery after initial watchful waiting strategy.*

Event	*Elective repair (n= 226)*	*Crossed to surgery (n= 99)*
Complications during surgery – n (%)		
Damage to epigastric or testicular vessels	2 (0.9)	3 (3.0)
Unintended nerve damage	2 (0.9)	1 (1.0)
Conversion to open repair	1 (0.4)	-
Peritoneal defect	3 (1.3)	-
Bradycardia during surgery	1 (0.4)	-
Cardiac arrest during anesthetic induction	-	1 (1.0)
Direct postoperative complications – n (%)		
Bleeding	2 (0.9)	2 (2.0)
Reoperation:		
Testicular ischemia	1 (0.4)	-
Urinary retention requiring catheterization	2 (0.9)	-
Infection	2 (0.9)	1 (1.0)
Seroma	1 (0.4)	-
Post-operative complications (≤ 1 month) – n (%)		
Wound infection	2 (0.9)	-
Hematoma		
Wound	10 (4.4)	-
Scrotal	8 (3.5)	1 (1.0)
Femoral	2 (0.9)	-
Seroma	10 (4.4)	1 (1.0)
Urinary tract infection	3 (1.4)	-
Urinary retention requiring catheterization	2 (0.9)	-
Pain during ejaculation	2 (0.9)	-

DISCUSSION

This multicenter randomized trial in men aged 50 years and older with mildly symptomatic or asymptomatic inguinal hernia could not rule out a relevant difference in favor of elective repair for the pain/discomfort scores after a follow-up of 24 months. The 95% CI of the difference of means ranged from -0.32 to -0.14. A difference of 0.20 or greater cannot be excluded and, therefore, our trial is inconclusive in this respect. For secondary endpoints the different measures of quality of life and the mean changes over time compared to baseline and study groups were slightly in favor of surgery.

The differences, however, were too small to be clinically relevant. With regard to the crossover rate approximately 60% of men assigned to watchful waiting did not need surgery during follow-up. In the group who did cross to surgery this was mostly driven by in an increase in symptoms – only in 2.3% of the patients crossed over it was due to an emergency setting such as incarceration. However, even these acutely performed procedures were without any negative sequelae. For example, no bowel resection had to be performed due to a prolonged state of ischemia. Although the difference in complication rate between the two groups is not significant, our study was not powered to find a relevant difference in complication rate. We feel that it should be communicated with the patient however, that watchful waiting could result in the necessity of an emergent repair later on, and that there is currently no evidence that an emergency procedure puts one at risk for permanent health disadvantages.

Similar results were reported by two earlier published trials.[5,13] No differences were found in postoperative complication rates and recurrence rates for patients assigned to elective repair and patients initially assigned to watchful waiting and crossed over to surgery. The recurrence rates reported in our study were high. About 9% in patients assigned to elective repair and 7% in operated patients initially assigned to watchful waiting. However, no difference in recurrence rates could be found between different surgical techniques, types of mesh, and participating centers. In both groups one re-operation was performed because of a hernia complication in a recurrent hernia. This shows that not only patients who were treated conservatively but also patients with a failed hernia repair are at risk for emergency surgery. As such these results justify watchful waiting as a reasonable alternative compared to surgery in the treatment of mildly symptomatic or asymptomatic inguinal hernia in men aged 50 years older.

Our results contribute to earlier published trials as the outcome measure and size of our study allowed for the detection of smaller but perhaps clinically relevant differences in pain/discomfort and quality of life during a certain period of time. It enables surgeons to discuss the potential benefits of inguinal hernia repair in men aged 50 years and older who are actually burdened by pain/discomfort preoperatively. Even if inguinal hernia were corrected, it would still not completely eliminate the risk of emergent repair owing to recurrent hernias. For patients who are too frail for surgery it can be argued that watchful waiting is a valid option as it rarely leads to an emergency operation.

In 2006 Fitzgibbons et al.[11] randomly assigned men aged 18 years and older with minimally symptomatic hernia to either open tension-free repair or watchful waiting. Similar to our study a 4-point scale was used as primary endpoint to measure the

mean difference in pain/discomfort score at 24 months, which was presented as a dichotomous variable. In contrast, we decided to use a more comprehensive manner by presenting pain/discomfort over time as a continuous variable enabling us to provide more detailed data between the two treatment groups and compared to baseline. Moreover, as Fitzgibbons et al.[11] included men aged 18 years and older, we focussed on men aged 50 years and older allowing us to draw more definite conclusions for this clinically relevant subgroup. The Fitzgibbons trial showed no significant difference in pain/discomfort and change in PCS from baseline between groups at two years of follow-up, concluding that watchful waiting is as an acceptable option for men with minimally symptomatic inguinal hernia.

In 2006 a second trial was published by 'O Dwyer et al.[12], in which male patients aged 55 years and older with asymptomatic hernia were randomized to either operation or observation. The primary endpoint was the mean difference in VAS scores rating pain/discomfort between treatment groups at 12 months of follow-up. No difference was observed between operation and observation with regard to the primary endpoint. Although this study did focus on patients aged 55 years and older, the sample size was small and the follow-up was limited.

Recently both studies published long-term results that showed crossover rates of 72% and 68% in patients who were initially treated conservatively after 7.5 and 10-years of follow-up respectively. It was also found that older men crossed over to surgery at a considerably higher rate than younger men.[5,13] Although we still have to wait for long-term data, subgroup analysis of our data found no differences in crossover rates between men aged 50 to 65 years or men aged 65 years and older.

This study has to be interpreted in light of limitations. This study allowed surgeons to use different operation techniques, which might have hampered the comparability between groups. In contrast this provided us with a better reflection of daily practice as both endoscopic and open repairs were allowed. Analytical adjustments were made for participating centers in the comparison of mean pain/discomfort scores over time to eliminate hospital preferences for different operation techniques. Secondly, less endoscopic repair and more spinal anesthesia were used compared to the general Dutch population who underwent inguinal hernia repair in 2005.[16] Nowadays endoscopic hernia repair is increasingly used and associated with less postoperative pain compared to open techniques, which perhaps makes surgical repair more appealing.[17] Furthermore local or regional anesthetics can be advantageous in treatment of older patients with multiple comorbidities.[16] Thirdly, Fitzgibbons et al.[5] and Chung et al.[13] already mentioned in their discussion that the answer to the high crossover rates in

both trials were to be explained by the recruitment process and the fact that elderly patients might have a tendency to minimize their symptoms more than younger patients. Because of this, elderly patients become eligible for the trial more easily despite having more advanced disease. This not only affects the generalizability, it also explains for the higher crossover rates in those studies. As in the trial by Fitzgibbons et al.[5,11] the majority of our patients were referred to the clinic by their general practitioner because of concern about the hernia after which they were invited to participate in the trial. Therefore it may not be valid to extrapolate the results of our trial to the entire population of men aged 50 years and older with mildly and asymptomatic inguinal hernia. Long-term follow-up will be needed to confirm these hypotheses stated by our colleagues. Finally from a policy maker perspective, it is not immediately clear if a relatively small reduction in pain scores over time is worth the potentially extra costs of performing surgery, especially when pain is minimal.

Our data could not rule out a relevant difference in favor of elective repair with regard to the primary endpoint. Nevertheless, in view of all other findings, we feel that our results justify watchful waiting as a reasonable alternative compared to surgery in male patients aged 50 years and older.

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ROLE OF FUNDING SOURCE

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to all the data in the study and had final responsibility for the decision to submit for publication.

CONFLICTS OF INTERESTS

All authors have seen and approved this manuscript. The authors of this manuscript have no conflicts of interest to disclose. Funding has been reported.

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THE SUPPLEMENTARY APPENDIX I

INCA (Inguinal Hernia: Conservative or Operative Approach) Trialists' Collaboration:

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THE SUPPLEMENTARY APPENDIX II

Randomization procedure

Patients were registered in an online database (Trial Online Process (TOP), designed and managed by HOVON data center, Rotterdam, The Netherlands) in which each patient received a unique trial code. The randomization process was performed during the first visit at the outpatient clinic of each participating center by telephone (block randomization) and later on by a computer-based randomization service in TOP. Patients were randomly assigned to watchful waiting or elective repair. Randomization was stratified for participating centers, age (men aged 50 to 65 years or 65 years and older) and for the duration the inguinal hernia was present at baseline (3 months or less and more than 3 months).

Data collected during follow-up

§ Patient's characteristics at baseline: body mass index (BMI), smoking status, health status, ASA classification, education level, and type of employment.

§ Comorbidities at baseline: The cardiovascular system (i.e., history of angina, hypertension requiring medication, history of myocardial infarction, history of cardiac arrhythmia, diabetes mellitus, history of transient ischemic attack (TIA) or stroke, medication usage (i.e., aspirin, anticoagulants), history of other cardiovascular disease (i.e., history of valve insufficiencies, abdominal aortic aneurysm (AAA), coronary artery bypass graft surgery (CABG))); The pulmonary system (i.e., chronic obstructive pulmonary disease (COPD), chronic cough, other pulmonary disease (i.e., history of lung embolism, sarcoidosis)); The digestive system (i.e., constipation, cirrhotic liver disease with ascites) and urinary tract (i.e., prostate cancer, benign prostate hyperplasia (BPH), urinary complaints, history of other diseases of the urinary tract (i.e., cancer of the bladder, history of prostatitis, or nephritic diseases)); musculoskeletal system (back problems: rheumatic diseases, herniated disc, back pain).

- § Hernia details at baseline: inguinal hernia (primary or recurrence), hernia side, hernia enlargement (past 6 weeks), reducibility, referent physician, the duration of inguinal hernia present at baseline (3 months or less and more than 3 months), positive family history of abdominal wall hernia, ultrasonography at baseline (i.e., hernia type, diameter of the defect).
- § Perioperative data: operation time, operation technique (i.e., Lichtenstein repair, total extra-peritoneal (TEP) repair, trans-abdominal pre-peritoneal (TAPP) repair, plug and patch repair, prolene hernia system (PHS), pre-peritoneal mesh repair (Kugel or Ugahary hernia repair)), type of mesh (flat mesh (i.e., polypropylene, polyester, large pore lightweight mesh), three-dimensional mesh (i.e. plug&patch repair, bilayered mesh, memory-ring patch)), surgical experience (less than 10, 10 to 25 and more than 25 procedures), type of anaesthesia, Nyhus classification[19], identification of the nerves (i.e., iliohypogastric nerve, ilioinguinal nerve, and/or the genital branch of the genitofemoral nerve), nerve handling, closure of the subcutis, closure of the skin, difficulty of the procedure, perioperative complications (i.e., damage to the vas deferens, epigastric or testicular vessels, nerve injury, peritoneal/hernia sac defects, cardiovascular or anesthetic complications), perioperative use of antibiotics, post-operative complications (i.e., wound infection, hematoma, seroma, ischemic orchitis, urinary retention requiring catheterization, urinary tract infection requiring antibiotics, epididymitis requiring antibiotics, reoperation, pain during ejaculation), hospitalization.
- § Long-term complications (i.e., hernia complication (incarceration, strangulation), hernia complication requiring intervention, moderate or severe pain (pain/discomfort score of 2 or higher), recurrence, reoperation, crossover rates).

Ethical considerations and monitoring

The study protocol was approved by the institutional review board (IRB) of Erasmus University Medical Center, Rotterdam (MEC-2004-298) and by the IRBs of each study center before local start of inclusion. An independent data and safety monitoring board (DSMB) was constituted before the start of the trial. This DSMB consisted of three independent surgeons and one statistician. All serious adverse events (SAEs), defined as incarceration and/ or strangulation, were to be reported to the IRB of each participating center by the local investigators. The progress of the trial and all serious adverse events were reported to the DSMB and the safety of the trial was examined. The trial was registered at the Dutch Trial Registry, recognized by the World Health Organisation, before enrollment began, and assigned to ID number: NTR629.

CHAPTER 4

Very low birth weight is an independent risk factor for emergency surgery in premature infants with inguinal hernia

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ABSTRACT

Background: Common surgical knowledge states that inguinal hernia repair in premature infants should be postponed until they reach a certain weight or age. Optimal management, however, is still under debate. The objective of this study was to collect evidence for the optimal management of inguinal hernia repair in premature infants.

Study Design: In the period between 2010 and 2013, data for all premature infants with inguinal hernia who underwent hernia correction within 3 months after birth in the Erasmus MC – Sophia Children's Hospital, Rotterdam were analyzed. Primary outcome measure was the incidence of incarceration and subsequent emergency surgery. In a multivariate analysis, Cox proportional hazards model served to identify independent risk factors for incarceration requiring an emergency procedure.

Results: A total of 142 premature infants were included in the analysis. The median follow-up was 28 months (range 15 to 39 months). Seventy-nine premature infants (55.6%) presented with a symptomatic inguinal hernia; emergency surgery was performed in 55.7%. Complications occurred in 27.3% of emergency operations versus 10.2% after elective repair; recurrences occurred in 13.6% versus 2.0%, respectively. Very low birth weight (≤ 1,500g) was an independent risk factor for emergency surgery, with a hazard ratio of 2.7 in the Cox proportional hazards model.

Conclusion: More than half of premature infants with an inguinal hernia have incarceration. Those with very low birth weight have a 3-fold greater risk of requiring an emergency procedure than heavier premature infants. Emergency repair results in higher recurrence rates and more complications. Elective hernia repair is recommended, particularly in premature infants with a very low birth weight.

INTRODUCTION

Inguinal hernia repair is the most frequently performed surgical procedure in neonates, especially in children born preterm. Up to 9.0% of children born preterm will undergo inguinal hernia repair before the age of 7 years, of whom more than half in the first year of life.[1,2] Factors that contribute to the increased risk of inguinal hernia in premature infants include a persistent processus vaginalis, male sex, gestational age, low birth weight, and prolonged mechanical ventilation.[2,3]

The optimal timing of inguinal hernia repair in premature infants is not clear. Common surgical knowledge is that it should be postponed until a certain weight or age is reach, because of technical challenges (particularly in very low birth weight [VLBW] premature infants), comorbidities, and potential anesthetic and surgical complications.[4-7] Conservative treatment, however, can be complicated by incarceration, followed by ischemia of the bowel and ovarian or testicular atrophy necessitating emergency repair in these fragile newborns, who are probably at even greater risk of complications in an emergency setting compared with an elective repair. In addition, delaying repair could increase the difficulty of the procedure because repeated herniation and reduction might result in a thickened hernia sac and fibrous adhesions between the hernia sac and the spermatic cord.[2,8]

The objective of this study was to collect evidence for the optimal management of inguinal hernia repair in premature infants by comparing the outcomes of emergency procedures with the outcomes of elective repair, and by identifying the risk factors for inguinal hernia in premature infants who become acutely symptomatic.

METHODS

A retrospective cohort study was performed at the Erasmus MC – Sophia Children's Hospital, a tertiary academic paediatric hospital in Rotterdam, The Netherlands. The Sophia Children's hospital is 1 of 6 referral hospitals for premature infants (*ie,* gestational age less than 37 weeks) in the Netherlands. Each referral hospital has its own unique region; Erasmus MC – Sophia Children's Hospital covers a population of >4.5 million inhabitants.

All premature infants operated on for an inguinal hernia within 3 months after birth between January 2010 and December 2013 were included. They were identified from the electronic hospital data systems and medical charts using Centraal Orgaan Tarieven Gezondheidszorg codes (unilateral inguinal hernia repair, CTG335700; bilateral inguinal hernia repair, CTG335701; incarcerated inguinal hernia repair without bowel resection, CTG335702; incarcerated inguinal hernia repair with bowel resection, CTG334639; recurrent inguinal hernia repair, CTG335710).

According to the hernia management chosen, two groups were distinguished: premature infants who underwent elective inguinal hernia repair and premature infants who needed an emergency procedure because of incarceration of contents in the hernia sac. Premature infants that presented with a symptomatic inguinal hernia at our emergency department that could not be manually reduced were operated on within 24 hours, and were defined as cases of incarcerated hernia with subsequent emergency surgery. A pediatric surgeon examined all premature infants at time of first presentation. In our hospital, an open technique was used for all primary inguinal hernia repairs; in case of a recurrence, hernia repair was performed using a laparoscopic approach. Time at risk was calculated from the date of first presentation at our hospital until the date of either elective repair or emergency procedure. Prolonged mechanical ventilation was defined as mechanical ventilation that was continued after the initial procedure was completed. Patient characteristics and clinical data were collected retrospectively in the search for potential risk factors. They included:

§ Patient's demographics (ie, sex, gestational age, and weight at birth).
§ Preoperative comorbidities associated with the pulmonary system (i.e. history of apnea, Infant Respiratory Distress Syndrome [IRDS], bronchopulmonary dysplasia, preoperative mechanical ventilation); cardiovascular system (ie, history of bradycardia, cardiac anomalies [atrial septal defect, ventricular septal defect, valve abnormalities, Tetralogy of Fallot], intraventricular haemorrhage); and digestive system (ie, GERD and necrotising enterocolitis).

- § Factors associated with the inguinal hernia (ie, palpable testis, hydrocele, incarceration, emergency procedure, other concurrent hernia such as umbilical hernia); hernia characteristics (ie, type of hernia such as uni-/bilateral; hernia side, ie, right, left, or bilateral); and presence of a contralateral hernia or orchidopexy during procedure).
- § Perioperative data (ie, gestational age at repair; weight at repair; type of procedure, ie, open or laparoscopic; duration of procedure; type of anaesthesia; duration of anaesthesia; type of ventilation; duration of ventilation; and re-intubation).
- § Postoperative data (ie, major complications, such as bowel resection, recurrence, testicular atrophy, spermatic cord injury; minor complications, such as haematoma, hydrocele, wound infection, high testicle; length of postoperative hospital stay; length of postoperative neonatal ICU stay, and prolonged mechanical ventilation).

Statistical analysis

SPSS software, version 21.0 (IBM Corp) was used for all statistical analyses. Chi-square and Mann-Whitney U tests were used to compare risk factors for emergency repair and elective repair in premature infants. Univariate regression analyses were performed to determine the relationship of incident cases of incarceration requiring emergency surgery with risk factors by analysing each potential risk factor separately. Multivariate regression analyses were performed using a Cox proportional hazards model to control for effects of multiple potential risk factors. Potential risk factors that were related to cases of incarceration requiring an emergency procedure or that were known in literature (ie, male sex, gestational age, weight of birth, pulmonary comorbidities, and mechanical ventilation) were included in the Cox proportional hazards model. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Between 2010 and 2013, one hundred and forty-two premature infants underwent inguinal hernia repair within 3 months after birth. One hundred and twenty-two (83.6%) were male, mean gestational age was 33 weeks + 4 days (SD 20 days), mean birth weight was 1,859g (SD 589g), and median time to follow-up was 28 months (interquartile range 15 to 39 months). Preoperatively, 43 (29.5%) patients had a history of apnea of prematurity, 29 (19.9%) had IRDS, 53 (36.3%) required mechanical ventilation, and 12 (8.2%) had bronchopulmonary dysplasia. Nineteen (13%) patients had a cardiac anomaly and 21 (14.4%) had a history of bradycardia. Of all premature infants, 11 (7.5%) had GERD, necrotizing enterocolitis developed in 4 (2.7%), 8 (5.5%) had intraven-

tricular haemorrhage, and 22 (15.1%) patients presented with a concurrent umbilical hernia. Mean duration of herniotomy was 29 min (SD 15 minutes), mean duration of anaesthesia was 82 min (SD 32 minutes), and 13 (9.2%) premature infants were operated on after the initial procedure for an inguinal hernia on the contralateral side. During follow-up, two premature infants died after 13 and 14 months, respectively. None of the deaths were related to the procedure for inguinal hernia repair.

Emergency repair

A total of 79 (55.6%) premature infants presented with a symptomatic inguinal hernia at our emergency room, 35 (43.3%) of those hernias could be reduced manually and 44 (55.7%) could not be reduced and required an emergency procedure. Mean time between first presentation at our hospital and emergency surgery was 2.5 days (SD 5.7 days) compared with 18.2 days (SD 11.0 days) for elective repair. Potential risk factors for emergency surgery and elective repair after univariate analysis are presented in Table 1. The postoperative complications rate for emergency surgery was 27.3% vs only 10.2% for elective repair (P = 0.013), and recurrence rates of inguinal hernia were significantly higher after emergency surgery (13.6% vs 2.0%; P = 0.011). Data on postoperative complications are presented in Table 2. Univariate regression analysis showed that gestational age (hazard ratio [HR] = 0.98; P = 0.003), IRDS (HR = 2.1; P = 0.027), and preoperative mechanical ventilation (HR = 2.5; P = 0.006) were associated with an emergency procedure. Premature infants with a very low birth weight (VLBW, ≤ 1,500g) had a 3-fold greater risk of incarceration with a subsequent emergency setting (HR = 3.0, 95% CI, 1.7 – 5.5; P < 0.001). The risk was 70.0% in the VLBW group compared with 23.7% in the group premature infants above 1,500g (Fig. 1). When we controlled for possible confounding variables in the multivariate regression analysis (male sex, gestational age, birth weight, IRDS, preoperative mechanical ventilation), VLBW remained an independent risk factor for incarceration requiring an emergency procedure (HR = 2.7; 95% CI, 1.1 – 6.4, P = 0.027). None of the other variables included in the multivariate regression analysis were found to be statistically significant.

Table 1. *Patient and hernia characteristics and comorbidities of premature infants with inguinal hernia who underwent hernia correction within 3 months after birth at the Erasmus MC – Sophia Children's Hospital, Rotterdam, The Netherlands between 2010 and 2013.*

	Emergency procedure (n = 44)	*Elective repair* (n = 98)	*p-value*
Patient characteristics			
Birth weight, g, mean (SD)	1638 (584)	1977 (561)	0.003*
Gestational age at birth, wk, mean (SD)	32.3 (3.5)	34.2 (2.3)	0.005*
Male sex, n (%)	41 (93.2%)	81 (82.7%)	0.120
Comorbidities, n (%)			
Cardiac anomalies	8 (19.5%)	11 (12.1%)	0.290
Bradycardia	11 (26.8%)	10 (11.0%)	0.037*
IVH	4 (9.8%)	4 (4.4%)	0.254
IRDS	14 (34.1%)	15 (16.5%)	0.039*
BPD	9 (22.0%)	3 (3.3%)	0.001*
Apneas	19 (46.3%)	24 (26.4%)	0.028*
Preoperative MV	14 (56.1%)	11 (33.0%)	0.004*
NEC	2 (4.9%)	2 (2.2%)	0.588
GERD	5 (12.2%)	6 (6.6%)	0.316
Umbilical hernia	6 (14.3%)	16 (17.0%)	0.804
Hernia characteristics, n (%)			
Left side	12 (27.3%)	35 (35.7%)	0.600
Right side	21 (47.7%)	40 (40.8%)	
Bilateral	11 (25.0%)	23 (23.5%)	
Palpable Testes	27 (61.4%)	67 (68.4%)	0.447
Hydrocele	10 (22.7%)	15 (15.3%)	0.342

**Statistically significant. P-values are 2-sided. For dichotomous variables chi-square test was performed and for continuous variables Mann-Whitney U test was performed. IVH, intraventricular haemorrhage; IRDS, infant respiratory distress syndrome; BPD, bronchopulmonary dysplasia; MV, mechanical ventilation; NEC, necrotising enterocolitis.*

Table 2. *Peri- and postoperative data and complications of premature infants with inguinal hernia who underwent hernia correction within 3 months after birth at the Erasmus MC – Sophia Children's Hospital, Rotterdam, The Netherlands between 2010 and 2013.*

	Emergency procedure (n = 44)	*Elective repair* (n = 98)	*p-value*
Peri- and postoperative data			
Gestational age at repair, wk, mean (SD)	39.6 (4.0)	43.8 (2.9)	< 0.001*
Weight at repair, g, mean (SD)	3021 (883)	3889 (862)	< 0.001*
NICU stay, d, mean (SD)	4.7 (9.0)	2.2 (4.8)	0.085
Hospital stay, d, mean (SD)	6.8 (16.3)	3.5 (6.7)	0.210
Prolonged MV, n (%)	11 (25.0%)	2 (2.0%)	< 0.001*
Reintubation, n (%)	5 (11.4%)	2 (2.0%)	0.030*
Orchidopexy during initial repair, n (%)	5 (11.4%)	6 (6.1%)	0.316
Contralateral repair after initial repair, n (%)	8 (18.2%)	5 (5.1%)	0.023*
Duration of anaesthesia, min, mean (SD)	95 (35)	76 (28)	0.001*
Time of herniotomy, min, mean (SD)	34 (16)	26 (14)	0.005*
Major complications, n (%)	**8 (18.2%)**	**4 (4.1%)**	**0.009***
Bowel resection	2 (4.5%)	-	0.094
Recurrence repair	6 (13.6%)	2 (2.0%)	0.011*
Testicular atrophy	2 (4.5%)	2 (2.0%)	0.588
Spermatic cord injury	-	2 (2.0%)	1.000
Minor complications, n (%)	**8 (18.2%)**	**8 (8.2%)**	**0.092**
Haematoma	2 (4.5%)	4 (4.1%)	1.000
Hydrocele	6 (13.6%)	4 (4.1%)	0.070
Wound infection	-	-	-
High testicle	2 (4.5%)	2 (2.0%)	0.588
Total complications, n (%)	**12 (27.3%)**	**10 (10.2%)**	**0.013***

**Statistically significant. P-values are 2-sided. For dichotomous variables chi-square test was performed. The number of premature infants with one or more complications are presented in bold type for the different sub-categories (minor, major, and total). MV, mechanical ventilation; NICU, neonatal ICU.*

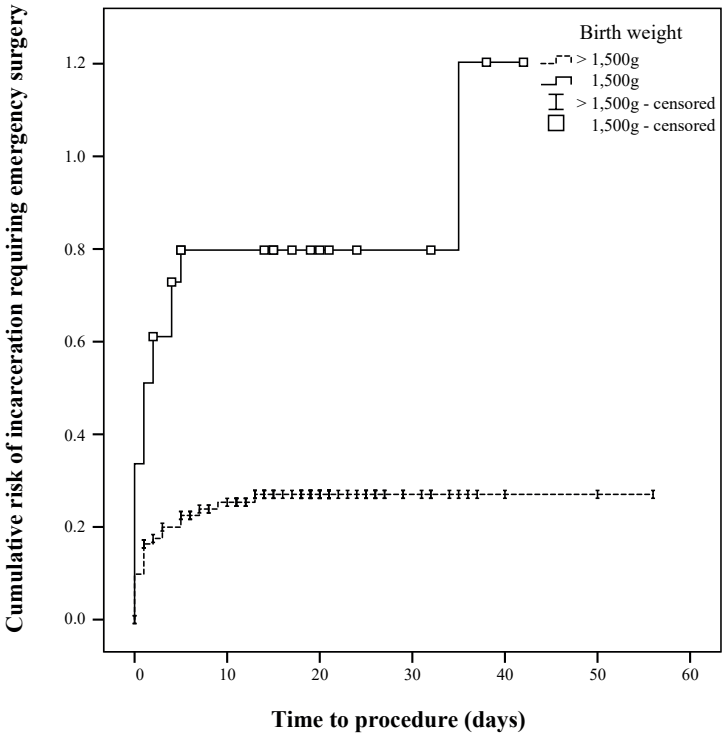

Figure 1. *Hazard function. Risk of incarceration requiring emergency surgery by weight of birth (≤1,500g or >1,500g) among premature infants. VLBW, very low birth weight.*

DISCUSSION

The current study reports that elective inguinal hernia repair is safe and successful in most premature infants and is associated with fewer complications. It also reports that postponing inguinal hernia repair in premature infants results in an incarceration requiring emergency correction in one-third of patients, and that emergency surgery in those premature infants is associated with a significantly higher incidence of postoperative complications as compared with elective repair. This appears to be particularly true for VLBW premature infants, as they were found to have a 3-fold greater risk of incarceration.

These are relevant results in the light of the fact that conflicting published data have made it hard to draw definite conclusions on the optimal management of inguinal hernia in premature infants. Although the levels of prematurity and dysmaturity are associated with high incidence of inguinal hernia, it is the technical challenges and risk of perioperative complications in these fragile newborns make us reluctant to per-

form early elective repair.[9,10] Many pediatric surgeons prefer to perform herniotomy when infants born prematurely reach a certain weight or age. Although this more conservative approach can minimize the risk of surgical and anaesthetic complications, it might also increase the risk of incarceration forcing an emergency procedure with potentially more negative sequelae compared with early elective repair.[2,11,12]

Earlier research on this issue resulted in contradictory outcomes.[2,4-6,9,10,12] However, none of the earlier studies performed a multivariate regression analysis to identify independent risk factors. In 2011, Lautz et al[2] compared premature neonates who presented with an incarcerated or non-incarcerated inguinal hernia and they provided data on timing for inguinal hernia repair. In this retrospective study they found a 2-fold greater risk of incarceration when repair is delayed beyond 40 weeks of gestational age. This result, however, was not corrected for multiple factors and, therefore, a gestational age beyond 40 weeks cannot be considered as an independent risk factor for incarceration.

The incarceration rate in the current study population is one of the highest described in literature.[2,3,10] This can be explained by the fact that the Erasmus MC – Sophia Children's Hospital is a tertiary academic pediatric hospital. It covers a population of >4.5 million inhabitants and is the only hospital of its region that is allowed to perform inguinal hernia repair in premature infants – both in the emergency setting and for the elective operation. More than half of all premature infants that presented with a symptomatic inguinal hernia that could not be manually reduced and required emergency surgery within 24 hours, resulting in a complication rate of 27.3%, which renders early elective repair more appealing. The use of contralateral inguinal exploration in premature infants is another topic still under debate.[13] In literature, incidences of metachronous inguinal hernia vary up to 18.6%.[14,15] In our study, the incidence of contralateral hernia after initial repair was considerably higher after emergency surgery (18.2%) compared with elective repair (5.1%). Because in this study, both the elective and emergency repairs were performed with an open procedure, this difference could not be explained by a difference in techniques used, as they (emergency vs elective repair) bear the same risk of overlooking a metachronous hernia. However, meticulous clinical examination of the contralateral side and its registration are still mandatory.

The current study has several shortcomings, most of which are attributable to the retrospective design. Selection bias could have occurred, as no protocol on timing of repair is available in our hospital for premature infants. In addition, the premature infants could have been diagnosed with an inguinal hernia earlier in a different hospi-

tal, resulting in a delay between diagnosis and first presentation in our hospital. This makes it difficult to draw general conclusions on the actual timing of repair.

Keeping these limitations in mind, this retrospective cohort shows that more than half of premature infants with an inguinal hernia experience incarceration, and that VLBW have a 3-fold greater risk of requiring an emergency procedure than heavier premature infants. Because emergency repair results in higher recurrence rates and more complications, it can even be argued that this particular group of premature infants should be operated on during their birth hospitalization. A multicenter, randomised controlled trial comparing direct and delayed inguinal hernia repair in premature infants should be conducted, stratifying for weight of birth (≤1,500g or >1,500g), to provide more evidence on optimal timing in this fragile group of patients. Until then, elective hernia repair, particularly in VLBW premature infants, is recommended.

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CHAPTER 5

Morbidity and mortality related to non-hepatic surgery in patients with liver cirrhosis: A systematic review

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ABSTRACT

Background: The aim of this study was to systematically review morbidity and mortality after non-hepatic surgery in patients with liver cirrhosis.

Methods: Comprehensive searches were conducted in PubMed, Embase and the Cochrane Library for articles using the words: liver failure, hepatic insufficiency, liver cirrhosis, cirrhosis, cirrhotic, surgical procedures, operative complications, operative mortality, postoperative complications, surgical complication, surgical risk, and hernia.

Results: Forty-six out of 5247 articles were selected after the initial search. The level of evidence provided in these articles varied greatly. Non-hepatic surgery of patients with liver cirrhosis resulted in an increased risk of postoperative morbidity and mortality compared with similar surgery of non-cirrhotic patients. Cholecystectomy, umbilical and inguinal hernia repair were associated with the lowest increased morbidity and mortality, whereas pancreatic, cardiovascular, and trauma surgery were correlated with the highest. The preoperative model for end stage liver disease (MELD) and Child-Turcotte-Pugh (CTP) scores appeared to be predictive of postoperative risks. The presence of portal hypertension and surgery in an emergency setting were associated with even higher mortality and morbidity rates.

Conclusion: This systematic review of the literature showed that, in patients with liver cirrhosis who undergo non-hepatic surgery, postoperative morbidity and mortality rates varied greatly depending on the severity of the cirrhosis and the surgical procedure. The majority of procedures can be safely performed in patients with low MELD scores and CTP grade A liver cirrhosis without portal hypertension.

INTRODUCTION

Hepatic surgery of patients with liver cirrhosis is associated with high morbidity and mortality.[1,2] Considerably more debate, however, concerns the increased postoperative risk in patients with liver cirrhosis undergoing non-hepatic surgery.[3] Literature shows overall mortality rates as high as 45% in patients with liver cirrhosis undergoing non-hepatic surgery.[4] It is, however, not clear which patients with liver cirrhosis are most at risk, and which procedures are most hazardous. This presumed increased risk often results in the advice to avoid surgery in this particular group of patients unless absolutely necessary.[5,6] Refraining from elective surgery in patients with cirrhosis, however, can result in emergency surgery which is associated with probably an even greater risk of morbidity and mortality in this vulnerable group of patients.[7-9] Emergency surgery in patients with liver cirrhosis has been shown to be associated with considerably longer post-operative hospitalization, higher morbidity, and a 7-fold increased risk of mortality compared to elective surgery.[9] In addition, patients with liver cirrhosis have been shown to undergo emergency surgery more often than patients without cirrhosis, and approximately 10% of all cirrhotic patients will require both elective and emergency surgery in the last years of their lives.[2,10] This implies that proper recommendations are required in patients with liver cirrhosis who have to undergo surgery. However, current recommendations for surgery in these patients are mostly derived from retrospective studies.[1,2] Literature on this topic is abundant but varies in quality and is full of individual, non-evidence-based opinions and assumptions. This study aims to review systematically morbidity and mortality accompanying non-hepatic surgery in patients with liver cirrhosis and will provide a risk assessment that enables the counseling of patients with liver cirrhosis undergoing non-hepatic surgery.

METHODS

Literature search strategy

A systematic search of MEDLINE, PubMed, Embase and the Cochrane library was performed for articles relevant to non-hepatic surgery in patients with liver cirrhosis, published between January 1990 and July 2011. To give accurate information and provide the best clinical evidence, literature before 1990 was not included in this systematic review. The following search terms were used to search all databases: liver failure, hepatic insufficiency, liver cirrhosis, cirrhosis, cirrhotic, surgical procedures, surgical complications, operative mortality, postoperative complications, surgical risk, and hernia. The following types of studies were excluded: interviews, case-reports,

letters, comments and editorials, papers on infants or adolescents, and papers written in a language other than English. Manual reference checks of included papers were performed to supplement the electronic searches.

Search strategy: Medline

(Hepatic Insufficiency[mesh] OR Liver Cirrhosis[mesh] OR Liver Cirr*[tw] OR liver insufficien*[tw] OR hepatic insufficien*[tw] OR Cirrhosis[tw] OR Cirrhotic[tw] OR Cirrosis[tw] OR Cirrotic[tw]) AND (Surgical Procedures, Operative/complications[mesh] OR Surgical Procedures, Operative/mortality[mesh] OR Postoperative Complications[mesh] OR surgical complication*[tw] OR surgical risk*[tw] OR Surgery complication*[tw] OR Surgery risk*[tw] OR operative complications[tw] OR postoperative complication*[tw] OR hernia[mh] OR hernia*[tw]) AND (English[lang]) NOT (editorial[pt] OR letter[pt] OR case reports[pt] OR comment[pt] OR interview[pt]) NOT (Child[mesh] NOT adult[mesh])

Search strategy: Embase

('liver failure'/exp OR 'Liver Cirrhosis'/exp OR ((Liver NEXT/1 Cirr*) OR (liver NEAR/3 insufficien*) OR (hepatic NEAR/3 insufficien*) OR Cirrhosis OR Cirrhotic OR Cirrosis OR Cirrotic):de,ab,ti) AND (((Postoperative OR surgical OR Surgery OR operative) NEAR/3 (Complication* OR risk* OR safety)):de,ab,ti OR hernia/exp OR hernia:de,ab,ti) AND ([English]/lim) NOT ([editorial]/lim OR [letter]/lim OR [note]/lim) NOT ([Child]/lim NOT [adult]/lim)

Literature screening

Studies were evaluated for inclusion by two independent researchers (BG, PJK) according to relevance to the subject. A random check was performed by a third person (GK). Study selection was accomplished through 3 phases of study screening. In phase 1, studies were selected on the basis of title. Keywords were "management", "surgical risk", "cirrhosis", and "surgery". If the following types of studies (interviews, case series, non-human, experimental, case-reports, letters, comments, editorials, papers on infants/adolescents, and papers written in a language other than English) were identified, they were excluded. In phase 2, abstracts were reviewed for relevance, and reviews, randomized controlled trials (RCTs), prospective cohort and large retrospective studies were selected and full-text articles were obtained. If good quality studies were lacking, smaller, retrospective or lesser quality studies were selected. In phase 3, full-text articles were reviewed. Included were studies that described management of patients with liver cirrhosis undergoing elective or non-hepatic emergency surgery. The studies had to describe one or more of the following outcome measures to be eligible for inclusion: severity of liver disease, type of surgical procedure, overall morbidity or mortality. Selected studies were categorized in one of the following groups

of non-hepatic surgery: surgical risk assessment, gastrointestinal surgery, abdominal wall surgery, cardio-thoracic and vascular surgery, trauma and orthopedic surgery, and other types of surgical procedures. Any discrepancies in inclusion were resolved by discussion between the reviewers under the supervision of a third person.

Data extraction and critical appraisal

The level of evidence of each paper was established on the basis of the Oxford Centre for Evidence-Based Medicine Level of Evidence scale.[11] The quality of the randomized controlled trials was assessed using the Jadad-criteria.[12] All aspects of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement were followed.[13]

RESULTS

Initial literature search revealed 5247 papers; 180 were selected on the basis of title because only articles of non-hepatic surgery in patients with liver cirrhosis were selected. After screening abstracts for relevance, 116 studies were excluded. After full text reading and assessment of the quality of the included papers, another 19 papers were excluded. One article was included after searching references. Finally, this systematic review was based on a total of 46 papers. Four reviews, 6 RCTs, 4 prospective studies and 32 retrospective studies were included. Studies were categorized into 6 groups. The PRISMA flow diagram for systematic reviews is presented in Figure 1.[13] Level of evidence of included papers and complication rates of different non-hepatic surgical procedures are presented in Table 1.

Surgical risk assessment

In the category of surgical risk assessment 5 retrospective studies were identified. All studies had level of evidence 2B. Overall postoperative morbidity in cirrhotic patients was 30.1% for different general surgical procedures. Mortality within 30 days of surgery was 11.6% for any type of procedure.[1] Patients with cirrhosis undergoing cholecystectomy, colectomy, coronary artery bypass graft (CABG), or abdominal aortic aneurysm (AAA) repair had a 3.4-fold, 3.7-fold, 8.0-fold and 5.0-fold greater risk of mortality when compared to non-cirrhotic patients. Patients with cirrhosis and portal hypertension who underwent the same procedures had a 12.3-fold, 14.3-fold, 22.7-fold and a 7.8-fold greater risk of mortality when compared to non-cirrhotic patients.[3] Laparoscopic procedures for various surgical indications had an overall morbidity and mortality of 16% and 0.6%, respectively.[14] Length of hospital stay and total hospital costs were higher with increased severity of liver disease for all operations.[3] Model

of End-stage Liver Disease (MELD) score was shown to be predictive and helpful for counseling patients prior to surgery.[10] Patients with a MELD score <8 who underwent elective surgery for various indications had a mortality of 5.7% compared with >50% in patients with a MELD score >20.[15]

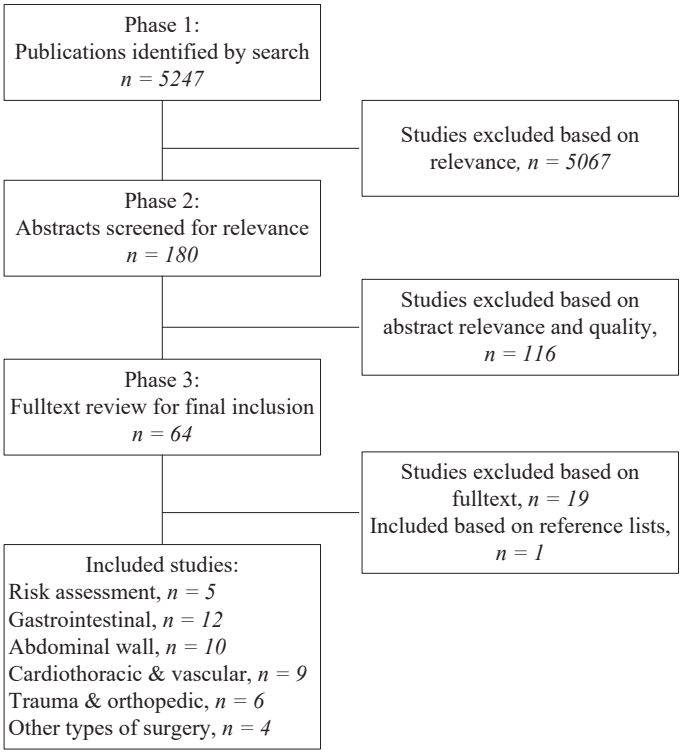

Figure 1. *PRISMA flow chart of the literature search.*

Table 1. Characteristics of included studies.

Author/ Type of surgery	*Level of Evidence*	*Jadad-criteria*	*No. of patients*	*Overall morb.*	*Overall mort.*	*CTP A morb.*	*CTP A mort.*	*CTP B morb.*	*CTP B mort.*	*CTP C morb.*	*CTP C mort.*	*MELD*
General surgical risk assessment												
Csikesz et al.	2B	-	22.569	-	-	-	-	-	-	-	-	-
Ziser et al.	2B	-	733	30.1	11.6	-	-	-	-	-	-	-
Cobb et al.	2B	-	21	16.0	0	-	-	-	-	-	-	yes
Northup et al.	2B	-	131	-	16.4	-	-	-	-	-	-	yes
Teh et al.	2B	-	772	-	5.7 (MELD<8), >50 (MELD >20)	-	-	-	-	-	-	yes
Gastrointestinal surgery												
Cholecystectomy												
Puggioni and Wong.	2A	-	400	20.9	0.6	-	-	-	-	-	-	-
El awadi et al.	2B	2	110									
Open:				35	0	-	0	-	0	-	-	-
Laparoscopic:				13	0	-	0	-	0	-	-	-
El Nakeeb et al.	2B	2										
Harmonic scalpel clipless:			120	8.3	0	-	0	-	0	-	-	-
Conventional:				15.0	0	-	0	-	0	-	-	-
Bessa et al.	2B	2										
Harmonic scalpel clipless:			40	25	0	-	0	-	0	-	-	-
Conventional:				35	0	-	0	-	0	-	-	-
Thulstrup et al.	2B	-	110	-	7.7	-	-	-	-	-	-	-

Table 1. Characteristics of included studies. *(continued)*

Author/ Type of surgery	*Level of Evidence*	*Jadad-criteria*	*No. of patients*	*Overall morb.*	*Overall mort.*	*CTP A morb.*	*CTP A mort.*	*CTP B morb.*	*CTP B mort.*	*CTP C morb.*	*CTP C mort.*	*MELD*
Ji et al.	2B	2	80									
Open:				30.0	-	-	-	-	-	-	-	-
Laparoscopic:				13.2	-	-	-	-	-	-	-	-
Hamad et al.	2B	2	30									
Open:				33	0	-	0	-	0	-	-	-
Laparoscopic:				33	0	-	0	-	0	-	-	-
Colorectal surgery												
Nguyen et al.	2B	-	4042	43	14	-	-	-	-	-	-	-
Gastric surgery												
Jeong et al.	3B	-	18	56	0	53.3	0	66.7	0	-	-	-
Pancreatic surgery												
Warnick et al.	3B	-	32	69	-	3	67	100	100	-	-	yes
Appendectomy												
Tsugawa et al.	3B	-	40	42.5	-	-	-	-	-	-	-	-
Poulson et al.	2B	-	69	-	9	-	-	-	-	-	-	-
Abdominal wall surgery												
Umbilical hernia repair												
Mckay et al.	3A	-	-	-	-	-	-	-	-	-	-	-

Table 1. Characteristics of included studies. *(continued)*

Author/ Type of surgery	*Level of Evidence*	*Jadad-criteria*	*No. of patients*	*Overall morb.*	*Overall mort.*	*CTP A morb.*	*CTP A mort.*	*CTP B morb.*	*CTP B mort.*	*CTP C morb.*	*CTP C mort.*	*MELD*
Ammar et al.	2B	2	80									
Mesh repair:				11	0	-	-	-	-	-	-	-
Primary closure:				14	0	-	-	-	-	-	-	-
Gray et al.	2B	-	120	9.5	-	-	-	-	-	-	-	-
Eker et al.	2B	-	30	7	0	-	-	-	-	-	-	yes
Belghiti et al.	3B	-	40	20	0	-	-	-	-	-	-	-
Carbonell et al.	2B	-	1197	16.5	2.5							
Hansen et al.	2B	-										
Inguinal repair:			201	-	2.7	-	-	-	-	-	-	-
Umbilical repair:			256	-	5.5	-	-	-	-	-	-	-
Marsman et al.	3B	-	34									
Umbilical repair:				18	0	-	-	-	-	-	-	-
Conservative treatment:				77	15	-	-	-	-	-	-	-
Inguinal hernia repair												
Patti et al.	2B	-	32	6.3	0	-	-	-	-	-	-	-
Oh et al.	2B	-	129	10.9	0.8	11.1	-	9.1	-	16.7	-	-
Cardiothoracic and vascular surgery												
Elective cardiac surgery												
Bizouarn et al.	2B	-	12	58.3	16.7	-	-	-	-	-	-	-
Shaheen et al.	2B	-	711	43.3	17	-	-	-	-	-	-	-

Table 1. Characteristics of included studies. *(continued)*

Author/ Type of surgery	*Level of Evidence*	*Jadad-criteria*	*No. of patients*	*Overall morb.*	*Overall mort.*	*CTP A morb.*	*CTP A mort.*	*CTP B morb.*	*CTP B mort.*	*CTP C morb.*	*CTP C mort.*	*MELD*
Marui et al.	2B	-	332	40.8	1.8	-	-	-	-	-	-	-
Hayashida et al.	5	-	-	-	-	-	-	-	-	-	-	-
Modi et al.	3A	-	-	-	-	-	-	-	-	-	-	-
Elective infrarenal aortic aneurysm repair.												
Marrocco et al.	3B	-	24	20.8	0	-	-	-	-	-	-	yes
Lung cancer surgery (NSCLC)												
Iwasaki et al.	4	-	17	29.5	5.9	0	0	30.8	7.6	-	-	-
Iwata et al.	4	-	37	13.5	2.7	-	-	-	-	-	-	-
Iwata et al.	4	-	33	18.2	6.5	-	-	-	-	-	-	-
Trauma and orthopaedic surgery												
Trauma surgery												
Georgiou et al.	2B	-	468	10.2	11.5	-	-	-	-	-	-	-
Demetriades et al.	2B	-	40	45.0	45.0	-	-	-	-	-	-	-
Lin et al.	2B	-	30	41.2	43.3	-	-	-	-	-	-	-
Hip & Knee surgery												
Hsieh et al.	3B	-	38	26.7	0	-	-	-	-	-	-	-

Table 1. Characteristics of included studies. *(continued)*

Author/ Type of surgery	*Level of Evidence*	*Jadad-criteria*	*No. of patients*	*Overall morb.*	*Overall mort.*	*CTP A morb.*	*CTP A mort.*	*CTP B morb.*	*CTP B mort.*	*CTP C morb.*	*CTP C mort.*	*MELD*
Cohen et al.	3B	-	29			14.3	4.8	28.6	14.3	100	100	-
Hip:				35.7	0	-	-	-	-	-	-	
Knee:				10	0	-	-	-	-	-	-	
Emergency hip:				80	60	-	-	-	-	-	-	
Shih et al.	3B	-	51									
Knee:				25.5	0	-	-	-	-	-	-	-
Other surgery												
Splenectomy												
Wang et al.	3B	-	96	17.7	0	-	-	-	-	-	-	-
Tomikawa et al.	3B	-	31	-	0	-	0	-	0	-	-	
Imura et al.	2B	-	18	33	-	-	-	-	-	-	66.7	-
Transurethral resection of the prostate (TURP)												
Nielsen et al.	2B	-	30	-	6.7	-	-	-	-	-	-	-

Gastrointestinal surgery in patients with liver cirrhosis

In the group of gastrointestinal surgery 1 review, 1 meta-analysis, 5 randomized controlled trials, and 6 retrospective studies were identified with levels of evidence ranging between 2A and 3B.

Cholecystectomy was the most frequently performed surgical procedure in patients with liver cirrhosis.[3] Open cholecystectomy in patients with cirrhosis resulted in morbidity rates ranging between 30% and 35% compared with morbidity rates after laparoscopic cholecystectomy ranging between 13% and 33%. No mortality was described after laparoscopic cholecystectomy; mortality rates after open cholecystectomy varied between 0% and 7.7%.[16-18] Morbidity rates after laparoscopic cholecystectomy in patients with cirrhosis without the use of clips was between 8.3% and 25.0% compared to rates between 15% and 35% for laparoscopic cholecystectomy with the use clips.[19,20] Compared with open cholecystectomy, laparoscopic cholecystectomy in cirrhotic patients was associated with fewer bleeding complications, shorter operating time, and shorter hospital stay.[21] However, laparoscopic cholecystectomy in cirrhotic patients had higher conversion rates during the procedure, longer surgical time, and more frequent bleeding complications compared to non-cirrhotic patients.[21] One study showed that open cholecystectomy in alcoholic cirrhotic patients had a 11-fold increased risk of 30-day mortality compared to open cholecystectomy of non-alcoholic cirrhotic patients.[22]

The estimated hazard ratio (HR) for mortality after colectomy was found to be 3.7 in cirrhotic patients, and 14.3 in patients with portal hypertension.[3] Overall morbidity after colorectal surgery in cirrhotic patients was shown to be 43%. In-hospital mortality after elective colorectal surgery was found to be 14% in cirrhotic and 29% in patients with cirrhosis and portal hypertension compared to 5% in non-cirrhotic patients (odds ratio (OR) 3.91 and 11.3, respectively). Emergency colorectal surgery led to an even higher mortality rate of 20.9% in cirrhotic patients, and 35.8% in patients with portal hypertension. Cirrhotic patients undergoing emergency surgery had a higher mortality rate compared to elective surgery (OR 2.40). Patients with portal hypertension and cirrhosis undergoing emergency surgery had an even higher mortality rate (OR 5.88).[3,23]

Overall morbidity after radical gastric surgery was shown to be 56% with a morbidity of 53.3% in patients with Child-Turcotte-Pugh (CTP) grade A liver cirrhosis and 67.7% in patients with CTP B liver cirrhosis.[24]

Open appendectomy in cirrhotic patients resulted in a 30-day mortality of 9% compared to 0.7% in non-cirrhotic patients.[25] Laparoscopic approach for an acute appendicitis in cirrhotic patients was shown to be superior with regard to postoperative pain (VAS scores, 35/100 vs. 60/100) and postoperative complications (wound infection: 0% vs. 5% and hemorrhage: 0% vs. 5%).[26]

Overall morbidity after pancreatic surgery was shown to be 69% in cirrhotic patients versus 44% in non-cirrhotic patients. Major morbidity varied greatly (47% vs. 22%) as did the number of reoperations (34% vs. 12%). This resulted in a longer ICU stay and a prolonged hospital stay in cirrhotic patients. Morbidity rates in patients with CTP grade A and CTP grade B liver cirrhosis were 67% and 100%, respectively. Mortality rates in patients with CTP grade A and grade B liver cirrhosis ranged between 3% and 100%, respectively.[5]

Abdominal wall surgery in patients with liver cirrhosis

In the group of abdominal wall surgery 1 review combined with a survey, 1 randomized controlled trial, 3 prospective studies and 5 retrospective studies were identified with levels of evidence ranging between 2B and 3B. It was shown that 20% of patients with liver cirrhosis will develop an umbilical hernia.[8,27] Overall morbidity after elective umbilical hernia repair varied between 7% and 20%. Overall mortality varied between 0% and 5.5%.[7-9,27] Conservative management of umbilical hernia in patients with cirrhosis and ascites resulted in higher mortality compared to elective repair.[8,27] Elective umbilical hernia repair in cirrhotic patients was shown to be safe and was not associated with higher complication rates than in non-cirrhotic patients. Emergency umbilical hernia repair, however, was associated with higher complication rates compared to elective repair in cirrhotic patients.[7-9,27] High CTP score, presence of ascites, symptomatic hernia, and emergency surgery were associated with a worse outcome.[7,28] Uncontrolled ascites was shown to result in a relative risk of 8.51 for umbilical hernia recurrence.[28] Recurrence of umbilical hernia was found to be lower after mesh repair (2.7%) compared to suture repair (14.2%). In this study, mesh repairs were more likely to become infected (16.2% vs. 8.5%) but the difference was not statistically significant.[29] In the same study, no significant differences were noted in the rate of other early postoperative complications such as transient ascitic fluid leakage. Umbilical hernia repair was shown to be safe under local anesthesia in patients with cirrhosis.[29]

Postoperative complications and long-term recurrence after inguinal hernia repair in cirrhotic patients did not differ compared to non-cirrhotic patients. Overall complication rates after inguinal hernia repair ranged between 6.3% and 10.9% in cirrhotic patients compared to 6.8% in non-cirrhotic patients. Overall mortality ranged between

0% and 0.8%. Elective repair of symptomatic inguinal hernia in patients with cirrhosis was recommended.[30] Even in patients with advanced and decompensated cirrhosis.[31] However, one study reported an overall mortality of 2.7% after inguinal hernia repair compared to 0.7% in non-cirrhotic patients (OR of 4.4).[32] Complication rates after inguinal hernia repair were shown to be independent of the CTP score.[30-32] Inguinal hernia repair outcomes were relatively unaffected in the presence of ascites.[9,33] Inguinal hernia repair in cirrhotic patients was shown to be a safe procedure under local or general anesthesia with the use of a polypropylene mesh whereas repair of a symptomatic inguinal hernia improved quality of life, particularly in patients with grade CTP C cirrhosis, and patients with refractory ascites.[31]

Cardio-thoracic and vascular surgery in patients with liver cirrhosis

In the group of cardiac-thoracic and vascular surgery 2 reviews, 1 prospective study and 6 retrospective studies were identified with levels of evidence ranging between 2B and 5.

Postoperative morbidity rates in patients with CTP A, B, and grade C liver cirrhosis undergoing elective cardio-vascular surgery have been shown to be 25% to 50% 100%, and 100%, respectively. The consensus among these clinical studies is that patients with CTP A cirrhosis tolerate cardiac operations. No mortality was observed among patients with CTP A cirrhosis undergoing elective cardiac surgery irrespective of the use of a cardiopulmonary bypass (CPB). Patients with more advanced cirrhosis (CTP B or C cirrhosis), however, had a significantly higher mortality rate (50-100%) after placement of a cardiopulmonary bypass.[34-36]

Patients with cirrhosis undergoing CABG had an increased risk of mortality (17 vs. 3%; OR 6.67), complications (43 vs. 28%; OR 1.99), and longer hospitalization and costs compared in non-cirrhotic patients. Predictors of mortality included age >60 years (OR 2.21), female gender (OR 1.92), ascites (OR 3.80), and congestive heart failure (OR 1.75). Mortality rate was 7.7% in patients with fewer than two complications compared in 59% for those with two or more complications (OR 17.48). Hospital volume and off-pump CABG did not affect mortality.[37] No difference in adjusted in-hospital mortality was found between patients with cirrhosis undergoing percutaneous coronary intervention (PCI), conventional CABG or off-pump CABG compared to non-cirrhotic patients.[38]

No intraoperative or 30-day mortality was recorded after elective open infrarenal AAA repair. No significant differences in terms of major perioperative complications were observed between cirrhotic patients and controls. Operating time and the need for in-

traoperative blood transfusion were significantly higher in cirrhotic patients. Length of hospitalization was nearly doubled in cirrhotic patients. CTP grade B was associated with higher need for intraoperative blood transfusions. The estimated survival at 2 years was 77.4% in cirrhotic and 97.8% in non-cirrhotic patients. Both patients with CTP B cirrhosis (100%) died within 6 months. CTP B cirrhosis and a MELD score >10 were associated with reduced midterm survival rates. MELD score ≥10 was associated with reduced midterm survival rates with an estimated survival at 2 years of 0% in patients with CTP B cirrhosis compared to 84.4% in CTP A cirrhosis. Patients with MELD <10 compared to MELD ≥10 had an estimated survival of 90% versus 47.6%.[6]

Lung surgery in cirrhotic patients with Non-Small Cell Lung Cancer (NSCLC) had an overall morbidity and mortality between 13.5 - 29.5% and 2.7% - 6.5%, respectively. Overall 1-, 3- and 5-year survival ranged between 77.3% to 87.8%, 57.0% to 59.9%, and 37.6% to 45.6%, respectively.[39-41]

Trauma and orthopedic surgery in patients with liver cirrhosis

In the group of trauma and orthopedic surgery, 6 retrospective studies were identified with levels of evidence ranging between 2B and 3B. Overall mortality of general cirrhotic trauma patients was 12% and 6% for the non-cirrhotic group (OR 5.65). ARDS, trauma-associated coagulopathy, and septic complications were significantly more common among patients with liver cirrhosis. Overall severe complication rate for the two groups was 10 and 4%, respectively (OR 2.05). For the subgroup of patients who underwent a laparotomy for trauma, the mortality rate increased to 40% compared to 15% in non-cirrhotic patients (OR 4.35).[42]

These results were supported by another study that focussed only on laparotomies in cirrhotic trauma patients. The overall mortality for patients with cirrhosis undergoing laparotomy for trauma was significantly higher compared to non-cirrhotic patients (45% vs. 24%, HR 7.60). Mortality for patients with an Injury Severity Score ≤15 was 29% for cirrhotic patients and 5% in non-cirrhotic patients; in patients with an Injury Severity Score of 16–25 mortality was 56% and 11%, respectively. Overall complication rate was 45% in cirrhotic patients and 23% in the non-cirrhotic group, but this result was not statistically significant. Longer ICU stay and higher hospital costs were reported in patients with cirrhosis undergoing trauma surgery compared to non-cirrhotic patients.[4] Analysis by ROC curve identified cirrhotic patients undergoing laparotomy for blunt abdominal trauma with a MELD score ≥17 as the best cut-off value for predicting postoperative death. Postoperative mortality of patients with MELD <17 was 6.2% compared with 85.7% in patients with a MELD score ≥17.[43]

In patients undergoing elective total hip arthroplasty (THA) or elective total knee arthroplasty (TKA), significant adverse outcomes (including major complications such as hepatic decompensation, and mortality) occurred in 20.7% of cirrhotic compared to 3.2% in non-cirrhotic patients. No significant differences were found between elective THA and TKA. However, 80% of cirrhotic patients undergoing emergency THA secondary to a fracture had major complications with a mortality rate of 60%.[44] These results were supported by another study that reported a 30-day complication rate of 26.7% in cirrhotic patients undergoing elective THA.[45] Overall complication rate after TKA was also significantly higher among patients with cirrhosis than in control patients, but no perioperative mortality was reported.[46] Advanced liver cirrhosis was associated with a higher risk of complications.[44,45] Major complications occurred in 14.3%, 28.6%, and 100% of cirrhotic patients with CTP A, B and C cirrhosis, respectively. Death occurred in 4.76%, 14.3%, and 100% of cirrhotic patients with CTP A, B, and C cirrhosis, respectively, but these results were statistically insignificant.[44]

First-time prosthetic hip infection (PHI) was described in 9.5% of patients with liver cirrhosis. Debridement with retention of the prosthesis (DWROP) was the initial treatment and cured the infection in 29% of the patients. Excision arthroplasty (EA) was required in 79% and eradicated PHI in 92% of cases. Recurrent PHI occurred in 30% of cirrhotic patients who had a re-implantation. Patients who developed hepatic decompensation after re-implantation had a significantly higher risk of recurrent PHI (RR 7.5).[47]

Other types of surgical procedures in patients with liver cirrhosis

In the group of splenectomy and transurethral resection of the prostate (TURP) 4 retrospective studies were identified with levels of evidence ranging between 2B and 3B.

Overall morbidity among cirrhotic patients after splenectomy was shown to range between 17.7% and 33%. No mortality was reported in patients with grade CTP A and grade B liver cirrhosis.[48,49] Mortality rate in patients with CTP grade C liver cirrhosis was shown to be 66.7%.[48-50] Overall survival rate after splenectomy of patients with cirrhosis was 83.3% at 1 year, and 62.7% at 2 years of follow-up. The survival rate of patients with CTP C cirrhosis was 80.0% at 1 year, and 60.0% at 2 years of follow-up. Postoperatively, portal pressure decreased after splenectomy in most patients by a mean of 4.7 mmHg.[48]

TURP in patients with cirrhosis was accompanied with a 30-day mortality of 6.7% compared to 2% in non-cirrhotic patients (OR 3.0).[51]

DISCUSSION

Our review of the literature showed that patients with liver cirrhosis who undergo non-hepatic surgery, exhibit postoperative morbidity and mortality rates that vary greatly depending on the severity of liver cirrhosis and the nature of the surgical procedure. Both CTP and MELD scores were shown to be predictive of postoperative morbidity and mortality in these patients. Portal hypertension and emergency surgery in patients with liver cirrhosis were associated with even higher morbidity and mortality rates irrespective of the surgical procedure compared to elective surgery. Patients with portal hypertension and cirrhosis undergoing emergency surgery had the highest mortality rates. A laparoscopic approach was often preferred over an open procedure.

Cholecystectomy and abdominal wall surgery in patients with cirrhosis were associated with the lowest morbidity and mortality and with the least increase in morbidity and mortality compared to non-cirrhotic patients. Laparoscopic cholecystectomy had better outcomes compared to an open approach. Elective umbilical hernia repair in cirrhotic patients was associated with low morbidity and mortality rates and had comparable postoperative mortality rates as non-cirrhotic patients. In umbilical hernia repair, emergency repair was associated with higher morbidity and mortality rates. Wait-and-see approach for patients with cirrhosis and umbilical hernia was shown to result in high mortality and morbidity but no RCT was conducted to compare that strategy to elective repair. Uncontrolled ascites was associated with umbilical hernia recurrence. It was also shown that elective umbilical hernia repair with mesh was safe and effective and no difference in surgical site infection or ascitic leakage was noted when compared to suture repair. Local anesthesia was found to have potential for umbilical and inguinal hernia surgery in cirrhotic patients but no RCT has been performed comparing different anesthesia techniques. Gastrointestinal surgery, appendectomy, colorectal surgery, gastric surgery and pancreatic surgery showed increased risks of morbidity and mortality. Patients with CTP grade A cirrhosis were shown to undergo pancreatic surgery with slightly increased morbidity and mortality compared to non-cirrhotic patients, but those who had CTP grade B and C liver cirrhosis were at increased risk of postoperative death. Comparable high risks were reported in patients with CTP grade B and C liver cirrhosis who underwent emergency trauma surgery, particularly laparotomy in trauma or (emergency) vascular surgery. It was recommended that all cirrhotic trauma patients undergoing laparotomy should be admitted to the ICU irrespective of severity of injuries. It was also shown that patients with CTP A cirrhosis were tolerating cardiac operations rather well but for patients with more severe cirrhosis, these operations should be considered most hazardous. No

difference in adjusted in-hospital mortality was found between patients with cirrhosis undergoing other cardiac surgery, such as PCI, conventional CABG or off-pump CABG.

Literature of non-hepatic surgery in cirrhotic patients is abundant and varies with respect to the level of evidence. However, the majority is not of sufficient quality to allow for solid conclusions. Quality assessment of the studies showed that studies with the highest level of evidence often did not provide data on severity of cirrhosis expressed in MELD or CTP scores. Therefore only morbidity and mortality rates in patients with cirrhosis compared to non-cirrhotic patients could be extracted from the literature. Studies that provided clinical data on CTP or MELD were often retrospective, limited in sample size, and prone to patient selection, resulting in lower levels of evidence. All these studies however did show worse outcomes for patients with more severe liver cirrhosis.

Future studies should focus on risk assessment for specific surgical procedures related to MELD or CTP scores in patients to improve decision-making and patient counseling. Secondly, the preventive effect of portal decompression through preoperative transjugular intrahepatic portosystemic shunting (TIPS) to allow non-hepatic surgery in selected patients with liver cirrhosis and portal hypertension should be studied. Several case studies show conflicting effects of this technique.[52,53] Furthermore, RCTs are needed that randomize cirrhotic patients with a surgically treatable diagnosis to a “wait-and-see” approach or the actual operation in an elective setting. In such trials, patients should also be stratified for MELD or CTP scores.

Summary

This review assesses systematically literature on morbidity and mortality after non-hepatic surgery in patients with liver cirrhosis. Level of evidence provided in the articles varied greatly. Non-hepatic surgery in patients with cirrhosis resulted in increased postoperative morbidity and mortality compared to similar surgery in non-cirrhotic patients. Cholecystectomy and umbilical and inguinal hernia correction were associated with the least increased morbidity and mortality, whereas pancreatic, cardiovascular, and trauma surgery were correlated with the highest risks. The preoperative MELD and CTP scores appeared to be predictive of postoperative risks. Portal hypertension and surgery in an emergency setting were associated with extra increased mortality and morbidity rates. The majority of non-hepatic surgical procedures can be safely performed in patients with low MELD scores or CTP grade A liver cirrhosis without portal hypertension. RCTs in this field are, however, often lacking. This implies that many important clinical questions remain unanswered; among them: the value of preventive preoperative measures such as TIPS placement to reduce risks in cirrhotic patients with portal hypertension and elective operation versus wait-and-see approach in cirrhotic patients with for instance abdominal wall hernias.

Practice points

- § MELD and CTP scores of cirrhotic patients predict outcomes in non-hepatic surgery.
- § Majority of non-hepatic surgery in patients with CTP grade A liver cirrhosis without portal hypertension is safe.
- § Avoid emergency surgery in cirrhotic patients.

Research agenda

- § Assess risks for specific surgical procedures related to MELD or CTP scores of patients in all future studies.
- § Assess the preventive effect of portal decompression through preoperative TIPS in patients with liver cirrhosis and portal hypertension who have to undergo non-hepatic surgery.
- § Randomize cirrhotic patients with a surgically treatable diagnosis to a “wait-and-see” approach or the actual operation in an elective setting stratified for MELD or CTP score.

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CHAPTER 6

A prospective study on elective umbilical hernia repair in patients with liver cirrhosis and ascites

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ABSTRACT

Background: Patients with both cirrhosis and ascites have a 20% risk of developing umbilical hernia. A retrospective study from our center comparing conservative management of umbilical hernia with elective repair in these patients showed a significant risk of mortality as a result of hernia incarceration in conservatively treated patients. The goal of this study was to assess the safety and efficacy of elective umbilical hernia repair in these patients prospectively.

Methods: Patients with liver cirrhosis and ascites presenting with an umbilical hernia were included in this study. For all patients, the expected time to liver transplantation was more than 3 months, and they did not have a patent umbilical vein in the hernia sac. The following data were collected prospectively for all patients: Child-Pugh-Turcotte (CPT) classification, model for endstage liver disease (MELD) score, kidney failure, cardiovascular comorbidity, operation-related complications, and duration of hospital stay. Mortality rates were registered in hospital records and verified in government records during follow-up. Mortality rates were registered in hospital records and verified in government records during follow-up. On completion of the study, a retrospective survey was performed to search for any patients who met the study inclusion criteria but were left out of the study cohort.

Results: In total, 30 patients (25 males) underwent operation at a mean age of 58 years (standard deviation [SD] ± 9 years). Of these 30 patients, 6 were classified as CPT grade A (20%), 19 (63%) as grade B, and 5 (17%) as grade C. The patients' median MELD score was 12 (interquartile range [IQR], 8–16). In 10 (33%) of the 30 patients hernia repair was performed with mesh. The median duration of hospital stay was 3 days (IQR, 2–4). None of the patients were admitted to the intensive care unit. Postoperative complications included pneumonia and decompensation of cirrhosis (1 case each), resulting in prolonged hospital stay for those 2 patients. After a median follow-up period of 25 months (IQR, 14–34), 2 (7%) of the 30 patients died; neither of the deaths were attributable to the umbilical hernia repair. A total of 2 patients suffered recurrence.

Conclusion: Elective umbilical hernia repair is safe and the preferred approach in cirrhotic patients with ascites.

INTRODUCTION

Patients with liver cirrhosis and ascites have a risk of 20% of developing an umbilical hernia in the course of their disease.[1] Possible factors that contribute to the development of umbilical hernia in these patients include increased intra-abdominal pressure due to ascites, weakening of the abdominal fascia and muscle wasting as a result of poor nutritional status, and dilation of the umbilical vein that enlarges the preexistent supra-umbilical fascial opening in patients with portal hypertension.[2]

Although the incidence of umbilical hernia is high in cirrhotic patients, an optimal treatment strategy is unclear. For many years, surgical dogma dictated a "wait and see" approach, and surgical repair of umbilical hernia was limited to patients who developed complications.[3-7] Conservative management, however, can be complicated by bowel incarceration or spontaneous rupture from necrosis of overlying skin and subsequent peritonitis. Such conditions force emergency repair in patients who are then at a greater risk of developing complications in an emergency setting than after elective surgery.[2,8-10]

This scenario appears to be particularly true in circumstances of acute removal of large amounts of ascites, such as large-volume paracentesis after transjugular intrahepatic portosystemic shunt (TIPS) or liver transplantation. Both of these procedures result in an acute decrease in the diameter of the fascial defect. In these instances, abdominal contents inside the hernia sac can become incarcerated.[7]

Currently, the natural course of umbilical hernia in patients with ascites is largely unknown, particularly in patients waiting liver transplantation, and prospective studies in this field are lacking.[6,8,11] A recent retrospective study from our center comparing conservative management of umbilical hernia in these patients with elective repair showed a significant risk of mortality resulting from hernia incarceration in conservatively treated patients.[8]

After this study was completed, the treatment strategy of patients with liver cirrhosis and ascites with an umbilical hernia was changed at our center from "wait and see" to an elective repair protocol. The objective of this study was to evaluate the results of this protocol of elective umbilical hernia repair in patients with concurrent ascites and liver cirrhosis prospectively.

METHODS

Between July 2004 and May 2010, all patients in the Erasmus University Medical Center with umbilical hernia, cirrhosis, and ascites were included in this study and followed prospectively. Liver failure with cirrhosis was diagnosed on clinical, biochemical, or histologic findings. Ascites was diagnosed with ultrasonography or computed tomography, and umbilical hernia was diagnosed on clinical examination.

All patients included in the study were scheduled for elective hernia repair unless their expected waiting time for a liver transplantation was less than 3 months or a patent umbilical vein was present in the wall of their hernia sac. Patients with an expected waiting time for transplantation of less than 3 months or in whom a patent umbilical vein was found on ultrasonography or computed tomography were excluded from the study.

Elective hernia correction was carried out after optimal management of ascites with 2 diuretics (spironolactone [Aldactone; GD Searle/Pfizer, New York, NY] and furosemide [Lasix; Sanofi-Aventis, Paris, France]), early nutritional support, and intravenous albumin to increase patients' serum albumin to greater than 30 g/L. No large-volume paracentesis was performed preoperatively. All patients who underwent elective and acute umbilical hernia repair within the study period at our institution were identified retrospectively to ensure that no patients who met the inclusion criteria were excluded from the final study cohort. The primary goal of the study was to investigate safety of elective umbilical hernia repair in cirrhotic patients.

The following data were collected prospectively for all patients: age, sex, nicotine and alcohol use, malignancy, chronic obstructive pulmonary disease, diabetes mellitus, chronic steroid use, primary or recurrent umbilical hernia, hernia size, serum bilirubin (μmol/L), serum albumin (g/L), serum creatinine (μmol/L), international normalized ratio, hepatic encephalopathy, Child-Pugh- Turcotte (CPT) classification, model for end-stage liver disease (MELD) score at the time of surgery, cardiovascular comorbidity, American Society of Anesthesiologists (ASA) score, presence of hernia strangulation or incarceration, use of mesh in hernia repair, mesh positioning, simultaneous liver transplantation, perioperative and postoperative complications, admission to the intensive care unit, and duration of hospital stay.

Mortality rates were registered in hospital records and verified in government records during follow-up. All patients were invited for clinical examination by 1 of the authors at the outpatient clinic to diagnose recurrence after a minimum follow-up

of 6 months. Statistical analyses were carried out with the SPSS statistical software package (SPSS Inc, Chicago, IL). The chi-square test and the Mann-Whitney U test were used for categorical and continuous variables, respectively. Values were considered statistically significant at 2-sided P values less than .05. Data were described as median and interquartile range (IQR).

RESULTS

Patient characteristics (Table 1). A total of 30 consecutive patients (25 males, 5 females) at a median age of 58.3 years (IQR, 51–65) were included in the elective repair protocol. Of these 30 patients, 7 (23%) were classified as CPT grade A, 18 (60%) as grade B, and 5 (17%) as grade C. The median MELD score was 12 (IQR, 8–16). Of the 30 patients, 6 (20%) had an ASA score of class II, 20 (67%) were class III, and 4 (13%) were class IV. A total of 53% of the patients were on the waiting list for liver transplantation.

Table 1. *Patient characteristics.*

	N = 30
Male, *n* (%)	5 (83)
Median age, y	58.3 (51–65)*
Primary umbilical hernia, *n* (%)	28 (93)
Recurrent umbilical hernia, *n* (%)	2 (7)
CPT classification, *n* (%)	
A	7 (23)
B	18 (60)
C	5 (17)
MELD score, median	12 (8–16)*
ASA class, *n* (%)	
I	0 (0)
II	6 (20)
III	20 (67)
IV	4 (13)

*IQR, Interquartile range; CPT, Child-Pugh-Turcotte; MELD, model for end-stage liver disease; ASA, American Society of Anesthesiologists. *Data in parentheses represents interquartile range.*

Comorbidities of patients in the protocol (Table 2). At the time of hernia repair, 6 (20%) of the 30 patients in the protocol reported smoking, and 7 (23%) had alcohol abuse noted in their medical history. Only 1 (3%) patients had a malignancy related to the liver. Of

the 30 patients, 6 (20%) reported chronic steroid use, and 6 (20%) suffered from type 2 diabetes mellitus.

Table 2. *Comorbidities of patients included in the protocol.*

	Elective repair (N = 30)
Smoking, *n* (%)	6 (20)
Alcohol abuse, *n* (%)	7 (23)
Malignancy, *n* (%)	1 (3)
Chronic steroid use, *n* (%)	6 (20)
Diabetes, *n* (%)	6 (20)

Operation characteristics and postoperative course (Table 3). All hernia repairs were performed in an elective setting with an open technique and under general anesthesia. In all patients, the presence of ascites was confirmed. In 10 (33%) of the 30 patients hernia repair was performed with a flat heavy weight polypropylene mesh. The use of mesh for hernia repair was at surgeon's discretion. Of these 10 repairs, 5 meshes were placed using the intraperitoneal (onlay) technique and 5 were placed with the preperitoneal (inlay) technique. Peritoneal tears that occurred during dissection of the hernial sac were closed with absorbable sutures.

Table 3. *Perioperative outcomes.*

	Elective repair (N = 30)
Operative time, min	79 (66–94)*
Defect size, mm	15 (9)‡
Mesh repair, *n* (%)	10 (33)
Duration of hospital stay, d	3 (24)*
ICU admission, *n* (%)	0 (0)

* *Data are presented as median (interquartile range).*
‡ *Data are presented as mean (standard deviation).*

Postoperatively, 2 patients experienced complications that necessitated prolonged hospital stay: 1 developed pneumonia and the other patient underwent decompensation of cirrhosis. The median hospital stay was 3 days (IQR, 2–4). None of the patients were admitted to the intensive care unit.

At a median follow-up of 10 months, 2 (7%) of the 30 patients died: 1 died from bacteremia associated with cholangitis and hepatorenal syndrome, and the other patient

committed suicide during follow-up. None of the deaths were assumed attributable to the umbilical hernia repair. After a median follow-up of 25 months (IQR, 14–34), 2 (7%) of the 30 patients suffered a recurrence. Both underwent the primary hernia repair without the use of mesh. No notable correlations could be found between either CPT classifications or MELD scores with postoperative complications and recurrences (P = .06 and P = .17, respectively).

Retrospective review. In the retrospective review, 163 patients were identified who underwent umbilical hernia repair at our institution during the study period. Of these 163 patients, 30 were in the protocol and are described above. Of the 133 patients not included in the protocol, 127 were not eligible for the study, but 6 of these patients had ascites and liver cirrhosis and should have been considered for inclusion in the protocol.

Of these 6 patients, 4 were not included in the study even though they met the inclusion criteria; they later underwent elective correction and did not experience any negative sequelae. The remaining 2 patients were excluded from the study because they were diagnosed with a patent umbilical vein and planned to undergo hernia correction during liver transplantation.

Unfortunately, the hernia correction proved to be unsuccessful for both patients. One of the patients developed an incarcerated umbilical hernia 3 months after transplantation, which was corrected successfully without negative sequelae, but the other patient was readmitted to the hospital 2 months after liver transplantation, also with an incarcerated umbilical hernia. In this case, the complication resulted in multiple organ failure and the patient's death.

DISCUSSION

In this prospective single-center study, the safety of umbilical hernia repair in cirrhotic patients with ascites was investigated in a series of 30 consecutive patients. All patients underwent operations in an elective setting. Previous retrospective studies[4,8] have demonstrated that conservative treatment of umbilical hernia in cirrhotic patients is associated with considerable morbidity and mortality. Hence, prospective series, such as this one, are needed to assess the safety and efficacy of elective umbilical hernia repair in this specific group of patients.

Patients with an expected waiting time to liver transplantation of less than 3 months were excluded from this study. The risk of an additional operation for these patients who typically have high MELD scores was considered greater than the risk of waiting 3 months until transplantation, because the hernia would be corrected during the transplantation procedure. Furthermore, patients with a patent umbilical vein were also excluded from the study. The repair of an umbilical hernia necessitates the complete freeing of the umbilical ring and the ligation of a possibly reopened umbilical vein. This reopened umbilical vein can be an important outflow for the portal circulation in patients with severe portal hypertension. If the vein is ligated during umbilical hernia repair, the outflow of the portal circulation is hampered, which can lead to acute portal vein thrombosis, subsequent acute failure of the liver necessitating emergency liver transplantation.[2,12]

In our study group, the incidence of complications after elective repair was low (7%) compared to complication rates reported in the literature (43%).[8] Other studies also have demonstrated that postoperative outcome in cirrhotic patients is correlated with the patient's CPT classification and, especially, with their MELD score.[11,13,14] In our series, however, no significant correlations were found between either a patient's CPT classification or MELD score and their postoperative outcome, but this finding could be due to the relatively low number of patients in our study.

In this study, elective hernia correction was carried out after optimal management of ascites by the use of diuretics, early nutritional support, and intravenous albumin to increase the patient's serum albumin to greater than 30 g/L. More invasive interventions to optimize the condition of the patient are possible, such as staged and concomitant peritoneovenous shunting in combination with hernia repair, preoperative placement of TIPS to control portal hypertension, or mechanical ascites management by temporary placement of peritoneal dialysis catheters to allow drainage of postoperative ascites.[1,15,16] None of these more invasive therapeutic modalities, however, were used preoperatively in this study.

At long-term follow-up, recurrences were found in 2 patients, both of whom had undergone primary hernia repair without the use of prosthetic mesh. The incidence of recurrences after umbilical hernia repair can be diminished markedly by using mesh, as demonstrated in this patient group and other studies.[17-19]

With the use of mesh, the chance of leakage of ascites is increased in cirrhotic patients; such leakage can lead to infection of the mesh and, more rarely, bacterial peritonitis. As a result, many surgeons may be reluctant to use mesh for umbilical hernia repair

in this patient group. In most cases, bacterial infection of meshes made of polypropylene or polyester can be treated with antibiotics, and removal of the mesh is rarely required.[20,21] Infection of the mesh was not observed in our series, nor are we aware of any studies in the literature in which an increased risk of mesh infection was observed in cirrhotic patients.

Of the 6 patients identified from the retrospective check for missed patients at our institution, 2 were considered for inclusion but excluded because of they had a patent umbilical vein. Both patients should have undergone elective umbilical hernia repair during the liver transplantation procedure, but this was mistakenly not performed with devastating results in 1 of the 2 patients.

Performing umbilical hernia repair simultaneously with liver transplantation appears to be the optimal setting by avoiding complications associated with an extra admission and the use of general anesthesia. Due to organ shortages, however, the waiting time for transplantation has increased considerably, exposing patients on the waiting list to a greater risk of developing incarceration of the hernia. This situation leads to an increase in the need for emergency – rather than elective – repairs.

Considering this fact, one could argue that elective repair of symptomatic umbilical hernia even in patients on the waiting list for transplantation is the safer strategy. Randomized studies, however, must be performed to create sufficient evidence for such a policy. Our results of elective umbilical hernia repair in cirrhotic patients are very encouraging and provide sufficient evidence to set up a randomized, controlled trial on this topic.

Before such trials are undertaken, however, one needs to consider that the repairs carried out in our study were performed at a liver transplantation center with considerable experience with this patient group. The multidisciplinary approach of preoperative, perioperative, and postoperative care may be responsible for the positive results of our study. For this reason, implementation of umbilical hernia repair in cirrhotic patients in other centers should also focus on the overall management of care.

In conclusion, elective umbilical hernia repair is a safe approach and seems preferable over conservative treatment in selected cirrhotic patients. We have reported the first prospective data that advocate elective umbilical hernia repair in cirrhotic patients. A prospective, randomized clinical trial is needed to support our findings, and thereby reach a greater level of evidence to encourage implementation of this treatment strategy in other liver transplantation centers.

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CHAPTER 7

Conservative treatment versus elective repair of umbilical hernia in patients with liver cirrhosis and ascites: A study protocol

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ABSTRACT

Background: The optimal management of patients with umbilical hernia and liver cirrhosis is not clear. The general surgical opinion is that umbilical hernia in patients with liver cirrhosis and ascites should not be corrected, because of the presumed high operative risks and high recurrence rates after elective repair. Conservative treatment, however, can also have severe complications resulting in emergency repair. In these patients such operations carry an even greater risk of complications than compared to elective operations. To date, no randomized controlled trial has been conducted on this subject.

Methods/Design: our trial is a multi-center, randomized controlled trial designed to compare watchful waiting to elective repair of umbilical hernia in patients with liver cirrhosis and ascites. The primary endpoint consists of a composite endpoint of overall morbidity related to the treatment of umbilical hernia after 24 months of follow-up. Secondary endpoints will include: cumulative hernia recurrence rate, classification of complications obtained during follow-up, postoperative pain and quality of life. A total of 100 patients will be randomized between the two groups. Patients will visit the outpatient clinic at 2-3 weeks and after 3, 12 and 24 months of follow-up.

Conclusion: This study will provide level 1b evidence to support the preference for either conservative treatment or elective repair of umbilical hernia in patients with liver cirrhosis and ascites.

Trial registration: Clinicaltrials.gov: NCT01421550

INTRODUCTION

Patients with liver cirrhosis complicated with ascites have a 20% risk of developing an umbilical hernia in the course of their disease.[1] Possible factors that contribute to the development of umbilical hernia in these patients include increased intra-abdominal pressure due to ascites, weakening of the abdominal fascia and muscle wasting as a result of a poor nutritional status, and dilatation of the umbilical vein that enlarges the preexistent supra-umbilical fascial opening in patients with portal hypertension.[2]

Optimal management of an umbilical hernia in patients with liver cirrhosis remains controversial. It is often advised that surgical correction of an umbilical hernia in patients with ascites should not be performed before liver transplantation. In those patients a "wait-and-see" approach is recommended, because of the presumed increased surgical risks and high recurrence rates after elective repair.[3-5] Conservative treatment, however, can be complicated by incarceration or spontaneous rupture and evisceration following necrosis of the overlying skin. This requires an emergency repair which puts patients at greater risk of complications – even greater than after elective repair.[6-8] If a patient is a candidate for liver transplantation and repair has not been performed prior to transplantation, umbilical hernia correction should be performed during liver transplantation because of the reported risk of postoperative strangulation of the bowel in uncorrected umbilical hernia resulting in serious morbidity and death.[8]

One specific group of patients still warrants conservative treatment of umbilical hernia or repair only during liver transplantation: patients with a patent umbilical vein. A reopened umbilical vein can be an important route of outflow for the portal circulation in patients with severe portal hypertension. In these patients, elective repair without liver transplantation has been reported to result in acute portal vein thrombosis and subsequent liver failure necessitating an emergency liver transplantation because of ligation of the umbilical vein during hernia repair.[2,7,9]

Because of all these increased risks, liver cirrhosis, particularly in the presence of portal hypertension was initially considered an absolute contraindication for elective umbilical hernia repair. Despite this widespread belief, some small retrospective and prospective series have shown good results with elective umbilical hernia repair for patients with liver cirrhosis.[6-8] However, no randomized controlled trial on this issue has been published.

The CRUCIAL trial was designed to determine the optimal management of umbilical hernia in patients with liver cirrhosis and ascites.

Objective

The objective of the CRUCIAL trial is to compare conservative treatment (watchful waiting) to elective repair of umbilical hernia in patients with liver cirrhosis and ascites. We hypothesize that elective repair of umbilical hernia will result in a significant reduction of overall complication rate and improved quality of life compared to conservative treatment in patients with liver cirrhosis and ascites.

Primary endpoint will be a composite endpoint of the overall morbidity related to the treatment of umbilical hernia after 24 months of follow-up. Secondary endpoints include cumulative hernia recurrence rate, classification of complications obtained during follow-up, and assessment of pain and quality of life.

METHODS AND STUDY DESIGN

Study design

The CRUCIAL trial has been designed as a prospective, multi-center, randomized controlled trial, in which conservative treatment is compared t0 elective repair of umbilical hernia in patients with liver cirrhosis and ascites.

The design of this protocol is in accordance with the CONSORT guideline.[10] Approval of the Medical Ethical Committee Erasmus MC, Rotterdam, The Netherlands, was obtained. In total a 100 patients will be included in this study. Patients will be randomized in one of two groups of 50 patients each. Group 1 includes patients with liver cirrhosis and ascites that will undergo elective umbilical hernia repair; group 2 includes patients with cirrhosis and ascites that will receive conservative treatment with regard to their umbilical hernia.

Randomization will be done in the Erasmus Medical Center for each participating center. Patients are randomly allocated to either conservative treatment or elective repair by means of sealed, numbered envelopes and will be opened in sequence. The randomization procedure will be stratified for participating center and for Model of End-stage Liver Disease (MELD) score ≤15 and >15. Blinding for the allocation is not possible in this study for the study participants, evaluators and surgeons.

Patients will visit the outpatient clinic after 2-3 weeks and after 3, 12 and 24 months. At 12 months of follow-up ultrasound imaging will be performed to detect recurrent umbilical hernia. All patients will be asked to fill out the Short-Form 36 (SF-36) and EuroQol (EQ-5D) to assess quality of life and a Visual Analogue Scale (VAS) to assess pain preoperatively and during follow-up.

Participants

All patients with liver cirrhosis and ascites who have a concurrent umbilical hernia will be assessed for eligibility. Informed consent is mandatory. Before eligible patients can be included, ultrasound imaging will be performed to determine the size of the umbilical hernia and the presence of a patent umbilical vein. If the umbilical vein is either closed or open, but the diameter doesn't exceeds 5 mm, the patient is permitted to participate in the CRUCIAL trial.

Umbilical hernia repair will also be performed in patients who are allocated to conservative treatment group and develop a symptomatic umbilical hernia during follow-up. Simultaneous umbilical hernia repair will be performed if a patient will undergo abdominal surgery or a liver transplantation before the umbilical hernia correction is performed as stated in the flowchart (Fig. 1).

Inclusion criteria are defined as follows:

§ Primary umbilical hernia
§ Liver cirrhosis
§ Ascites (proven or treated)
§ Age ≥ 18 years
§ Signed Informed consent

Exclusion criteria:

§ Recurrent umbilical hernia
§ Midline laparotomy in the medical history
§ ASA (American Society of Anaesthesiologists) score IV or above
§ Incarcerated umbilical hernia necessitating an emergency procedure
§ The presence of a patent umbilical vein larger than 5mm
§ Expected time to liver transplantation more than 3 months

Interventions

Preoperative work-up

Elective repair of the umbilical hernia will be performed within 8 weeks after the randomization procedure. Prior to the randomization procedure, ultrasound imaging will be performed to determine the presence of a patent umbilical vein. Patients who undergo elective repair of the umbilical hernia will be admitted to the hospital two days prior to the procedure. The presence of tense ascites (i.e. more than 5 liters) will be treated with diuretic therapy or with drainage, and if necessary, albumin levels will be corrected until > 30 g/L.

Intra-operative procedure

All repairs of the umbilical hernia, either elective repair or emergency surgery after conservative treatment, will take place using a method for which consensus is reached by all participating centers. This includes a para-umbilical incision, dissection (avoiding resection) of the hernia sac and restoration of the sac and its contents into the abdominal cavity. Intra-operative resection of the sac must be recorded on the patient's operation report. Repair should take place using non-absorbable monofilament sutures combined with a flat polypropylene mesh placed preferably in the on-lay position or in the pre-peritoneal plane.[11] The overlap achieved in repair should be at least 3 cm's in each direction of the circular mesh. Closure of the subcutaneous tissue and skin may be achieved using a method chosen by the individual surgeon. If a patient with liver cirrhosis and concurrent umbilical hernia will undergo liver transplantation during follow up, repair should also take place using preferably non-absorbable monofilament sutures combined with a flat polypropylene mesh placed in the on-lay position or in the pre-peritoneal plane.

The preferred method of anaesthesia in the current trial is general anaesthesia. The use of local or spinal anaesthesia is permitted if there are contra-indications for general anaesthesia. Single dose Kefzol® (Cefazoline) should be administered as antibiotic prophylaxis 10 to 30 minutes preoperatively. Furthermore, routine administration of thrombosis prophylaxis should be considered in the form of bodyweight adjusted Low Molecular Weight Heparin.

Case record form (intra-operative procedure) asks for completion of all fields noted, such as technical details of procedure (incision, size of the defect and the use of mesh and drains), duration of procedure, complications during procedure, thrombosis prophylaxis, intravenous antibiotics and method used for anaesthesia.

In mesh hernia repair the umbilical defect should not be enlarged during the repair procedure. If the surgeon sees need to enlarge the umbilical defect during the operation (which is not the preferred procedure) the enlargement of the defect must be noted in the operation report. The surgeon is permitted to close the fascia defect using sutures if possible in a "tension free fashion" to protect the mesh from contact with umbilical skin. In order to protect the viscera it is possible to place omentum or the remains of the hernia sac between viscera and mesh. The use of drains is permitted. Closure of the subcutaneous tissue and skin may be achieved using a method chosen by the individual surgeon.

Peri-operative management of clotting disorders

Without signs of bleeding complications, prolonged prothrombin time (PT) or a platelet count below 30 should not be corrected.[12] If necessary, for instance in bleeding complications, correct PT/INR with low-volume coagulation factor concentrates, like co-fact®. Preferably not with FFP's because of a fluid overload side effect, potentially leading to more bleeding complications because of a rise venous pressure.[13]

Postoperative procedure

Post-operative analgesics may consist of tramadol 50 mg three times daily and paracetamol four times daily 500 mg (or equivalent) administered orally for six days after surgery. Surgical wounds are examined for signs of haematoma and seroma. Albumine levels should be >30 g/L before the patient is allowed to return home. Diuretics controls and post-operative care will be performed at the outpatient clinic of the department of Hepatology. Postoperative care will be in close collaboration with a specialized hepatologist and concordant with good standard of care for operated patients with liver cirrhosis.

Outcome measures

Primary endpoint in this study is a composite endpoint of the overall morbidity (percentage of patients with at least one hernia-related complication) after 24 months of follow-up. Overall morbidity, which is divided in minor and major complications, can be found in Table 1.

Secondary endpoints are: cumulative recurrence of umbilical hernia after repair in the separate groups, and grading of the primary endpoint (overall morbidity) with use of the Landelijke Heelkundige Complicatie Registratie (LHCR) grading tool; per patient the maximal observed grade will be determined and compared between the two groups. Pain will be evaluated with VAS and quality of life will be evaluated with SF-36 and EQ-5D questionnaires.

All complications defined in Table 1, both conservative treatment and elective repair, will be scored with the LHCR for grading complications in surgical patients (Table 2). The following surgical procedures will not be scored as complications: liver transplantation, elective or emergency repair of the umbilical hernia. In each patient the maximal observed grade will be determined and compared between the two groups.

Table 1. *Minor and major complications.*

Minor complication	*Major complication*
Superficial/deep SSI	Mortality
Seroma	Evisceration
Pneumonia	Strangulation
Haematoma	Incarceration
Urinary tract infection	Bowel ischemia
Non-closure of surgical wound at 4 weeks	Necrosis/rupture of the overlying skin of the umbilical hernia
	Postoperative leakage of ascites more than 2 weeks after surgery
	Liver failure
	Infectious ascites
	Decompensated cirrhosis
	Organ space SSI
	Unexpected ICU admissions related to umbilical hernia or umbilical hernia repair

Table 2. *The Landelijke Heelkundige Complicatie Registratie (LHCR) grading tool.*

Grade	*Description of complications*
0	No health disadvantage, no real complication
1	Temporary health disadvantage, recovery without (re) operation
2	Recovery after (re) operation
3	(likely) permanent damage or invalidity
4	Death

Sample size calculation

Group sizes are based on chi-square tests with alpha = 0.05, a power of 90% and are based on an expected decrease in overall complication rate at 2-years from 50 to 15% due to elective umbilical hernia repair.[8] This requires 42 patients per treatment group. Accounting for approximately 15% dropout during the trial and 5% lost to follow-up, a total of 50 patients per group need to be recruited.

Statistical analysis

Hundred patients with an umbilical hernia will be included in the study. Patients will be randomized in one of two groups of 50 patients each stratified by center and MELD ≤15 and >15. Data will be analyzed on an "intention to treat" basis.

Categorical variables will be presented as numbers (percentage). Continuous variables will be presented as medians (range). Categorical variables will be compared using the Chi-square test. Continuous variables will be compared using the Mann-Whitney U test.

Kaplan-Meier curves will be constructed to determine the cumulative complication rate of the umbilical hernia in the two study arms (elective repair versus conservative treatment). Comparison will be done using the LOGRANK test. Quality of life will be compared using Repeated measurements ANOVA. The Mann-Whitney U test will be used for the analysis of the maximal observed grade per patient according to the LHCR grading tool.

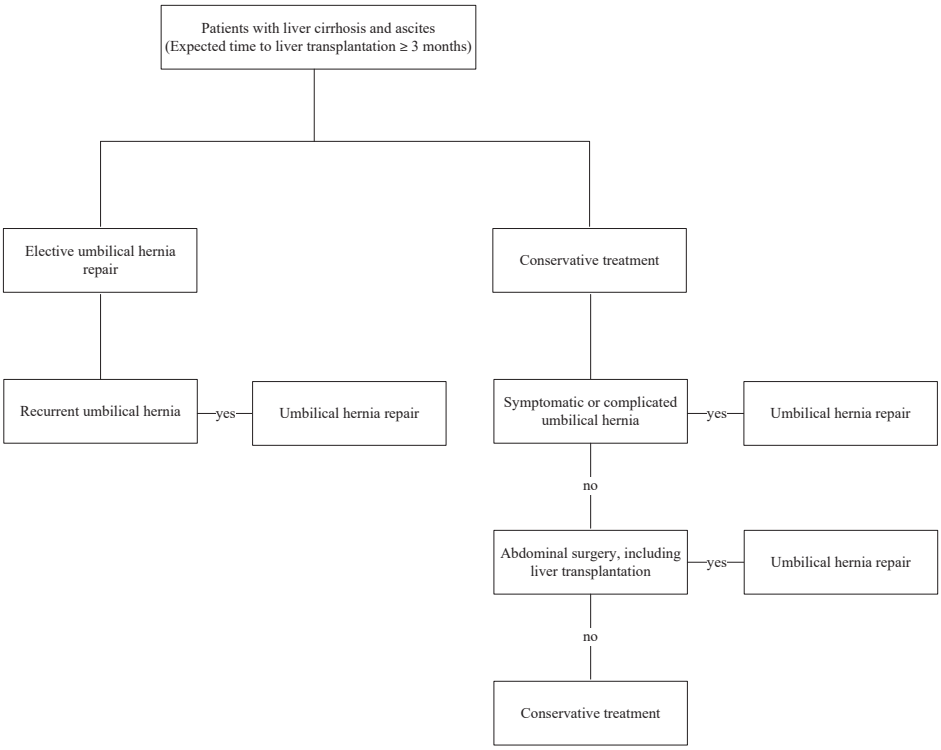

Figure 1. *Flowchart.*

All analyses will be conducted using SPSS (version 17.0, SPSS Inc, Chicago, USA). P-values <0.05 (two-sided) will be considered statistically significant.

Clinical follow-up and data collection

Morbidity will be assessed after 2-3 weeks (routine follow-up). In addition at 3, 12 and 24 months post-operative follow-up will be performed. The investigator will examine and discuss with the patients if there are any complaints related to the umbilical hernia. The patient will undergo ultrasound imaging at the 12-month follow-up to detect recurrent hernias. The patients are asked to complete a SF-36 and EQ-5D questionnaire (as part of the quality of life evaluation) at baseline, 3, 6, 12 and 24-months of follow-up. VAS will be employed to evaluate pain at baseline and after 3, 6, 12 and 24 months. In addition VAS will be done directly postoperative and at day 1 until 6 in operated cases for an umbilical hernia.

The operative data will be collected during surgery and filled out immediately after the operation by the investigator through an online case record form. The follow-up data will also be collected by the investigator, using the same system. The case record forms are only accessible by logging in to a specially designed and secured website (https://www.crucialtrial.nl). All personal data is coded. A data check will be performed by comparing the patient records with the completed case record forms manually. Only the coordinating investigator and the principal investigator have access to the coding system. All data are imported into a secured database on a server of our institution and are managed by the coordinating investigator, according to the hospital guidelines. All data will analyzed in collaboration with the trial statistician at the end of the trial.

Monitoring

Adverse events are defined as any undesirable experience occurring to a subject during a clinical trial, whether or not considered related to the investigational intervention. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded. A serious adverse event (SAE) is any untoward medical occurrence that results in death; is life threatening (at the time of the event); requires hospitalization or prolongation of existing inpatients' hospitalization; results in persistent or significant disability or incapacity; is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome. All SAEs will be reported to the accredited Medical Ethical Committee (MEC) that approved the protocol, according to the requirements of that MEC. Serious Adverse events are major complications, unforeseen ICU admissions related to umbilical hernia or umbilical

hernia repair and reoperations. Adverse Events are minor complications, prolonged admission, readmission related to elective repair or conservative treatment.

An independent data and safety monitoring committee will evaluate the progress of the trial and will examine safety parameters every 6 months. All involved physicians will repetitively be asked to report any potential adverse events caused by the study protocol. These adverse events will be listed and discussed with the monitoring committee. The monitoring committee can ask for a full report in order to discuss a specific adverse event. A copy of this report will be sent to the central ethics board and to the involved physicians. All deceased patients will be evaluated by the safety committee for cause of death and possible trial related serious adverse effects. Every death will be reported to the central ethics board and the local ethics board. The Data Safety Monitoring Board will consist of an epidemiologist/statistician, a hepatologist and an independent surgeon.

DISCUSSION

Management of umbilical hernia in patients with liver cirrhosis is a subject of debate.[8,14,15] Historically, elective hernia repair was deemed hazardous for patients with an umbilical hernia, because of the presumed increased surgical risks and the high recurrence rates after repair. Instead, watchful waiting was often advised, particularly in patients with asymptomatic umbilical hernia.[3,4]

More recent publications have shown that patients who are treated conservatively are at risk of developing complications of the hernia due to incarceration, rupture of the overlying skin or recurrent infections of ascites.[6-8] To date, no randomized controlled trial on this matter has been conducted. The CRUCIAL trial will provide level 1b evidence to support the preference for either conservative treatment or elective repair of umbilical hernia in patients with liver cirrhosis and ascites.

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CHAPTER 8

Umbilical hernia management during liver transplantation

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ABSTRACT

Purpose: Patients with liver cirrhosis scheduled for liver transplantation often present with a concurrent umbilical hernia. Optimal management of these patients is not clear. The objective of this study was to compare the outcomes of patients who underwent umbilical hernia correction during liver transplantation through a separate infra-umbilical incision with those who underwent correction through the same incision used to perform the liver transplantation.

Methods: In the period between 1990 and 2011, all 27 patients with umbilical hernia and liver cirrhosis who underwent hernia correction during liver transplantation were identified in our hospital database. In 17 cases, umbilical hernia repair was performed through a separate infra-umbilical incision (separate incision group) and 10 were corrected from within the abdominal cavity without a separate incision (same incision group). Six patients died during follow-up; no deaths were attributable to intra-operative umbilical hernia repair. All 21 patients who were alive visited the outpatient clinic to detect recurrent umbilical hernia.

Results: One recurrent umbilical hernia was diagnosed in the separate incision group (6%) and four (40%) in the same incision group ($p = 0.047$). Two patients in the same incision group required repair of the recurrent umbilical hernia; one of whom underwent emergency surgery for bowel incarceration. The one recurrent hernia in the separate incision group was corrected electively.

Conclusion: In the event of liver transplantation, umbilical hernia repair through a separate infra-umbilical incision is preferred over correction through the same incision used to perform the transplantation.

INTRODUCTION

Patients with liver cirrhosis complicated with ascites have a 20% risk of developing an umbilical hernia in the course of their disease.[1] Possible factors that contribute to the development of umbilical hernia in these patients include increased intra-abdominal pressure due to ascites, weakening of the abdominal fascia and muscle wasting as a result of poor nutritional status, and dilatation of the umbilical vein that enlarges the pre-existent supra-umbilical fascial opening in patients with portal hypertension.[2]

Optimal treatment of an umbilical hernia in patients with liver cirrhosis remains controversial. It is often advised that surgical correction of an umbilical hernia before liver transplantation (LT) in patients with ascites should not be performed. In those patients a "wait-and-see" approach is recommended, because of the presumed high surgical risks and high recurrence rates after elective repair.[3-5] Conservative management, however, can be complicated by incarceration or spontaneous rupture and evisceration following necrosis of the overlying skin. This requires an emergency repair which puts patients at greater risk of complications – greater than after an elective correction.[6-8] If a patient is a candidate for LT and repair has not been performed prior to LT, umbilical hernia correction should be performed during transplantation, because of the reported risk of postoperative strangulation of the bowel in an uncorrected umbilical hernia resulting in serious morbidity or death.[8]

Two techniques for hernia repair during LT are most commonly used, either through a separate infra-umbilical incision or from within the abdominal cavity through the same incision used to perform the liver transplantation. The decision, however, of which technique for umbilical hernia repair during LT should be used, is based on the surgeon's personal preference; no studies on this matter have been published as yet. The objective of this study is to evaluate which of the two techniques to repair an umbilical hernia during LT is to be preferred.

METHODS

Patient records between the period 1990 and 2011 at Erasmus University Medical Center were screened for the combined search terms liver cirrhosis, umbilical hernia and liver transplantation. Patients were included in the analysis when the following inclusion criteria were met: End-stage liver disease, scheduled for liver transplantation and an umbilical hernia confirmed by physical examination which was repaired during LT.

According to the hernia correction technique chosen during LT, two patient groups were identified: patients who underwent umbilical hernia repair through a separate infra-umbilical incision (separate incision group) and patients who underwent umbilical hernia correction from within the abdominal cavity without a separate incision (same incision group). The choice of technique for umbilical hernia repair was made at the surgeon's discretion. All fascia defects were closed using interrupted PDS sutures. The two techniques to correct the umbilical hernia during LT were not standardized. Surgical records were reviewed to identify the type of incision used to correct the umbilical hernia and to identify the type of hernia repair, either primary suture or mesh repair. The occurrence of local wound complications related to the umbilical hernia repair and the presence of ascites during LT were also retrieved from the records.

Patients identified in this search were followed at our institution; they all underwent a physical examination and if necessary an additional ultrasonography of the umbilical region to detect hernia recurrence.

This retrospective cohort study used SPSS 17.0 (SPSS Inc., Chicago, IL, USA) for statistical analysis. Chi-square test and Mann-Whitney U- test were used for categorical and continuous variables. Mean follow-up (defined as time from LT to death, hernia correction or date of physical examination or ultrasound), age, sex, and labMELD score were compared between the two groups. The values are expressed as mean ± standard deviation (SD) or percentages. The Chi-squared test was used to assess the difference in proportions of hernia recurrences between the two groups. A p-value of less than 0.05 was considered significant.

RESULTS

Study population

Between January 1990 and December 2011 a total of 717 liver transplantations was performed; 27 of these patients underwent umbilical hernia repair simultaneously (4%). The mean labMELD score of these 27 patients was 16.8 (SD 4.6). At the time of LT, 19 of them had at least mild-to-moderate ascites. Seventeen patients were included in the separate incision group and 10 in the same incision group. Age and sex did not differ significantly between the two groups. A total of six patients (22%) died during follow-up due to causes not related to the umbilical hernia or its repair. In Table 1, the demography of the studied population is shown.

Table 1. *Demography of the patient groups.*

	Separate incision group	*Same incision group*
N	17	10
Male (%)	12 (71%)	5 (50%)
Mean age (SD)	51.6 (11.3)	47.2 (14.5)
Mean labMELD score (SD)	16.5 (4.7)	17.3 (4.8)
Follow up in months (SD)	31.1 (29.2)	25.7 (33.1)

Duration of follow-up did not differ between both groups: 25.7 (months; SD 33.1, same incision group) versus 31.1 (SD 29.2, separate incision group), P = 0.659. Overall complication rate did not differ significantly between the same incision group and the separate incision group (50% vs 24%; P = 0.219). Recurrence rate in the separate incision group and same incision group (6% vs 40%, respectively) differed significantly, P = 0.047, whereas labMELD scores were comparable between the 2 groups. The outcomes are compared in Table 2.

Table 2. *Complications reported after initial management.*

Hernia management	*Recurrence rate*	*Overall complications rate*	*Nature of complications*
Separate incision group (n = 17)	1 (6%)	4 (24%)	Seroma (n = 2) Wound infection (n = 1) Recurrence (n = 1)
Same incision group (n = 10)	4 (40%)	5 (50%)	Relaparotomy for postoperative hemorrhage (n = 1) Recurrence (n = 4); *including 1 incarcerated hernia followed by emergency surgery.*

The recurrence rate (6% versus 40%) differed significantly between the two groups (P = 0.047).

Separate incision group

In 10 out of 17 patients (59%), the presence of ascites was confirmed during LT. The mean (SD) labMELD score for the separate incision group was 16.5 (4.7). Umbilical hernia repair was performed with primary suturing in 15 out of 17 patients (88%); in 2 patients, abdominal wall reconstruction consisted of preperitoneal polypropylene onlay mesh repair. The skin of the separate incision was closed using intracutaneous running absorbable monofilament sutures (Monocryl 4.0, Ethicon). Local wound complications occurred in 3 of 17 patients (18%); 2 patients had a seroma and 1 who underwent mesh repair suffered a wound infection, which was treated locally without negative sequelae. Four out of 17 (24%) patients died during follow-up. Hernia correction-related mortality was not observed in this group. One of 17 patients in the

separate incision group suffered a hernia recurrence (6%) 19 months after primary repair, which was operated upon electively. The two patients who underwent hernia repair using mesh prosthesis did not suffer recurrence.

Same incision group

In 9 out of 10 patients (90%), the presence of ascites was confirmed during LT. The mean (SD) labMELD score for the separate incision group was 17.3 (4.8). In all cases umbilical hernia repair was performed with primary suturing. Two deaths (20%) were recorded during follow-up, which were not related to the hernia correction. In four out of ten patients (40%), a recurrent umbilical hernia was diagnosed at follow-up. Two recurrent hernias (50%) were corrected; one patient was operated on electively and one patient (25%) presented with an incarcerated hernia necessitating emergency surgery. One patient in the same incision group suffered postoperative hemorrhage at the site of the hernia correction. The patient had to undergo a re-laparotomy through the same incision used for LT to control the bleeding.

DISCUSSION

Umbilical hernia correction during LT results in high rates of hernia recurrence. This retrospective cohort study suggests that correction of the umbilical hernia during LT through a separate infra-umbilical incision is to be preferred over correction from within the abdominal cavity without a separate incision.

Management of an umbilical hernia in patients with liver cirrhosis is subject of debate.[8-10] Historically, elective hernia repair was deemed hazardous for patients with an umbilical hernia, because of the presumed high surgical risks and the high recurrence rates after repair. Instead, a wait-and-see approach was commonly advised, particularly in asymptomatic patients.[3,4]

More recent publications, however, have shown that patients treated conservatively are at risk of developing complications of the hernia due to incarceration, rupture of the overlying skin or recurrent infections of ascites.[6-8] This awareness has changed the management of these patients to a more aggressive approach of correcting umbilical hernias electively, even for patients awaiting LT if the expected waiting time exceeds three to six months.[6-8]

Despite this growing awareness of potential hazards of umbilical hernias in patients with liver cirrhosis and a more aggressive approach to elective repair, most patients

with an asymptomatic umbilical hernia are still treated conservatively, particularly those with more advanced liver disease.[10,11] This results in patients presenting with a concurrent umbilical hernia in up to 20% of liver transplantations. If left uncorrected, these hernias can lead to serious postoperative morbidity and even mortality after LT.[6-8]

One specific group of patients still warrants conservative treatment of umbilical hernia or repair only during LT: patients with a patent umbilical vein. A reopened umbilical vein can be an important rout of outflow for the portal circulation in patients with severe portal hypertension. In these patients, elective repair without LT has been reported to result in acute portal vein thrombosis and subsequent liver failure necessitating emergency LT, because of ligation of the umbilical vein during hernia repair.[2,7,12]

The present study has several limitations. The first limitation is the relatively small sample size. Due to this, adjusting or stratifying for possible confounders that could explain the difference in recurrences between the two groups was not possible. Despite this small sample size, the difference in recurrence between the two types of surgical correction was found to be significant. Secondly, it could be argued that the choice of a surgeon to use a certain technique was biased by patient characteristics that could influence recurrence rate. Patients in the two groups, however, were shown to be comparable with respect to severity of liver disease as labMELD was comparable in both groups. In addition, due to the retrospective nature of the study and the fact that no strict protocols were used to correct the hernias, the conclusion should be interpreted with further caution.

Intraoperative ascites is a known risk factor for postoperative hernia recurrence.[6,10,13] Although preoperative ascites was observed more frequently in the same incision group, this difference was not statically significant. Furthermore, neither technique was standardized, which restricts the comparability between the groups. The hernia sac was not resected in all patients in the same incision group and only two of the patients in the separate incision group underwent mesh-repair.

The use of mesh under these conditions is controversial. However, routine use of mesh repair in patients undergoing concomitant LT and umbilical hernia repair has never been studied. It is often believed that under those circumstances, the use of mesh could potentially lead to higher incidences of infection of the wound, infection of the mesh, and postoperative leakage of ascites through the mesh.[8,14,15] In 2010, however, a randomized controlled trial conducted by Ammar et al. showed that mesh repair was superior to suture repair with respect to recurrence (2.7% vs 14.2%, $P < 0.05$)

in patients with liver cirrhosis who underwent umbilical hernia repair outside the LT setting.[16] However, in that study, mesh repairs were more likely to become infected (16.2% vs. 8.5%), but this result was not statistically significant.[16] In the current study, one of the two patients who underwent mesh repair suffered wound infection, which was treated locally; neither patient suffered hernia recurrence.

In conclusion, this study shows high recurrence rates of umbilical hernia repairs during LT and it suggests that correction during LT using a separate infra-umbilical incision leads to fewer recurrences of umbilical hernias during follow-up compared to correction of the umbilical hernia from within the abdominal cavity without a separate incision. Future studies, preferably randomized multicenter studies with standardized operation techniques using non-absorbable sutures and more liberal use of prosthesis in the absence of septic complications, are warranted to provide more robust evidence for the difference in recurrence and allow for adjusting for possible confounders.

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CHAPTER 9

Incisional hernia after liver transplantation: Risk factors and health-related quality of life

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ABSTRACT

The aim of this cross-sectional study was to analyze the incidence of incisional hernia after liver transplantation (LT), to determine potential risk factors for their development and to assess their impact of incisional hernia on health-related quality of life (HRQoL).

Patients who underwent LT through a J-shaped incision with a minimum follow-up of 3 months were included. Follow-up was conducted at the outpatient clinic. Short form 36 (SF-36) and body image questionnaire (BIQ) were used for the assessment of HRQoL.

A total of 140 patients was evaluated. The mean follow-up period was 33 (SD 20) months. Sixty patients (43%) were diagnosed with an incisional hernia. Multivariate analysis revealed surgical site infection (OR 5.27, $p = 0.001$), advanced age (OR 1.05, $p = 0.003$), and prolonged ICU stay (OR 1.54, $p = 0.022$) to be independent risk factors for development of incisional hernia after LT. Patients with an incisional hernia experienced significantly diminished HRQoL with respect to physical, social, and mental aspects.

In conclusion, patients who undergo LT exhibit a high incidence of incisional hernia, which has a considerable impact on HRQoL. Development of incisional hernia was shown to be related to surgical site infection, advanced age and prolonged ICU stay.

INTRODUCTION

Liver transplantation (LT) has evolved from a life-saving operation with high mortality in the 70's and 80's of the past century to a standardized procedure with a reported 1-year survival rate of over 90%, depending on the initial indication.[1,2] During this evolution, focus has shifted from preventing peri-operative mortality and major complications to managing long-term side-effects of immune suppressive therapy and improving quality of life after LT.[3-6]

With improved long-term survival after LT, incisional hernia has become a frequently diagnosed and clinically more relevant complication with incidences varying between 1.7 and 34.3%.[7-16] Incisional hernias form not only an aesthetic problem, but they may also reduce quality of life and can lead to serious morbidity due to incarceration or strangulation.[16-18] Therefore, prevention of this late complication has become increasingly important. Many causative factors for incisional hernias have been identified retrospectively in patients after LT: recipient's age, male sex, body mass index (BMI), indication for transplantation and underlying liver disease, pulmonary complications, wound infections, number of reoperations, immunosuppressive regimen, and incision type.[14,16,19,20]

Traditionally, the classic 'Mercedes Benz star' incision or 'rooftop' incision was used predominantly to perform LT. More recently, smaller incisions like a subcostal incision with or without a mediocranial extension ('J-shaped' or 'hockey-stick' incision) are now preferred, since they have been shown to provide adequate access for LT with presumably less abdominal wall trauma, resulting in a reported lower incidence of incisional hernia.[1,11,21,22]

Prospective data on independent risk factors for the development of incisional hernia after LT are sparse and none have evaluated the impact of incisional hernia after LT on health-related quality of life (HRQoL). The aim of this cross-sectional study was to assess the incidence of clinically detectable incisional hernias, to evaluate risk factors for the development of incisional hernia, and to determine the impact of incisional hernia on HRQoL in patients all of whom underwent LT through a J-shaped incision.

METHODS

A cross-sectional study was performed of patients who underwent LT between January 2004 and November 2010 at the Erasmus University Medical Center. All patients who

underwent LT through a J-shaped incision with a minimum follow-up of 3 months were asked to participate in the study and invited to the outpatient clinic for a physical examination. The medical ethics committee at Erasmus University of Rotterdam approved the study, and written informed consent was obtained from all participants. All patients who participated in the study were examined by an experienced surgeon to assess the incidence of incisional hernias after LT. In each patient, the physical examination was performed in both a supine and erect position, in rest and during the Valsalva maneuver. Incisional hernia was defined as a palpable defect in the abdominal wall of the incision used for LT, performed during the initial study period, resulting in a herniation of abdominal contents. If an incisional hernia was diagnosed, data on hernia location, hernia size and if corrected data on recurrence were collected. If patients underwent repair of an incisional hernia, a flat heavyweight polypropylene mesh was used if gross contamination was not present at the time of correction. This mesh was placed in the pre-peritoneal plane preferably. Antibiotic prophylaxis was administered to prevent infection of the prosthesis.

The J-shaped incision, consisting of a right subcostal incision combined with a mediocranial extension towards the xyphoid, was used primarily to gain access to the abdominal cavity in all cases. Routinely, a table-mounted abdominal wall retractor (Thompson Surgical Instruments, Incorporated, Traverse City, MI, USA) was used during the entire procedure. At completion of the procedure the abdominal wall fascia was closed by a single-layer mass closure technique with a running, slowly absorbable, monofilament suture loop (PDS 0, Ethicon). The skin was closed using intracutaneous running absorbable monofilament sutures (Monocryl 4.0, Ethicon). Thirty minutes preoperatively, a single dose Cefalozine (1500mg) was administered as antibiotic prophylaxis unless another antibiotic regimen was prescribed because of earlier infections in the patient's recent medical history. An additional dose of Metronidazole (500 mg) in case of expected bilioenteric reconstruction. When patients had considerable ascites at the first exposure of the abdominal cavity, passive abdominal drainage was only performed after LT. No T-tubes or stents were used during the biliary reconstruction. All biliary reconstructions were duct-to-duct unless primary sclerosing cholangitis or another disease was present affecting the extrahepatic bile duct. In these patients a bilio-enteric reconstruction was created, using a Roux-en-Y loop. Relaparotomies were always performed through the same incision created during LT. Postoperatively, dual or triple immunosuppressive therapy consisting of low-dose steroids, and Tacrolimus (Prograf, Astellas Pharma) and/or Mycophenolate Mofetil (MMF, CellCept, Roche), was administered for three months. All patients were withdrawn from steroid therapy except those with an underlying immune-regulated liver disease.

Patient characteristics and clinical data were collected prospectively in the search for potential risk factors, including: age, sex, underlying liver disease, cardiovascular diseases (cardiac arrhythmia, ischemic heart disease or other cardiovascular disease), chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM), medical history of other hernia (inguinal-/umbilical hernia/acute dehiscence), Body Mass Index (BMI) at time of LT, Child-Turcotte-Pugh (CTP) score at time of LT, Model of End-stage Liver Disease score based on laboratory findings solely at the time of LT (labMELD), intraoperative presence of ascites, procedure time of LT, intra-operative blood loss, length of hospital stay, length of postoperative intensive care unit (ICU) admission, immunosuppressive regimen (dual or triple), postoperative complications including wound complications, surgical site infection, pneumonia, biopsy-proven acute graft rejection, and number of relaparotomies.

To compare HRQoL among patients with an incisional hernia after LT to those without, patients were asked to fill in quality of life questionnaires, the Short Form (36) Health Survey (SF-36) and the Body Image Questionnaire (BIQ) prior to physical examination.[23-25] The SF-36 consists of 36 items that allow measurement of eight health domains, including: physical functioning, physical role functioning, bodily pain, general health perception, vitality, social functioning, emotional role functioning, and mental health.[25] In addition, physical and mental health are scored with the SF-36 physical component summary and SF-36 mental component summary, respectively. SF-36 scores range from 0 to 100, with higher scores implying a better quality of life.

The BIQ consists of eight items evaluating body image and cosmetics after surgery, and two items evaluating self-confidence.[23-25] The body image scale measures patients' perception of and satisfaction with their own body and it explores patients' attitude towards their bodily appearance (items 1, 2, 3, 4, 5); each item can be awarded 1 to 4 points (1 = "no, not at all" to 4 = "yes, extremely"). The cosmetic scale assesses the degree of satisfaction of the patient with respect to the physical appearance of the scar (items 6–8); item 6 ranges from 1 ("very unsatisfied") to 7 ("very satisfied"), item 7 ranges from 1 ("revolting") to 7 ("beautiful") and item 8 is a scoring scale from 1 to 10, with higher scores implying more satisfaction. Two items (9, 10) evaluate self-confidence of the patient *before* and *after* LT; both items can be awarded 1 to 10 points (1 = "not very confident" to 10 = "very confident").

Statistical analysis

SPSS 17.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Chi-square test, Mann-Whitney U-test and independent sample t-test were used for categorical, continuous variables and analysis of quality of life. Univariate and multivariate analy-

ses of various factors were performed with logistic regression analysis to determine HRQoL, potential and independent risk factors for the occurrence of incisional hernia. In univariate and multivariate analysis, risk factors were adjusted for length of follow-up; SF-36 components and BIQ questions were adjusted for age and sex. Values were considered statistically significant at p-values less than 0.05.

RESULTS

Of all 201 patients who were transplanted through a J-shaped incision, 140 provided informed consent and were examined. The remaining 61 were deceased (n = 40) or emigrated/refused to participate (n = 21) and could not be included. Patient characteristics and clinical data are set out in table 1. The mean follow-up period was 33 (SD 20) months. Sixty patients (43%) were diagnosed with a clinically detectable incisional hernia after physical examination. Twenty-one of those 60 incisional hernias (35%) were located in the subxyphoidal part of the incision, 18 (30%) were located in the middle part of the incision, and 9 (15%) were located laterally. In 12 patients (20%) the incisional hernia was located at more than one location. The mean diameter of the incisional hernia was 3.4 cm (SD 5.5).

Ten of the 60 patients (17%) who developed an incisional hernia underwent hernia repair during follow-up; eight patients of these ten were operated electively and one patient in an emergency setting due to incarceration of the small bowel after a mean follow-up of 17 months (SD 12). Furthermore, four patients underwent acute dehiscence repair after LT. All four patients developed an incisional hernia after acute dehiscence repair during follow-up; one of these four patients underwent an elective incisional hernia repair 19 months after LT. In all incisional hernia repairs a mesh was used. Two patients developed an infection of the mesh; in both cases the infected mesh had to be removed.

Univariate analysis (adjusted for follow-up duration) demonstrated age (p = 0.02), preoperative BMI (p = 0.012), ICU stay (p = 0.022), surgical site infection (p = 0.004), and hernia in the medical history (p = 0.036) to be potential risk factors for development of incisional hernia after LT. Sex (p = 0.133), follow-up time (p = 0.076), labMELD score at time of LT (p = 0.423), relaparotomy frequency (p = 0.057), immunosuppressive regimen (p = 0.772), and biopsy-proven acute graft rejection (p = 0.078) were not identified as risk factors for incisional hernia after LT. (Table 2)

Table 1. *Patient characteristics and clinical data.*

Characteristics	*Total (n = 140)*
Sex, (%)	
Male	90 (64)
Female	50 (36)
Age (years), mean (SD)	49 (12)
Body mass index (at LT), mean (SD)	26 (4)
Follow-up (months), mean (SD)	33 (20)
Total # with Liver Disease, (%)	
Hepatitis	41 (29)
Alcoholic	30 (21)
HCC	33 (24)
Cryptogenic	13 (9)
PSC	37 (26)
PBC	5 (4)
Autoimmune	2 (1)
Acute liver failure	20 (14)
Budd-Chiari syndrome	1 (0.7)
Other	10 (7)
Child Pugh Score, (%)	
A	24 (17)
B	57 (41)
C	59 (42)
labMELD, median (range)	15 (6-40)
Preoperative ascites, (%)	93 (66)
Procedure time LT (min), median (range)	441 (254-822)
Blood loss (liter), median (range)	3.2 (0.1-25.0)
Duration hospital stay (days), median (range)	20 (10-77)
Duration ICU stay (days), median (range)	4 (2-70)
Relaparotomy, (%)	53 (38)
Immunosuppressive regimen, (%)	
Dual	29 (21)
Triple	111 (79)
Acute graft rejection, (%)	30 (21)
Surgical site infection, (%)	28 (20)
Diabetes, (%)	45 (32)
Cardiovascular disease, (%)	42 (30)
COPD, (%)	12 (9)
Other hernia in medical history, (%)	47 (34)

LT, liver transplantation; PBC, primary biliary cirrhosis; labMELD, Model of End-stage Liver Disease, only based on laboratory variables; COPD, Chronic obstructive pulmonary disease; Other hernia in medical history includes: inguinal-/umbilical hernia/acute dehiscence.

Table 2. *Univariate analysis: potential risk factors for incisional hernia development.*

	Patients with IH (n = 60)	*Patients without IH (n = 80)*	*p – value**
Follow-up (months), mean (SD)	37 (19)	31 (20)	0.076
Sex, mean (SD)			
Male	43 (72)	47 (59)	0.113
Female	17 (28)	33 (41)	
Age (years), mean (SD)	51 (10)	47 (14)	0.020
Body mass index (at LT), mean (SD)	26 (5)	25 (4)	0.012
labMELD, median (range)	11 (6-40)	11 (6-40)	0.423
Surgical site infection, percentages (%)	19 (32)	9 (11)	0.004
Relaparotomy, percentages (%)	28 (47)	25 (31)	0.057
Duration ICU stay (days), median (range)	5 (2-70)	4 (2-46)	0.022
Immunosuppressive regimen, percentages (%)			
Dual	13 (22)	16 (20)	0.772
Triple	47 (78)	64 (80)	
Acute graft rejection, percentages (%)	8 (13)	22 (28)	0.078
Other hernia, percentages (%)	26 (43)	21 (26)	0.036

**p-values are adjusted for follow-up duration. IH, incisional hernia; LT, liver transplantation; labMELD, Model of End-stage Liver Disease, only based on laboratory variables; Other hernia in medical history includes: inguinal-/umbilical hernia/acute dehiscence.*

Multivariate logistic regression analysis after adjustment for follow-up duration revealed surgical site infection (OR 5.27, 95% CI 1.94 to 14.35; p = 0.001), older age (OR 1.05, 95% CI 1.02 to 1.09; p = 0.003) and prolonged ICU stay (OR 1.54, 95% CI 1.06 to 2.22; p = 0.022) to be independent risk factors for incisional hernia in patients who underwent LT through a J-shaped incision.

A total of 122 patients (87%) completed quality of life questionnaires. Patients with an incisional hernia scored significantly lower (i.e. experienced worse quality of life) on the SF-36 components: physical role functioning (p = 0.026), vitality (p = 0.004), social functioning (p = 0.002), emotional role functioning (p = 0.005), mental health (p = 0.042) and mental component summary (p = 0.001). (Table 3)

Patients with an incisional hernia after LT were significantly less satisfied with the body image (p = 0.016). These patients answered significantly less favorably the item: "*Do you think the surgery has damaged your body?* " (p = 0.007). Patients with an incisional hernia after LT also scored significantly lower on the cosmetic scale (p = 0.033). These patients answered significantly less favorably the item: "*How satisfied are you with your scar?"* (p = 0.036). Within the group of patients with an incisional hernia, no difference in HRQoL was observed with regard to the location of the diagnosed incisional hernia.

Table 3. *Mean SF-36 scores and SD for patients with and without an incisional hernia.*

Short form 36 component	*Patients with IH*			*Patients without IH*				
	N	**Mean**	**SD**	**N**	**Mean**	**SD**	**p - value***	**(p – value)**
Physical functioning	54	65.9	26.2	65	73.2	28.0	0.053	0.204
Role physical	51	43.6	42.4	60	62.9	42.6	**0.026**	**0.020**
Bodily pain	53	72.3	26.7	65	79.2	24.2	0.149	0.113
General health perceptions	54	52.5	23.2	65	58.0	22.8	0.139	0.197
Vitality	54	51.9	22.6	65	63.5	18.9	**0.004**	**0.003**
Social functioning	54	66.9	26.5	66	80.1	23.3	**0.002**	**0.003**
Role emotional	50	68.7	44.9	61	90.7	26.1	**0.005**	**0.003**
Mental health	54	73.5	18.3	65	79.9	17.0	**0.042**	**0.028**
Physical component summary	50	41.4	11.5	59	44.8	10.9	0.138	0.137
Mental component summary	50	48.2	11.7	59	54.9	8.4	**0.001**	**0.001**

** Mann-Whitney U test (univariate); p-values after adjustment for age and gender (multivariate) are shown in parentheses; SF 36, short form 36; SD, standard deviation; IH, incisional hernia.*

Multivariate analysis of SF-36 components, the body image scale and the cosmetic scale, after adjustment for age and gender, did not change the results significantly, except for the body image item: *"Is it difficult to look at yourself naked?"* After adjustment for age and sex, patients with an incisional hernia scored significantly more points (i.e. had more difficulty looking at their body naked, p = 0.016). (Table 4)

Table 4. *Mean BIQ scores with SD for patients with and without an incisional hernia.*

Body image questionnaire		*Patients with IH*			*Patients without IH*			
	Scale	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**p - value***	**(p – value)**
Body image									
Are you less satisfied with your body since the surgery?	1-4	51	1.9	1.1	63	1.6	0.8	0.132	0.055
Do you think the surgery has damaged your body?	1-4	51	2.0	0.8	62	1.6	0.6	**0.007**	**0.003**
Do you feel less attractive as a result of your surgery?	1-4	50	1.7	0.9	63	1.5	0.7	0.237	0.203
Do you feel less feminine/ masculine as a result of your surgery?	1-4	51	1.4	0.8	62	1.2	0.6	0.088	0.121
Is it difficult to look at yourself naked?	1-4	51	1.6	0.9	63	1.3	0.6	0.073	**0.016**
Cosmesis									
On a scale from 1 to 7, how satisfied are you with your scar?	1-7	51	4.5	1.9	63	5.2	1.9	**0.036**	**0.022**
On a scale from 1 to 7, how would you describe your scar?	1-7	51	4.2	1.5	62	4.7	1.4	0.102	0.075
Could you score your own scar on a scale from 1 to 10?	1-10	55	6.1	2.7	75	6.2	3.4	0.268	0.590
Self-confidence									
*How confident were you **before** your operation?*	1-10	54	6.7	2.8	75	5.9	3.4	0.353	0.317
*How confident were you **after** your operation?*	1-10	55	6.0	3.0	76	5.9	3.5	0.501	0.945
Body image scale	5-20	51	16.5	3.6	63	18.0	2.4	**0.016**	**0.009**
Cosmetic scale	3-24	51	15.3	4.9	63	17.1	4.3	**0.033**	**0.016**

*Mann-Whitney U test (univariate); p-values after adjustment for age and gender (multivariate) are shown in parentheses; BIQ, body image questionnaire; SD, standard deviation; IH, incisional hernia.

DISCUSSION

This cross-sectional study shows that patients who undergo LT through a J-shaped incision have a high incidence of incisional hernia and that these patients experience diminished HRQoL compared to those who do not develop an incisional hernia. Furthermore, the presence of an incisional hernia was shown to be related to surgical site infection, older age and prolonged ICU stay. These results underscore the importance of this late complication in patients after LT. Especially, because these patients are often not considered to be at high risk typically for an incisional hernia in contrast to patients with obesity or abdominal aneurysms.[25-31] Poor preoperative nutritional status, long duration of the operation, poor immunologic status due to postoperative immunosuppressive medication and the underlying liver disease in patients undergoing LT could all contribute.

Incisional hernias after LT have been reported with growing incidence in recent years, reflecting improved survival after LT and probably greater awareness of the development of incisional hernias.[11,14-16,21] However, in contrast to the current study, several studies have shown lower incidences of incisional hernia after LT.[12,13,20,22] If incisional hernias are asymptomatic, it is conceivable that patients are often not examined with a specific focus on incisional hernias at the outpatient clinic, which could have led to an underestimation of the incidence in these studies. Furthermore, diagnosing abdominal wall hernias retrospectively solely based on questionnaires have also been shown to be unreliable and follow-up must be done by physical examination.[32] Therefore, all patients included in this study underwent physical examination with a special focus on incisional hernia.

A recent retrospective study also reported a high overall incidence (32.4%) of incisional hernias after LT.[16] The authors identified early use of mammalian target of rapamycin inhibitors as the most important independent risk factor for incisional hernia development after LT. The current study reports an even higher incidence of incisional hernia but without use of this immunosuppressive regimen. In addition to rapamycin, Montalti et al. identified MELD scores higher than or equal to 22 and male sex as independent risk factors for the development of incisional hernia after LT.[16] Whereas, the current study identified surgical site infection, older age and prolonged ICU stay as risk factors related to incisional hernia development after LT, which is more in line with previous studies of risk factors for incisional hernia development after abdominal surgery for other indications.[14,20,22]

In this cross-sectional study, 20% of patients developed surgical site infections. Several studies suggested PSC as risk factor for surgical site infections after LT due to the frequent presence of infected bile and the need for bilioenteric anastomoses in the majority of these transplant patients.[33-35] However, the association between PSC and the presence of surgical site infections could not be found in this study. Infection of the surgical site is already considered to be an important risk factor contributing to the development of incisional hernia in non-transplant patients.[18,36,37] This study provides evidence that surgical site infections are the most important risk factor for the development of incisional hernias in LT patients as well. Negative effects of immunosuppressive therapy after LT on the patient's immune system can further contribute to the high incidence of surgical site infections and therefore the increased incidence of incisional hernia due to disturbed and delayed wound healing in the early postoperative period after LT.[3,14] However, intensity of immunosuppressive therapy could not be verified as an independent risk factor for the development of incisional hernia after LT in the current study.

Aging is also associated with a decline in many functions of the immune system.[38] It has been argued that changes in the immune system may lead to more surgical site infections.[39] Although, the current study found older age to be an independent risk factor for incisional hernia development in patients after LT, changes in the immune system leading to infection in patients of older age are not fully understood.[38,39] This has also been suggested, but not as independent risk factor, in an earlier study by Gomez et al.[19]

Malnutrition, with an incidence of up to 40% of patients in the ICU, is shown to be associated with impaired immune function, impaired ventilatory drive, and weakened respiratory muscles, leading to prolonged need for ventilator support in critically-ill patients.[40] This might explain the association found in the current study between prolonged ICU stay and incisional hernia development after LT. Muller et al. also suggested this association in an earlier report.[1]

Although most incisional hernias in patients included in this study were without symptoms, HRQoL assessed by both SF-36 and BIQ (body image scale *and* cosmetic scale) revealed impaired outcomes for patients with an incisional hernia after LT compared to those without an incisional hernia. Patients with LT and an incisional hernia experienced worse HRQoL as given by the SF-36 components: physical role functioning, vitality, social functioning, emotional role functioning, mental health and mental component summary and were reported to be generally less satisfied according to both the body image scale and the cosmetic scale. The highest impact on HRQoL

according to the SF-36 was observed for the component 'role emotional', which scored 22 points lower on a 0 – 100 scoring scale in the presence of an incisional hernia in patients after LT. Patients suffering from an incisional hernia were reported to be less satisfied with their scar. This negative impact of incisional hernias after LT on HRQoL further underscores the importance of prevention of this complication.

In the current study, only patients operated through a J-shaped incision with a minimum follow-up of 3 months were included. In our institution the J-shaped incision is considered to be the optimal incision since it combines minimal abdominal wall trauma with sufficient access to the abdominal cavity to perform LT safely. The optimal incision to perform an LT however is still a subject of debate.[11,16,22] It is hypothesized that this small incision may also have contributed to the high incidence of incisional hernias in the current study because of increased mechanical strain on the wound due to wound retractors, necessary to provide adequate access.[1] Therefore, conversion of the J-shaped incision into the Mercedes incision may be of additional value in specific cases, such as very obese patients, in order to provide an adequate access but to avoid the wound damage caused by excessive traction. It may also be that in the current study, in contrast to other studies, irrespective of which incision type was used, the higher incidence can be explained by the fact that all incisional hernias were diagnosed and addressed because of the special focus on finding an incisional hernia. This may also have contributed to the high rate of elective incisional hernia repairs in this study. Unfortunately, the optimal incision type, that combines adequate access to the suprahepatic inferior vena cava, liver hilum and both liver lobes with prevention of long-term complications, such as incisional hernias after LT, remains to be determined, just like the optimal closing technique. As reported in this study, 65% of the incisional hernias diagnosed, were located in the subxyphoidal part and in the middle part of the incision. Presumably, in the J-shaped incision, the point of higher tension is at the junction of the subcostal incision with the midline incision. Therefore, it might be advantageous to apply one additional stich using a non-absorbable/absorbable suture in this point in order to reinforce the closing, as a possible measure to decrease the incidence of the incisional hernia using the J-shaped incision. Randomized controlled trials on incision types, closure techniques, and prophylactic mesh use and studies that focus on prevention of surgical site infections are needed to tackle this often underestimated complication after LT.

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CHAPTER 10

General discussion and future perspectives

Inguinal hernia repair is the most frequently performed general surgical procedure worldwide.[1,2] The incidence of inguinal hernias is positively correlated with the patients' age.[3] With advancing age, there is a disbalance in collagen synthesis towards more collagen degradation and less collagen formation and cross-linking.[4-7] On the other side of the age spectrum, very young patients are also at risk for developing an inguinal hernia. The reason for this increased risk is the presence of a patent processus vaginalis which seems not only associated with congenital inguinal hernias in premature born infants, but also associated with indirect inguinal hernias which are acquired later in life.[8,9] Other factors that are found to be associated with the incidence of inguinal hernias are male sex, smoking, diabetes mellitus, physical activities, and a positive family history.[3,10-17] In a post-hoc analysis of a large population based cohort study, we focussed on incidence and risk factors for inguinal hernias in men aged 45 years and older. The hazard ratio was approximately 2 in men aged 75 years and older compared to men aged under 65 years. Literature suggests that excess body weight is associated with an increased risk of inguinal hernias, because it is believed to affect the intra-abdominal pressure.[18] Interestingly, subgroup analysis in our study showed that a BMI over 30 kg/m^2 was associated with a lower incidence of inguinal hernia compared to participants with a BMI under 25 kg/m^2. These results were supported by data of two earlier published large population based cohort studies.[3,14]

As mentioned before the incidence of an inguinal hernia increases with age, especially in men from the fifth to the seventh decade of life. Interestingly, in this population more than one-third of inguinal hernias are reported to be mildly symptomatic or asymptomatic at first presentation.[19-21] Two randomized trial already focussed on the role of a watchful waiting strategy compared to elective surgery in treatment of men with minimally symptomatic inguinal hernias. These trials, however, could not show superiority of one treatment over the other with respect to inguinal hernia pain or discomfort.[22,23] We decided to perform a non-inferiority trial comparing watchful waiting and elective repair of mildly symptomatic or asymptomatic inguinal hernias with special focus on men aged 50 years and older. This specific group was chosen because they particularly have more concomitant diseases and usually tend to have less physical constraints in their daily activities compared to their younger and more mobile counterparts. It can be imagined that especially at this age the risk of complications due to the procedure may not outweigh the benefits of surgery if an inguinal hernia is asymptomatic at first presentation. Using a 0.20-point difference as a clinically relevant margin, it was hypothesized that watchful waiting was non-inferior to elective repair. The results of our trial showed that the mean pain/discomfort score over 24 months is on average 0.23 points lower in the elective repair group (95% CI -0.32 to -0.14). As such, our data could not rule out a relevant difference in favor of elective repair with

regard to the primary endpoint. Because the 95 percent confidence interval of the difference of means ranged from -0.32 to -0.14, a difference of the pre-defined margin of 0.20 points or greater cannot be excluded and, therefore our trial is inconclusive in this respect. Secondary endpoints included quality of life questionnaires which were slightly in favor of elective repair. These differences, however, were too small to be clinically relevant. About one-third of the patients, initially assigned to watchful waiting, crossed over to surgery. This was mostly driven by an increase in pain or discomfort and in only 2.3 percent of the patients an emergent repair had to be performed due to an incarceration. The long-term results of the earlier mentioned randomized trial reported crossover rates up to 80 percent in men aged over 65 years old after 10 years of follow-up.[19,24] It recommended surgical repair of asymptomatic inguinal hernias in medically fit men as most men will develop symptoms over time. However, subgroup analyses of our data found no differences in crossover rates between men aged 50-65 or 65 years and older. Although our data could not rule out a relevant difference in favor of elective repair with regard to the primary endpoint, we conclude , in view of all other findings, that our results justify watchful waiting as a reasonable alternative compared to surgery in frail patients.

The risk of an inguinal hernia is not only increased in middle-aged and elderly individuals, but also in the youngest amongst us.[25,26] Factors that are associated with an increased risk of inguinal hernias in premature born infants include a patent processes vaginalis, male sex, gestational age, low birth weight, and prolonged mechanical ventilation.[26,27] Many paediatric surgeons prefer to perform a herniotomy when the prematurely born infant reach a certain weight or age. Although this somewhat conservative approach may minimize the risk of surgical and anaesthetic complications, it might also increase the risk of incarceration forcing an emergency procedure with a potential risk of ischemia of the bowel or testicular atrophy.[26,28-32] In literature very little is known on timing of inguinal hernia repair in prematurely born infants. In our retrospective study we showed an association between very low birth weight (birth weight under 1500g) and risk of incarceration. Prematurely born infants of 1500 grams or less had a 3-fold greater risk of incarceration with subsequent emergent repair compared to prematurely born infants over 1500 grams.

Another group of frail individuals who are generally advised to refrain from surgery unless it is absolutely necessary are patients with liver cirrhosis and ascites. Patients with liver cirrhosis and refractory ascites have a 20 percent risk of developing an umbilical hernia during the course of their disease.[33] Possible factors that contribute to umbilical hernia formation in this group of patients include increased intra-abdominal pressure due to ascites, weakening of the abdominal wall due to muscle wasting as a

result of poor nutritional status and dilatation of the umbilical vein that enlarges the preexistent umbilical opening in patients with portal hypertension.[34] Currently there are no guidelines for umbilical hernia management and timing of repair in patients with liver cirrhosis and ascites. Again, surgical dogma dictates not to perform umbilical hernia repair in these patients.[35-37] However, refraining from umbilical hernia repair in patients with liver cirrhosis could lead to complications such as incarceration or strangulation of the bowel leading to emergency surgery.[38,39] Even a relative simple procedure such as the repair of an umbilical hernia could have deleterious effects on the remaining liver function. In these patients the timing of the umbilical hernia repair is also essential, because concordant progression of the cirrhosis could hamper the possibility of future surgery. Currently a randomized controlled trial is managed comparing watchful waiting and elective repair, which will provide evidence that will help to create guidelines for management of umbilical hernias in patients with liver cirrhosis and ascites.

In contrast to inguinal and umbilical hernias, incisional hernias are postoperative complications after abdominal surgery with incidences between 11 and 20 percent and even up to 35 percent in several high risk groups.[40-42] With improved long-term survival after liver transplantation, an incisional hernia has become a frequently diagnosed and clinically more relevant complication with reported incidences as high as 34 percent.[43,44] Factors that are found to be associated with incisional hernias after liver transplantation include age, male sex, body mass index, pulmonary complications, wound infections, immunosuppressive regimen and incision type.[45-48] Traditionally the classic 'chevron' incision (a bilateral subcostal laparotomy with medial extension) was the incision of choice to enter the abdominal cavity. More recently smaller incisions like a subcostal incision with or without a mediocranial extension (J-shaped incision) are preferred. The J-shaped incision still provides sufficient access to the abdominal cavity but with less abdominal wall trauma, which should theoretically reduce the incidence of incisional hernias.[44,49-51] Despite promising results of the J-shaped incision reported in an earlier published retrospective study, the incidence of incisional hernias found in our prospective study was unexpectedly high. An incidence of 43 percent was reported, while only 7 percent was found in the previous published retrospective study.[44] In contrast to prospective studies, it should be mentioned that retrospective studies on incisional hernias after surgery tend to underestimate the incidence of incisional hernias as most of the asymptomatic hernias are often not diagnosed and therefore not reported by those studies. Surgical site infections and age were found to be associated with the presence of an incisional hernia. Except for these factors, a clear explanation for the high incidence in this study could not be given. It was hypothesized that the increased mechanical strain on the laparotomy wound due

to wound retractors, which were used to provide adequate access to the abdominal activity, could have compromised vascularization and subsequent wound healing. The well vascularized abdominal wall, however, should provide sufficient wound healing in contrast to the aponeurotic closure in midline laparotomies. Recently, a randomized controlled trial focusing on the optimal suture technique after midline laparotomies showed that the small bites suture technique is more effective than the traditional large bites technique for prevention of incisional hernias in midline incisions.[52] In liver transplantation meticulous closure of the fascia is recommended to further reduce the incidence of incisional hernias.

To conclude, surgical repair of abdominal wall hernias such as the inguinal hernia, umbilical hernia and incisional hernia are the most frequently performed general surgical procedures worldwide and considered the ideal learning procedures for young residents. In a generally healthy population, the odds of serious complications due to the procedure are fairly low. However, there are groups of frail individuals who are more prone to complications and morbidity, even if it involves a procedure such as the one at hand. Refraining from surgery in these individuals however, could also lead to complications such as incarceration or strangulation of the bowel, which subsequently could result in emergency surgery with an even higher risk of serious complications. In these individuals, timing of the surgical procedure is essential, because concordant progression of the underlying disease (such as liver cirrhosis) could hamper the possibility of future surgery. As an example, even a relatively simple procedure such as the repair of an umbilical hernia could have deleterious effects on the remaining liver function in patients suffering from liver cirrhosis.

FUTURE DIRECTIONS AND POLICY IMPLICATIONS

History has taught us that knowledge of anatomy is the cornerstone of abdominal wall surgery and treatment of abdominal wall hernias. Abdominal wall surgery with all its anatomical complexities is still mostly practised by general surgeons and residents. But there is a growing tendency to perform abdominal wall and hernia surgery in dedicated hernia centers. Experts in the field of hernia surgery tend to have less complications compared to general surgeons and residents.[53] As this is still at an early stage, more extensive anatomical training by cadaver dissections and personal tuition for residents should be incorporated – especially in the beginning of their training, in order to lay a solid foundation, and later, further reduce preventable complications such as recurrent inguinal hernias and chronic pain as this is no longer acceptable in modern hernia surgery. As such, training modules for abdominal wall surgery for

residents should be designed and incorporated by these dedicated hernia surgeons. To improve knowledge and technical skills, abdominal wall hernia registration systems should be implemented to centralize data of patients with complex hernias from hernia centers, as these patients are currently operated by a few dedicated hernia experts with a tailor-made approach for each individual patient. Together we can further standardize care with regard to the numerous and still rising amount of techniques and materials. In modern times like these abdominal wall hernias with all its complexity should be considered and treated as a separate surgical entity and performed in hernia centers by dedicated experts in the field to further improve care of patients with (complex) abdominal wall hernias.

This thesis addresses some of the questions raised by the European Hernia Society in the latest draft of the upcoming guidelines on management of asymptomatic individuals with inguinal hernias. Our data conforms that the risk of complications – incarceration or strangulation of the bowel, following a watchful waiting strategy is low in asymptomatic individuals with inguinal hernias and, therefore, could be recommended safely. It provides information on the crossover rate from watchful waiting to surgery, which is mostly driven by an increase in pain or discomfort and not due to an emergent repair. The question then arises if most asymptomatic individuals with inguinal hernias will indeed develop symptoms over time and, will they also require hernia surgery in the future? This is a more difficult question to answer. One could argue that a substantial part of the asymptomatic or mildly symptomatic individuals with inguinal hernias are treated conservatively by their general practitioners and only a fraction of these patients are eventually referred to a hospital. The supposedly asymptomatic individuals that were included in our trial could therefore be more symptomatic compared to the population visiting their general practitioners. This could result in higher crossover rates as observed in our study. Nevertheless, our data still showed that the majority of patients randomized to watchful waiting remained asymptomatic and did not need surgery after 3 years of follow-up. One could argue that with more statistical power and the pre-defined margin of 0.20 points for the 4-point pain scale, we might be able to prove that elective repair is 'superior' compared to watchful waiting. Instead of just concluding this thesis with a standardized statement such as 'more extensive trials are needed to replicate our results', our methodology and results could be translated and add to the discussion on treatment of asymptomatic individuals with inguinal hernias. This should involve information on development on pain and discomfort and quality of life over time, which can be used for a more tailor-made approach in this group of patients in light of personalized medicine. Not only patient's health-related quality of life, but also life style and social factors should be incorporated in this shared decision-making process leading

up to the optimal decision in hernia management on the individual level – instead of focussing solely on group level results, which are likely to be small given our results, and more likely to be close to our cut off value of 0.2. For shared decision making, physicians need to communicate to the patient personalized information about the possible outcomes of their inguinal hernia management. Whether the magnitude of the expected benefit (e.g. the risk of incarceration or strangulation of the bowel leading to emergency repair) would outweigh the disadvantages of immediate inguinal hernia surgery (e.g. co-morbidities, risk of postoperative complications, recurrence, and chronic pain) can be discussed with the individual patient sitting in front of the physician in order to reach agreement on the inguinal hernia management.

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CHAPTER 11

Summary and conclusions

Abdominal wall surgery is comprised of surgical procedures used in the treatment of abdominal wall hernias. Abdominal wall hernias discussed in this thesis are inguinal hernias, umbilical hernias, and incisional hernias. In general, repair of these hernias are considered relatively simple procedures with a low risk of serious complications. There are, however, groups of frail patients prone to abdominal wall hernias due their age or underlying disease in which hernia repair should be carefully planned or sometimes avoided as not only surgery, but also a watchful waiting strategy can lead to serious complications. In **Chapter 1** a general outline of this thesis is given and the topic of abdominal wall surgery is introduced with a special focus on incidence, risk factors and hernia management in specific groups of frail patients.

The incidence of an inguinal hernia appears to increase with age, especially in men through the fifth to seventh decade of life. In **Chapter 2** the results on incidence and risk factors for inguinal hernias among Dutch males aged 45 years and older who participated in the Rotterdam Study are presented. A total of 416 incident cases (7.2%) of inguinal hernia in 5,780 male participants were found after a follow-up of more than 20 years. The age-adjusted hazard ratio was 12.4 in favour of men compared to women. Multivariate analysis showed ageing to be a risk factor for inguinal hernias with an increase in hazard of 1.03 per year. The hazard of an inguinal hernia almost doubled in men aged 75 years and older compared to men aged under 65 years. Increased body mass index showed to have a protective effect on inguinal hernias.

In **Chapter 3** the results of a multicenter randomized trial are described which compared watchful waiting to elective repair of asymptomatic or mildly symptomatic inguinal hernias in male patients aged 50 years and older after a follow-up of 3 years. Two hundred and thirty-four patients were randomized to elective repair and 262 to watchful waiting. Using a 0.20-point difference as a clinically relevant margin, it was hypothesized that watchful waiting was non-inferior to elective repair. The results of our trial showed a difference in means (watchful waiting minus elective repair) of -0.23 (95% CI -0.32 to -0.14) with regard to the primary endpoint (4-point pain and discomfort score) after 2 years of follow-up. Because the 95 percent confidence interval of the difference of means ranged from -0.32 to -0.14, a difference of 0.20 or greater cannot be excluded and, therefore, the trial was inconclusive in this respect. In the watchful waiting group 35.4 percent underwent inguinal hernia repair due to some degree of pain or discomfort and 2.3 percent required emergency surgery due to incarceration or strangulation of the bowel. Postoperative morbidity and mortality were comparable between the elective repair group and operated men initially assigned to the watchful waiting group. Recurrence rates of inguinal hernias were approximately 9.0 percent in both groups after 3 years of follow-up. No difference in

recurrence rates could be found between different surgical techniques, types of mesh and between participating centers.

The risk of an inguinal hernia is not only increased in the middle-aged and elderly, but also in the youngest amongst us. In **Chapter 4** risk factors for emergency surgery in prematurely born infants with an inguinal hernia were studied. In this retrospective study, data from 142 prematurely born infants (gestational age less than 37 weeks) who underwent inguinal hernia repair within 3 months after birth were analyzed. More than half of these prematurely born infants presented at the hospital with a symptomatic inguinal hernia, of which 55.7 percent required emergency surgery because of incarceration. Postoperative complication rates and recurrence rates were significantly higher in prematurely born infants following emergency surgery compared to prematurely born infants who underwent elective repair. Multivariate analysis showed 'very low birth weight' (birth weight of 1,500g or less) to be an independent risk factor with a 3-fold greater risk of incarceration with subsequent emergent repair compared to prematurely born infants weighing over 1,500 grams.

Another group of frail patients who are generally advised to refrain from surgery unless it is absolutely necessary are patients with liver cirrhosis and ascites. In **Chapter 5** an overview of morbidity and mortality for different non-hepatic procedures, including abdominal wall hernia repair in patients with liver cirrhosis is provided. The level of evidence of included studies in this review varied greatly. Postoperative mortality and morbidity were higher in patients suffering from liver cirrhosis compared to matched patients without liver cirrhosis who underwent non-hepatic surgery. In addition to the Child-Turcotte-Pugh (CTP) score the preoperative model for end stage liver disease (MELD) was found to be an adequate prediction model for assessment of the 30-day postoperative mortality in patients with liver cirrhosis after non-hepatic procedures (c-statistic = 0.80). With regards to abdominal wall hernia management, reported overall morbidity after elective umbilical hernia repair in patients with liver cirrhosis ranged between 7 and 20 percent and the overall mortality ranged between 0 and 5.5 percent. In the presence of portal hypertension or in case of emergency surgery, the results were even less favorable. In the presence of refractory ascites the risk of a recurrent umbilical hernia was increased with a relative risk of 8.5 percent after primary umbilical hernia repair. One randomized trial was performed comparing primary suture versus mesh repair in patients with liver cirrhosis. Recurrence rate was 2.7 percent in the mesh repair group compared to 14.2 percent in the primary suture group. In the mesh repair group the number of surgical site infections was almost doubled compared to the primary suture group. The percentage of surgical site infection was not significantly different between groups. The reported overall

morbidity after inguinal hernia repair was comparable to patients without liver cirrhosis. The overall mortality ranged between 0 and 2.7 percent. Complications after inguinal hernia repair appeared to be independent of CTP grade and not affected by the presence of (refractory) ascites. The majority of non-hepatic surgical procedures could be performed safely in patients with liver cirrhosis and low MELD scores or CTP grade A without portal hypertension. It was suggested that inguinal hernia repair could even be performed in patients with CTP grade C liver cirrhosis and in the presence of refractory ascites.

Patients with liver cirrhosis and refractory ascites have a 20 percent risk of developing an umbilical hernia in the course of their disease. In **Chapter 6** the results of a prospective study on the feasibility and safety of elective repair of an umbilical hernia in patients with liver cirrhosis and ascites are presented. A total of 30 patients underwent elective umbilical hernia repair. In 33 percent of patients a mesh was used. More than two-third of patients were classified as CTP grade B or C with a median MELD score of 12. Complications occurred in only 2 patients without negative sequelae. After a median follow-up period of 25 months 2 deaths occurred, of which none were related to the surgical procedure.

In **Chapter 7** the study protocol of a multicenter randomized controlled trial, which stems from the previously mentioned prospective study, is presented. This trial was designed to compare watchful waiting to elective repair of an umbilical hernia in patients with liver cirrhosis and ascites. The trial was designed to include a total of 100 patients to be randomized between the two strategies, stratified for participating center and MELD score. The primary endpoint consisted of a composite endpoint of overall morbidity related to the umbilical hernia treatment after 24 months of follow-up. Secondary endpoints included cumulative recurrence rate, classification of complications obtained during follow-up, pain and quality of life. The objective of this trial was to determine the superiority of elective repair to watchful waiting in management of umbilical hernias in patients with liver cirrhosis and ascites.

Candidates for liver transplantation who did not undergo umbilical hernia repair prior to the transplantation should be corrected during transplantation. In **Chapter 8** two different approaches for umbilical hernia repair during liver transplantation are compared. In a retrospective study patients who underwent umbilical hernia repair through a separate umbilical incision and patients who underwent umbilical hernia correction from within the abdominal cavity without a separate incision through the subcostal laparotomy wound used for the transplantation were compared. A total of 27 patients were included in the analysis with a mean MELD score of 17. In the group

in which the umbilical hernia was repaired through the laparotomy wound 40 percent of patients were diagnosed with a recurrent umbilical hernia compared to only 6 percent in the group in which a separate umbilical incision was used. The results of our study suggest that umbilical hernia repair during liver transplantation using a separate umbilical incision is associated with less recurrent umbilical hernias compared to repair from within the abdominal cavity through the subcostal laparotomy used for transplantation.

In contrast to inguinal and umbilical hernias, incisional hernias are postoperative complications after abdominal surgery. In **Chapter 9** the results of a cross-sectional study in which the incidence of an incisional hernia was assessed, identified potential risk factors are presented and its impact on quality of life after liver transplantation using a right-sided subcostal (J-shaped) incision was evaluated. The incidence of incisional hernias after liver transplantation through a J-shaped incision was 43 percent, which was 6 times higher compared to the retrospective data published prior to this study. Surgical site infection and age were found to be the most important risk factors for incisional hernias after liver transplantation.

CHAPTER 12

Dutch summary

Buikwandchirurgie omvat operatieve ingrepen ter behandeling van buikwandbreuken. De buikwandbreuken die in dit proefschrift worden besproken zijn liesbreuken, navelbreuken en littekenbreuken. In het algemeen worden operaties die bedoeld zijn om een buikwandbreuk te corrigeren als relatief simpele operaties beschouwd met een laag risico op ernstige complicaties. Er zijn echter groepen van kwetsbare patiënten bij wie chirurgische correctie van een buikwandbreuk zorgvuldig gepland of zelfs vermeden dient te worden omdat de keuze om wel of juist niet te opereren kan leiden tot ernstige complicaties. In **Hoofdstuk 1** wordt een overzicht van het proefschrift gegeven en wordt het onderwerp buikwandchirurgie geïntroduceerd. Er wordt daarbij in het bijzonder op incidentie, risicofactoren en behandeling (operatief of niet-operatief) van buikwandbreuken bij specifieke groepen van kwetsbare patiënten ingegaan.

De incidentie van liesbreuken lijkt toe te nemen met de leeftijd, met name bij mannen in de leeftijdsgroep van 50 tot 70 jaar. In **Hoofdstuk 2** worden de incidentie en risicofactoren van liesbreuken bij Nederlandse mannen van 45 jaar en ouder binnen de 'Rotterdam Study' beschreven. Er werden 416 liesbreuken gevonden bij 5780 mannelijke deelnemers (7.2%) gedurende een tijdsperiode van meer dan 20 jaar. In vergelijking met vrouwen is het risico op het krijgen van een liesbreuk zo'n 12 keer hoger – gecorrigeerd voor leeftijd. In een model waarin meerdere risicofactoren tegelijkertijd werden meegenomen, bleek dat met elk kalenderjaar de hazard (een maat voor het risico) op het krijgen van een liesbreuk met 3 procent toeneemt. De hazard met betrekking tot het krijgen van een liesbreuk was bijna twee maal zo hoog bij mannen van 75 jaar en ouder in vergelijking met mannen jonger dan 65 jaar. Een verhoogde 'body mass index' leek een beschermend effect op het ontstaan van een liesbreuk te hebben.

In **Hoofdstuk 3** worden de resultaten van een gerandomiseerde studie beschreven, waarin een afwachtend beleid versus een electieve operatieve behandeling vergeleken werd bij mannen van 50 jaar en ouder met een asymptomatische of mild symptomatische liesbreuk gedurende een periode van 3 jaar. In totaal hadden 234 mannen geloot voor operatie en 262 mannen voor een afwachtend beleid ten aanzien van hun liesbreuk. Vooraf werd bepaald dat een verschil van 0.2 punten op een 4-punts pijnschaal als klinisch relevant moest worden gezien. De resultaten van deze studie laten zien dat de waarschijnlijke werkelijke waarde van het verschil tussen opereren en afwachten met 95 procent betrouwbaarheid tussen de 0.14 en 0.32 punten ligt. Hoewel het lijkt dat een electieve operatie beter in termen van de genoemde pijnschaal is, kan niet worden uitgesloten dat het werkelijke verschil kleiner is dan 0.2 punten. In de groep van patiënten waarbij een afwachtend beleid werd gevoerd, onderging 35 procent van

de mannen alsnog een operatie door toename van ongemak en/of pijnklachten. Bij deze groep moest bij 2.3 procent vanwege een beklemde liesbreuk een spoedoperatie uitgevoerd worden. Het aantal postoperatieve complicaties bij de geopereerde groep en bij patiënten van de 'observatie' groep, die alsnog een operatie ondergingen, verschilden niet. Een recidief liesbreuk werd bij 9.0 procent van de deelnemers na 3 jaar follow-up vastgesteld, ongeacht de groep, waarvoor zij initieel hadden geloot.

Het risico op het krijgen van een liesbreuk is niet alleen verhoogd bij mannen van 50 jaar en ouder, maar ook bij pasgeborenen. In **Hoofdstuk 4** worden de risicofactoren voor een spoedoperatie met betrekking tot liesbreuken bij prematuur geboren baby's besproken. In dit retrospectieve onderzoek werden de statussen geanalyseerd van 142 prematuur geboren baby's (geboren na een zwangerschapsduur van minder dan 37 weken), bij wie een liesbreukoperatie binnen 3 maanden na de geboorte werd verricht. Meer dan de helft van de prematuur geboren baby's presenteerde zich in het ziekenhuis met een symptomatische liesbreuk waarvan bij ruim de helft een spoedoperatie in verband met een beklemde liesbreuk werd verricht. Het aantal postoperatieve complicaties en recidief liesbreuken waren significant hoger in de groep van prematuren na een spoedoperatie in vergelijking met de groep van prematuren bij wie een geplande liesbreukoperatie werd uitgevoerd. In de multivariate analyse was 'zeer laag geboortegewicht' (geboortegewicht van 1500 gram of minder) een risicofactor voor het ondergaan van een spoedoperatie als gevolg van een beklemde liesbreuk met een 3 maal hoger risico ten opzichte van prematuren met een hoger geboortegewicht (meer dan 1500 gram).

Een andere groep van kwetsbare patiënten, bij wie over het algemeen geadviseerd wordt om niet te opereren – tenzij absoluut noodzakelijk – zijn patiënten met levercirrose en ascites. In **Hoofdstuk 5** wordt een overzicht gegeven van de morbiditeit en mortaliteit bij patiënten met levercirrose na niet-hepatische chirurgie. In het overzicht worden ook patienten besproken die operaties ondergaan die niet de buikwand betreffen. De kwaliteit van de geïncludeerde studies in dit review varieerde sterk. Er werden bij patiënten met levercirrose een hogere postoperatieve morbiditeit en mortaliteit geobserveerd in vergelijking met patiënten zonder levercirrose na niet-hepatische chirurgie. In aanvulling op de Child-Turcotte-Pugh (CTP) score bleek het pre-operatieve model voor eindstadium leverziekte (MELD) score een betrouwbaar model voor de voorspelling van de 30-daagse postoperatieve sterfte in deze patiëntengroep (c-statistic = 0.80). In de beschreven studies varieerde de morbiditeit na een electieve navelbreukcorrectie tussen de 7 en 20 procent; de mortaliteit varieerde tussen 0 en 5,5 procent. Het risico op postoperatieve complicaties was nog hoger in de aanwezigheid van portale hypertensie of in het geval van een spoedoperatie bij

patiënten met levercirrose. In de aanwezigheid van refractaire ascites was het relatieve risico op een recidief navelbreuk na een primaire navelbreukcorrectie bijna 9 maal hoger in vergelijking met patiënten met levercirrose zonder refractaire ascites. Een gerandomiseerd onderzoek werd verricht bij patiënten met levercirrose, waarin een primaire navelbreukcorrectie met 'mesh repair', waarbij een polypropyleen mat wordt ingehecht in de verzwakte buikwand, vergeleken werd. Het percentage recidief navelbreuken was 2.7 procent in de groep met 'mesh repair' in vergelijking met 14.2 procent in de groep na primaire navelbreukcorrectie. In de groep met 'mesh repair' was het aantal wondinfecties bijna verdubbeld ten opzichte van de groep na primare navelbreukcorrectie; dit verschil was echter niet significant verschillend. De morbiditeit na liesbreukchirurgie bij patiënten met levercirrose was niet verhoogd in vergelijking met patiënten zonder levercirrose. De mortaliteit na liesbreukchirurgie varieerde tussen 0 en 2.7 procent. Het aantal complicaties na liesbreukchirurgie was onafhankelijk van de CTP score of de aanwezigheid van (refractaire) ascites.

Patiënten met levercirrose en refractaire ascites hebben een kans van 20 procent op het ontwikkelen van een navelbreuk gedurende het ziektebeloop. In **Hoofdstuk 6** worden de resultaten van een prospectieve studie over de haalbaarheid en de veiligheid van electieve navelbreukchirurgie bij patiënten met levercirrose en ascites beschreven. In totaal 30 opeenvolgende patiënten onderging een electieve navelbreukcorrectie. In een derde van de patiënten werd gebruik gemaakt van 'mesh repair'. Meer dan tweederde van de patiënten werd geclassificeerd als CTP score B of C met een gemiddelde MELD score van 12. Bij slechts 2 patiënten werden complicaties gezien met voorspoedig herstel, waarbij geen interventie noodzakelijk was. Er werd geen mortaliteit gerelateerd aan de navelbreukcorrectie gezien.

In **Hoofdstuk 7** wordt het onderzoeksprotocol van een gerandomiseerde studie gepresenteerd, die voortvloeide uit de eerder genoemde prospectieve studie. Deze studie werd ontworpen om observatie met electieve correctie van een navelbreuk te vergelijken bij patiënten met levercirrose en ascites. Het primaire eindpunt bestond uit een samengestelde eindpunt van totale morbiditeit gerelateerd aan de navelbreukbehandeling met een follow-up van 2 jaar. Secundaire eindpunten omvatten het totaal aantal recidief navelbreuken, de ernst van de complicaties, gerapporteerd tijdens de follow-up en geanalyseerd met behulp van de landelijke complicatie registratie, en kwaliteit van leven. Het doel van deze studie was om de superioriteit van een electieve operatieve behandeling ten opzichte van een afwachtend beleid van navelbreuken bij patiënten met levercirrose en ascites aan te tonen.

Patienten die nog een navelbreuk hebben terwijl ze een levertransplantatie ondergaan, hebben een groot risico op beklemming van die navelbreuk na de transplantatie. Dit komt mogelijk doordat er na de levertransplantatie minder ascites wordt gevormd, waardoor de buik samenvalt en er een risico bestaat dat de inhoud van de buik wordt 'gevangen' in de breukpoort. Het wordt dan ook geadviseerd om een dergelijke breuk tijdens de levertransplantatie te corrigeren. Dat kan op twee manieren. In **Hoofdstuk 8** werden deze twee verschillende benaderingen voor navelbreukcorrectie tijdens levertransplantatie vergeleken. In een retrospectieve studie werden patiënten geanalyseerd bij wie een navelbreukcorrectie via een aparte incisie onder de navel werd verricht en patiënten bij wie een navelbreukcorrectie vanuit de buikholte via dezelfde subcostale laparotomie, zoals gebruikt voor transplantatie, werd verricht. In totaal 27 patiënten werden geanalyseerd met een gemiddelde MELD score van 17. In de groep waarbij de breuk werd gecorrigeerd via de subcostale incisie werd in 40 procent van de patiënten door middel van een echo een recidief navelbreuk geconstateerd, in vergelijking met slechts 6 procent in de groep waarbij de navelbreukcorrectie werd verricht via een aparte incisie rond de navel. De resultaten van deze studie suggereerden dat een navelbreukcorrectie tijdens levertransplantatie via een aparte inciesie rond de navel met minder recidief navelbreuken geassocieerd was in vergelijk met correctie vanuit de buikholte via dezelfde subcostale laparotomie, zoals gebruikt voor levertransplantatie.

In tegenstelling tot een liesbreuk en een navelbreuk wordt een littekenbreuk als een postoperatieve complicatie na een buikoperatie beschouwd. In **Hoofdstuk 9** worden de resultaten van een crossectionele studie gepresenteerd, waarin de incidentie op, risicofactoren van en impact van littekenbreuken op de kwaliteit van leven na levertransplantatie met gebruik van een rechtszijdige subcostale ('J-vormige') incisie geëvalueerd werden. De incidentie van littekenbreuken was 43 procent na levertransplantatie door middel van een J-vormige incisie. Deze incidentie was 6 maal hoger dan in de retrospectieve data, voorafgaand gepubliceerd. In de multivariate analyse bleken 'wondinfectie' en 'leeftijd' de belangrijkste risicofactoren voor het krijgen van een littekenbreuk na levertransplantatie middels een J-vormige incisie te zijn.

About the author
PhD Portfolio
List of publications
Acknowledgements

ABOUT THE AUTHOR

Barry de Goede was born on November 5th 1986 in Vlaardingen. During his undergraduate years he participated in (inter)national level judo and at the age of 16 he attained the rank of first dan (black belt). After graduating from the 'Stedelijk Gymnasium Schiedam' in 2001, he started his academic career at the University of Utrecht at the Department of Pharmacy. In 2002 he attended medical school at the Erasmus University Medical Center. He simultaneously participated in the Netherlands Institute for Health Sciences (NIHES) Master program in clinical research which eventually resulted in a PhD position at the Liver Transplantation research group under supervision of prof.dr. H.J. Metselaar and prof.dr. G. Kazemier and the REPAIR research group under supervision of prof.dr. J. Jeekel and prof.dr. J.F. Lange, both at Erasmus University Medical Center. In 2015 he obtained his M.D. license, after which he started working as a surgical resident at the Department of Surgery at the IJsselland Hospital in Capelle a/d IJssel. He started his surgical residency in July 2016 at the IJsselland Hospital in Capelle a/d IJssel (supervisors: dr. I. Dawson and dr. B.P.L. Wijnhoven).

PhD PORTFOLIO

Research skills

2008 – 2011 Master of Science in Clinical Research, Netherlands Institute for Health Sciences (NIHES), Erasmus University Medical Center, Rotterdam, the Netherlands
Including a summer programme at Harvard School of Public Health, Harvard University, Boston Massachusetts, USA

Additional courses

2010 Basic course on regulations in clinical research

2010 Good clinical practice course

2010 Scientific English writing course

Teaching activities

2010 – 2012 Skills lab instructor, extracurricular classes on anatomy and surgical skills, Erasmus University Medical Center, Rotterdam, the Netherlands

(Inter)national conferences

2016 Watchful waiting versus surgery of mildly symptomatic or asymptomatic inguinal hernia in men aged ≥ 50 years, European Hernia Society, Rotterdam, the Netherlands – *Oral presentation*

2015 Very low birth weight is an independent risk factor for emergency surgery in premature infants with inguinal hernia, World Conference on Abdominal Wall Hernia Surgery, Milan, Italy – *Oral presentation*

2014 Een laag geboortegewicht is een onafhankelijke risicofactor voor het ondergaan van een spoedoperatie bij prematuur geboren kinderen met een liesbreuk, Najaarsdag, Nederlandse Vereniging voor Heelkunde, Utrecht, the Netherlands – *Oral presentation*

2013 Meta-analysis of glue versus sutured mesh fixation for Lichtenstein inguinal hernia repair, European Hernia Society, Gdańsk, Poland – *Oral presentation*

2013 Meta-analysis of glue versus sutured mesh fixation for Lichtenstein inguinal hernia repair, European Association of Endoscopic Surgery, Vienna, Austria – *Oral presentation*

2012 A meta-analysis of laparoscopic versus open cholecystectomy for patients with liver cirrhosis and symptomatic gallbladder stones, European Association of Endoscopic Surgery, Brussels, Belgium – *Oral presentation*

2012 A meta-analysis of laparoscopic versus open cholecystectomy for patients with liver cirrhosis and symptomatic gallbladder stones, European Society of Surgical Research, Lille, France – *Oral presentation*

2012 A meta-analysis of laparoscopic versus open cholecystectomy for patients with liver cirrhosis and symptomatic gallbladder stones, Chirurgendagen, Nederlandse Vereniging voor Heelkunde, Veldhoven, the Netherlands – *Oral presentation*

2012 A meta-analysis of laparoscopic versus open cholecystectomy for patients with liver cirrhosis and symptomatic gallbladder stones, International Liver Transplantation Society, San Francisco, California, USA – *Poster presentation*

2012 Non-hepatic surgery in patients with liver cirrhosis: A systematic review of the literature, American Hernia Society, New York, USA, – *Poster presentation*

2012 A prospective study on incidence and risk factors for incisional hernia in liver transplantation patients, Najaarsdag, Nederlandse Vereniging voor Heelkunde, Rotterdam, the Netherlands – *Poster presentation*

2012 Chirurgie in patiënten met levercirrose, Najaarsdag, Nederlandse Vereniging voor Heelkunde, Rotterdam, the Netherlands – *Oral presentation*

2011 A prospective study on incidence and risk factors for incisional hernia in liver transplantation patients, European Hernia Society, Gent, Belgium – *Oral presentation*

2011 A prospective study on incidence and risk factors for incisional hernia in liver transplantation patients, European Society of Surgical Research, Prague, Czech Republic – *Oral presentation*

2011 A prospective study on incidence and risk factors for incisional hernia in liver transplantation patients, International Liver Transplant Society, Valencia, Spain – *Poster presentation*

2011 A prospective study on incidence and risk factors for incisional hernia in liver transplantation patients, Bootcongres, Nederlandse Transplantatie Vereniging, Amsterdam, the Netherlands – *Poster presentation*

2010 A prospective study on elective umbilical hernia repair in patients with liver cirrhosis and ascites, European Hernia Society, Istanbul, Turkey – *Oral presentation*

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