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ANTERIOR CRUCIATE LIGAMENT INJURIES – STUDIES ON THE ADVERSE EVENTS AND LONG-TERM OUTCOMES

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Anterior cruciate ligament injuries - studies on the adverse events and long-term outcomes

Thesis for Doctoral Degree (Ph.D.)

By

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“Mistakes are portals of discovery“

James Joyce

Popular science summary of the thesis

The anterior cruciate ligament (ACL) is one of the important structures in the knee. It helps to keep the knee stable during physical activities like running, jumping and sporting. An ACL injury often happens during sports or activities that involve sudden stops, changing in directions or jumps. The most common sports where the ACL is injured in is football, handball and skiing.

A patient with a torn ACL can either be treated with physiotherapy aiming to strengthen the muscles around the knee or by surgery followed by physiotherapy. The recommended surgical option is ACL reconstruction (ACLR), where the surgeon uses a graft to replace the torn ligament. In Sweden, almost 4000 ACLRs take place each year.

This thesis focuses on the adverse events and long-term outcomes following an ACL injury.

Firstly, in order to identify the main adverse events regarding an ACL injury, the reasons for filing a compensation claim to the national insurance company (Löf) were investigated. Five hundred and thirty eligible claims were found in a 10-year period. Two thirds of the claims were accepted and the rest were rejected. The most common reasons for accepted claims where deep infections following ACLR, followed by surgical errors and delays in diagnosis and treatment.

Secondly, the consequences of deep infection following ACLR were investigated. Data from various national registries were used to identify the study participants. The outcome of surgery was evaluated using patients' questionnaires. The study showed that patients with deep infection have worse outcome and twice the risk of re-doing the surgery, compared to patients without infection.

Thirdly, the role of various infectious agents on the clinical presentation of deep infections were examined. The study showed variations in the duration between the surgery and the start of infection treatment and in the results of blood investigations that aid in monitoring the infection, depending on the causative infectious agent.

Lastly, the long-term results of early ACLR were investigated. The study showed that good outcome can be achieved when performing ACLR within 10 weeks after injury. However, there is a high risk of developing osteoarthritis after an ACL injury, and surgery does not seem to prevent that from happening.

Abstract

The overall aims of this thesis were to identify the main adverse events after anterior cruciate ligament (ACL) injuries, to study the clinical presentation and the consequences of the adverse event (post-operative septic arthritis), and to report the long-term outcomes of patients who underwent acute anterior cruciate ligament reconstruction (ACLR) and those who underwent delayed ACLR.

Study I investigated the reasons behind compensation claims filed to the patient insurance company (Löf) by patients with ACL injuries from 2005 to 2014. A total of 530 eligible claims were identified. 352 claims (66%) were accepted and 178 rejected. The most common reasons for accepted claims included post-operative septic arthritis, followed by suboptimal surgery and delays in diagnosis and treatment.

Study II examined patient-reported outcomes and the 5-year risk of revision surgery for patients who suffered from septic arthritis after ACLR. Patients found in the Swedish National Knee Ligament Register (SNKLR) with a primary ACLR using a hamstring or patellar tendon (n=23,075) were included from 2006 to 2013. 268 patients with septic arthritis were found by linking data from SNKLR with data from the Swedish national board of health and welfare. The results showed that patients with septic arthritis had worse scores of Knee injury and Osteoarthritis Outcome Score (KOOS) and the European Quality of life Five Dimensions index (EQ-5D) at all follow-up occasions. Additionally, the 5-year risk of revision was almost twice as high for the septic arthritis patients.

Study III, a subgroup analysis was performed for 158 patients with septic arthritis identified in Study I. The aim was to describe the clinical characteristics of the common infectious agents that cause septic arthritis following ACLR, in order to provide better understanding of their impact on the clinical presentation of the disease, with the objective of improving the diagnostic process. Coagulase-negative Staphylococci were responsible for the majority of the infections (60%), followed by Staphylococcus aureus and Cutibacterium acnes. Patients infected with Staphylococcus aureus had the highest CRP levels, and the shortest duration from the time of ACLR to the first irrigation and debridement operation.

Study IV analyzed the long-term outcomes of acute ACLR and delayed ACLR. 70 patients were randomized between 2006 and 2013 into two groups: acute ACLR within 8 days after injury and delayed ACLR after normalized range of motion (ROM) within 6-10 weeks after injury. 53 patients (out of 70) participated in a long-term follow-up with an average of 13 years after surgery. Satisfactory knee function was observed in both groups. No differences between the groups were found in terms of ROM, anterior knee laxity or isokinetic knee strength tests. KOOS pain and symptoms scores were worse (p=0.019, 0.008) for patients in the delayed group. 13 patients (30%) showed signs of OA in the index knee, compared to 4

patients (9%) in the contralateral knee. 10 patients (48%) in the delayed group showed signs of OA, compared to 3 patients (13%) in the acute group.

In conclusion, the most common reasons for accepted compensation claims after ACL injuries are post-operative septic arthritis, suboptimal surgery and delays in diagnosis and treatment. Patients with septic arthritis have poorer PROMs and higher 5-year risk of revision ACLR. Variations were observed in the clinical presentation of septic arthritis after ACLR depending on the causative infectious agent, with low-virulent agents being responsible for the majority of the infections. ACLR performed within 10 weeks after injury results in satisfactory long-term clinical and patient-reported outcomes but with an increased risk for osteoarthritis compared to the contralateral knee.

List of scientific papers

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. **Compensation claims following anterior cruciate ligament injuries reported to the patient insurance company in Sweden in 2005-2014**

   Osama Omar, Dzan Rizvanovic, Markus Waldén, Karl Eriksson, Björn Barenius, Anders Stålman

   Acta Orthopedica 93, 97–102. 2022/01/3

II. **Poorer patient-reported outcome and increased risk of revision at a five-year follow-up among patients with septic arthritis following anterior cruciate ligament reconstruction: a register-based cohort study of 23,075 primary anterior cruciate ligament reconstructions**

   Jesper Kraus Schmitz, Osama Omar, Adam Nordkvist, Henrik Hedevik, Per-Mats Janarv, Anders Stålman

   Knee Surgery, Sports Traumatology, Arthroscopy 31, 4090-4089, 2023/07/03

III. **Variations in the clinical presentation of septic arthritis following anterior cruciate ligament reconstruction based on the causative infectious agent: Insights from a nationwide case-series of 158 patients**

   Osama Omar, Jesper Kraus Schmitz, Karl Eriksson, Björn Barenius, Anders Stålman

   Submitted

IV. **Satisfactory long-term results with early anterior cruciate ligament reconstruction, but with an increased risk for osteoarthritis compared to the contralateral knee: A 13-year follow-up of a randomized controlled trial**

   Osama Omar, Alexander Hallgren, Tobias Wörner, Anders Stålman, Karl Eriksson, Björn Barenius

   Manuscript

Contents

List of abbreviations

ACL	Anterior cruciate ligament
ACLR	Anterior cruciate ligament reconstruction
ADL	Activity of daily life
AP	Anteroposterior
BMI	Body mass index
BPTB	Bone-patella tendon-bone
C.acnes	Cutibacterium acnes
CI	Confidence interval
CoNS	Coagulase-negative Staphylococci
EQ-5D	The European quality of life five dimension
I&D	Irrigation and debridement
ICD	International classification of diseases
IKDC	Internatioal knee documenation committee
KOOS	Knee injury and osteoarthritis outcome score
LSI	Limb symmetric index
MRI	Magnetic resonance imaging
OR	Odds ratio
PASS	Patient acceptable symptom state
PIN	Personal identification number
PL	Posterolateral
PROM	Patient reported outcome measure
ROM	Range of motion
S.aureus	Staphylococcus aureus
SD	Standard deviation
SNKLR	Swedish national knee ligament register
Qol	Quality of life

1 Introduction and background

1.1 Anatomy of the ACL

The knee joint is a hinge joint that consists of multiple structures that work together to provide movement and stability. The main articulation is between the femur and the tibia. The patella is a sesamoid bone that lies anteriorly and is attached to the quadriceps tendon and the patellar ligament and glides within the trochlea of the femur. The joint surfaces are covered with articular cartilage and the menisci serve as shock absorbers and play a role in the stability of the joint.

The stability of the knee is multifactorial. The anterior cruciate ligament (ACL) and the posterior cruciate ligament (PCL) help with sagittal stability, while the medial and lateral collateral ligaments help with side-to-side stability [94].

The ACL originates from the Intercondylar ridge of the eminences of the tibia and inserts to the medial wall of the lateral femur condyle. The attachments of the ACL are often called “footprints”. The ACL fibers are arranged in two bundles that are named for their relative attachment of the tibia: anteromedial (AM) and posterolateral (PL) [17, 32].

The length of the ACL has been estimated in the anatomical studies to be 31-38 mm and the width is 10-12 mm [85]. The blood supply of the ACL comes from the middle geniculate artery that originates from the popliteal artery [40]. The nerve supply comes from the posterior articular nerve which is a branch of the tibial nerve [13].

Good understanding of the anatomy of the ACL is important to be able to perform ACL reconstruction (ACLR).

1.2 Epidemiology of the ACL injury

The ACL injury is a common injury that usually takes place during sporting activities. The common mechanism of injury is non-contact sudden change of direction, pivoting or landing from a jump. The most common sports involved in ACL injuries in Scandinavia are football, alpine skiing and handball [31].

In Sweden, the incidence of ACL injury is 78/100 000 person-years, and around 50% of these injuries are treated with ACLR [58]. To compare, in the United States of America, it is estimated that over 200,000 ACL injuries take place each year, with around 60% of these injuries treated with ACLR [15].

The Swedish national knee ligament registry (SNKLR) reported a total of 4324 ACL surgeries registered during 2022 in their latest annual report. The average age of undergoing primary ACLR for has steadily increased from 26 in 2005 to 29 in 2022. The percentage of women who underwent either primary or revision ACLR between 2005 and 2022 is 44 % [70].

It is rare for the ACL injury to be an isolated injury. According to Olsson et al. [61], 88% of the ACL injuries were associated with concomitant structural injuries such as injury to the menisci, collateral ligament or the articular cartilage.

A systematic review by Wiggins et al. [93] showed that there is a 15% risk for a secondary ACL injury after the initial ACL injury. According to the same study, 7 % of the reinjuries tend to happen the ipsilateral side and 8% tend to happen on the contralateral side.

The risk of revision ACLR in the literature has been reported to be between 2.1% and 7.7% [33, 81].

1.3 Diagnosis of the ACL injury

The ACL injury should be suspected when patients present to the clinic with a swollen knee after a traumatic knee injury. Maffulli et al. showed that the ACL injury is the most common cause of acute hemarthrosis in the knee after an injury during sporting activities [49].

The typical patient's history would be injury during sporting with pivoting or hyperextension, usually followed by rapid swelling of the knee. Some individuals hear a "pop" sound. Stability tests are usually hard to perform during the acute phase due to pain, but should be performed when possible. Joint aspiration would reveal hemarthrosis and sometimes facilitate physical examination.

The most commonly used stability tests are Lachman tests, anterior drawer test and pivot shift test. Benjaminse et al. [11] reported that Lachman test has higher sensitivity in

detecting ACL injuries when compared to the pivot shift test. On the other hand, pivot shift test has very high specificity and poorer sensitivity in detecting ACL injuries.

Plain X-rays are usually normal in ACL injuries, but they may show a Segond fracture (avulsion fracture on the lateral aspect of tibial epiphysis), which is a pathognomonic sign of an ACL injury [86] (figure 1).

MRI is widely used for detecting ACL injuries due to its non-invasiveness and its ability to detect associated injuries like collateral ligament injuries, meniscus tears and cartilage injuries.

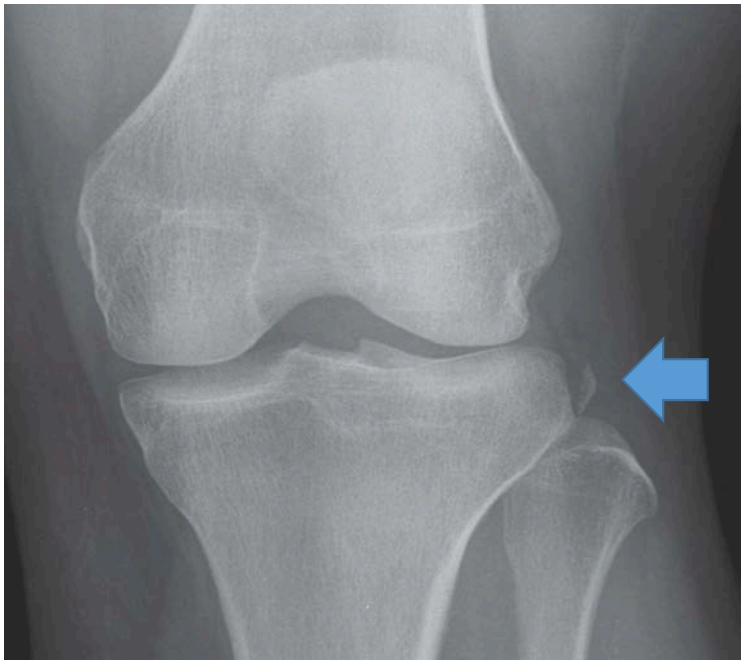

Figure 1. Plain x-ray examination for a patient with a Segond fracture “avulsion fracture on the lateral aspect of tibial epiphysis”, which is a pathognomonic sign of an ACL injury

1.4 Treatment of the ACL injury

The aim of treatment is to restore knee stability based on the specific physical demands and preferences of the patient, whether in daily life activities, work or sports.

The treatment options for the ACL-injured patient include either undergoing early ACLR followed by rehabilitation, or initializing rehabilitation as the primary therapy and considering ACLR if symptomatic instability persists. Approximately 50% of all ACL injuries in Sweden are treated with ACLR [70].

In general, there is an agreement among experts that patients who are highly active and wish to return to demanding physical activities should be offered an early ACLR. While patients with lower physical demands maybe recommended a period of structured physiotherapy initially, with the possibility of performing ACLR later [26].

In recent years, new studies have shown some promising results regarding primary ACL repair, a method that has been historically abandoned due to its poor outcome when compared to ACLR [44, 51, 88]. However, satisfactory long-term results are still lacking, and ACLR remains the main surgical treatment option for the ACL-injured patient.

1.4.1 Anterior cruciate ligament reconstruction (ACLR)

ACLR is performed by creating a new ligament using a graft. Grafts can either be autografts (taken from the patient's own tissue) or allografts (taken from a donor's tissue). The most commonly used grafts are hamstring, patellar and quadriceps tendon (figure 2).

The graft is positioned in the place of the old ACL and then fixed with screws, cortical buttons or other fixation methods. In 1980, David Dandy, a surgeon from the United Kingdom, performed the first arthroscopically assisted ACLR [30]. Since then, the technique has undergone significant advancements over the years.

1.4.2 Timing of the surgery

The literature from 1938 and 1950 focused on the importance of early surgical treatment of all ligament injuries, especially the ACL [60, 62]. In 1990, Shelbourne et al. reported higher risk of arthrofibrosis when surgery was performed within one week of the injury [79]. Consequently, it has been widely accepted since then to delay surgery until the range of motion of the knee is restored, at lease 3 weeks after the injury. However, more recent studies have shown that ACLR can be performed safely within one week of the injury [89].

Frobell et al. [28] published a randomized controlled trial in 2010 regarding the timing of surgery and concluded that a strategy of rehabilitation plus early ACLR was not superior to a strategy of rehabilitation plus optional delayed ACLR. As a result, it is widely accepted in Sweden to start the treatment with a period of structured rehabilitation and delayed ACLR if functional instability persists, leading to an increase in time to surgery.

In 2022, Bergerson et al. [12] reported in a large register-based study superior outcome of early ACLR compared to initial non-reconstructive treatment with late crossover to surgery. Although, they defined early surgery as ACLR within one year of the injury.

Lee et al. published a systematic review in 2018, and concluded that early ACLR results in comparable clinical and stability outcomes, compared to delayed ACLR [43]. They reported that the definition of early ACLR ranged broadly from 9 days to 5 months, while the definition of delayed ACLR ranged from 10 weeks to >24 months. Thus, it is hard to reach any conclusion regarding the timing due to the broad and overlapping cutoffs between the definition of early and delayed ACLR in the literature. The median time from injury to surgery in Sweden between 2005 and 2020 was 246 days, and in 2022 it was 174 days [70].

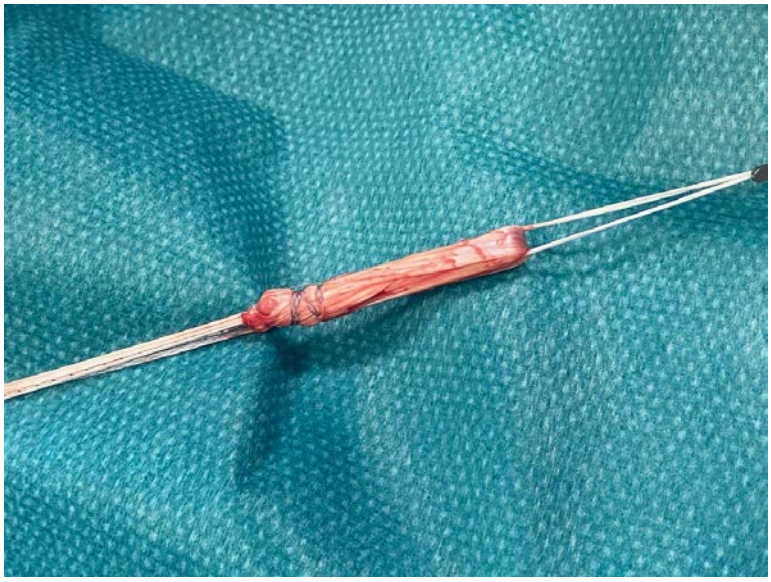

Figure 2. A hamstring autograft used for ACLR

1.5 Measuring the outcome of treatment of the ACL injury

The aim of treatment of the ACL injury is to restore knee stability based on the specific physical demands and preferences of the patient, whether in daily life activities, work or sports. Measuring the outcome of treatment can be done with several methods, discussed below.

1.5.1 Clinical assessment of knee function

The clinical assessment of knee function usually includes measuring laxity, range of motion and muscle strength. Regarding laxity, anterior tibial translation can be examined by Lachman test, Lever sign and the anterior drawer sign. Rotational laxity can be examined using the Pivot shift test. Sokal et al. has conducted a systematic review and reported that the diagnostic accuracy of these clinical tests is comparable [83]. However, the challenge with these tests lies in their dependence on the examiner and lack of precision. This led to the development of instrumented laxity measurement that provides precise and reproducible measurements.

The KT-1000 arthrometer is the most studied instrument for quantifying anterior knee laxity [25]. After attaching the arthrometer to the lower leg, just above the ankle, the examiner will perform a Lachman's test and the arthrometer will show the translation of the tibia in millimeters on the screen. Multiple measurements are usually needed to get an accurate measurement. The Rolimeter is another device that offers a simpler alternative to the KT-1000 and it has been shown to produce comparable results to the KT-1000 [77].

Range of motion (ROM) measurements refer to measuring the extent of achievable movement in the knee during flexion and extension, usually using a universal goniometer. A method reported to have good intra-rater reliability [63]. Symptomatic deficit in range of motion is often defined as arthrofibrosis [50].

Measuring the thigh circumference proximal to the most proximal part of the patella is a common method for testing muscle strength following ACLR [10]. Isokinetic muscle measurements have good intra-rater reliability in patients following ACLR. It is, therefore, the recommended gold standard in evaluating knee muscle strength in this patient group [87]. It involves using a special machine (Biodex) to evaluate the strength and performance of the muscle while controlling the speed of the movements.

Hop testing is usually used in assessing the outcome after ACLR, as it has been reported to be a valid and reliable outcome measure [71]. There are many variants of the hop test such as the single leg hop test, the triple hop test and the crossover hop test.

1.5.2 Patient reported outcome measures (PROMs)

The term PROM refers to questionnaires that collect health outcomes directly from the people who experience them [20]. Over the past few decades, there has been a significant increase in the use of PROMs in both clinical orthopedic practice and research [29]. The basic requirement that a PROM must fulfill is that it should have good validity, reliability and responsiveness, as well as no ceiling or floor effect [48]. The International Knee Documentation Committee Subjective Knee Form (IKDC-SKF) is a knee specific measure of symptoms, function and sports activity, and it is one of the most commonly used PROMs after ACLR injury [35]. Another widely used PROM is the Knee Injury and Osteoarthritis Outcome Score (KOOS) [74], which was developed to asses both short-term and long-term consequences and function in patients with knee injury and osteoarthritis. KOOS is the primary PROM used by many ACL quality registers [31].

The KOOS consists of five, separately scored, subscales: pain, other symptoms, function in daily living, function in sport and recreation and knee related quality of life [74]. Another questionnaire that is used by the SNKLR is the European Quality of Life Five Dimension (EQ-5D) [5, 67]. It is a generic health-related quality of life instrument that assesses the patient's overall health status and is not knee-specific.

One problem of the PROMs is that they are presented in research papers as absolute numbers and it might be challenging to apply them clinically. Two terms have emerged to provide thresholds to make the interpretation of KOOS more relevant clinically; Patient Acceptable Symptom State (PASS) and Treatment Failure (TF) [73]. The PASS thresholds for the KOOS subscales, validated by Muller et al. [56], and the TF thresholds defined by Ingelsrud et al. [34] were utilized in this thesis. The specific thresholds applied were as follows:

- KOOS Pain: PASS=88.9, TF=57
- KOOS Symptoms: PASS=57.1, TF=56
- KOOS ADL: PASS= 100, TF=71
- KOOS Sports: PASS = 75, TF=28
- KOOS Qol: PASS = 62.5, TF=28

1.5.3 Radiological assessment of osteoarthritis (OA)

Although ACLR may restore functional stability in the short-term, many studies have reported that there is still a high risk of developing OA in the long-term [9, 45, 90].

Several classification systems are used to grade OA based on findings from weight-bearing x-rays. The most commonly used classifications are: Kellgren-Lawrence [39], Ahlbäck [4] and Fairbank [27]. According to Kellgren-Lawrence [39], OA is graded as follows:

- Grade 0: No joint space narrowing or reactive changes.
- Grade 1: Doubtful joint space narrowing and possible osteophytic lipping.
- Grade 2: Definite osteopyhtes and possible joint space narrowing.
- Grade 3: Moderate osteophytes, some joint space narrowing, some sclerosis and possible bone end deformity.
- Grade 4: Large osteophytes, marked joint space narrowing, severe sclerosis and possible and definite bone end deformity.

1.6 Adverse events following an ACL injury

Adverse events can be defined as undesirable incidents or negative outcomes that may arise following an ACL injury. These events may arise during diagnosis or treatment of the injury. One major challenge observed in the literature regarding adverse events is that they are often underreported [54].

Septic arthritis following ACLR is a major adverse event and will be discussed separately in the next chapter. Missed or delayed diagnosis is another major adverse event. Arastu et al. [6] reported that less than a third of the patients with an ACL injury receive the correct diagnosis at the primary medical consultation. Despite the fact that most patients describe a typical injury mechanism, present with characteristic symptoms and seek medical consultation within one week of the injury.

Suboptimal surgery and technical errors have been reported to be a common cause of adverse events [68]. Among these errors, incorrect graft placement and graft fixation errors have been reported as prevalent issues in the Nordic countries [57, 59, 68].

Other adverse events may include pulmonary embolism, deep vein thrombosis and nerve injuries.

1.6.1 Septic arthritis following ACLR

The incidence of septic arthritis following ACLR has been reported in large registry-based studies to be between 0.8% and 1.1 [16, 41]. Although rare, it is a severe and devastating adverse event. The treatment of septic arthritis usually involves multiple irrigation and debridement (I&D) operations and long-term administration of antibiotics.

The clinical presentation of septic arthritis following ACLR has mainly been studied within single institutions with small numbers of infected patients [8]. The clinical presentation may vary depending on several factors, but patients with septic arthritis usually present with joint swelling, pain, impaired range of motion and sometimes redness. Systemic signs of infections such as fever and chills maybe present. The diagnosis is usually confirmed by synovial fluid analysis [23]. According to a systematic review conducted by Kursumovic et al. [42], coagulase-negative staphylococci (CoNS) were the most common infectious agent, followed by Staphylococcus aureus (S.aureus). Although the review included 16 studies, the total number of infected patients across all studies was 147.

The outcome of ACLR complicated by septic arthritis has mainly been studied in small series in the literature. Makhni et al. [52] conducted a systematic review on the topic including 19 studies and 203 infected patients. They reported that the outcomes of patients with septic arthritis are comparable with those in patients in whom infection does not develop. This includes postoperative ROM, residual instability, and return to preinjury level of activity. Interestingly, they concluded as well that patients with septic arthritis are associated with reduced functional outcomes based on the differences found in IKDC scores. Although, these findings are limited by the fact that most of the studies included in the review were retrospective case-series with different types of biases introduced into the data collection and analyses.

There is also a lack of studies reporting on the rate of revision ACLR among patients with primary ACLR complicated by septic arthritis.

1.7 The patient insurance system in Sweden

There are several ways to identify adverse events that can occur after an injury or a procedure. In study I, adverse events were identified through studying compensation claims reported to the Swedish national insurance company (Löf). In Sweden, all individuals treated by the publicly financed health care system are insured against preventable adverse events.

The Swedish patient insurance system is based on a no-fault patient-injury compensation plan [21]. Patient malpractice claims are handled administratively and compensated after an expert physician review confirms that the patient injury resulted from medical error [65]. This system is mostly seen in countries with universal health care coverage and aims to reduce errors and improve safety without blaming the medical practitioner [36].

In 2022, 20,500 compensation claims were reported to Löf. 38% of the claims processed that year were accepted. Orthopedic surgery was the predominant specialty being responsible for approximately 20% of the reported claims [46].

To compare, the United states of America uses a system based on malpractice tort lawsuits. This system aims to deter physicians from practicing beyond their expertise, punish those who practice low-quality care and compensate patients injured by low-quality care [84].

1.8 Registers in Sweden

In Sweden, there is a large number of registers that are useful for medical research. They can be divided into national public authority registers and health quality registers.

1.8.1 The personal identification number

The Swedish Personal Identification number (PIN), functions as a distinctive identifier within the health care system and various sectors of Swedish society. Additionally, the PIN plays a pivotal role as the primary variable in extensive register linkages for medical research [47].

1.8.2 The National Patient Register

Established in the 1960s, as the national board of health and welfare started to gather information about in-patients at public hospitals. At that time, the register covered 6 out of 26 health councils in Sweden. Since 1987 it started to cover all in-patient care in Sweden. Since 2001, it covers even outpatients doctor visits, including day surgery and psychiatric care from both private and public caregivers, excluding primary health care [92].

Data that can be gathered from this register can be divided into 4 categories:

- Patient data (PIN, gender, age, place of residence).
- Geographical data (Conty Council, hospital/clinic, department).
- Adminitistartive data (In-patient: date of admission, date of discharge, length of stay unplanned/planned admission, admitted to, discharged to, Outpatient: date of admission, date of discharge, unplanned/planned admission, acute care data).
- Medical data (main diagnosis, secondary diagnosis, external cause of injury, procedures).

The diagnoses are coded according to the International Classification of Diseases (ICD) 10th revision (ICD-10) [92].

1.8.3 The Swedish prescribed drug register

Established in 2005 and covers all prescribed drugs dispensed at pharmacies in Sweden.

Data that can be gathered from this register is patient data (PIN, age, gender, place of residence), drug name, the prescription details, as well as information about the prescriber [91].

1.8.4 The Cause of Death register

The cause of death register is a high-quality complete register of all deaths in Sweden since 1952. It contains patient data (PIN, age, gender, place of residence) as well as underlying cause of death based on ICD codes [82].

1.8.5 Health Quality Registers

A health quality register contains individualized data about medical interventions, procedures and outcomes after treatment. Each register is supported by an organization of health care professionals and patient representatives. It is annually monitored and approved for financial support by an executive committee. There are more than 100 national health quality registries in Sweden [69].

1.8.6 The Swedish National Knee Ligament Registry (SNKLR)

Data from SNKLR has been used in all four studies included in this thesis. The register started in 2005 by a group of ACL surgeons. It comprises patients undergoing primary ACLR and ACLR revisions, as well non-operative treatment of ACL injuries. The register covers 90% of all ACL procedures performed in Sweden. It consists of two parts: patients' part and surgeons' part. The patients part includes baseline data like BMI and smoking, the KOOS and EQ-5D. The surgeons part includes activity at injury, time from injury to surgery, operating time, graft selection and fixation technique [5].

2 Research aims

The aims of the thesis were to investigate the following aspects of the ACL injury:

• To investigate the reasons of adverse events and treatment errors following an ACL injury, as identified in compensation claims reported to the national insurance company (Löf).

-Study I

• To analyze Patient Reported Outcome Measures (PROMs) and examine the five-year risk of revision surgery after primary ACLR complicated by septic arthritis.

-Study II

• To describe the clinical characteristics of the common infectious agents that cause septic arthritis following ACLR, in order to provide better understanding of their impact on the clinical presentation of the disease.

-Study III

• To analyze the long-term outcomes of ACLR in a randomized controlled trial comparing acute and delayed reconstruction.

-Study IV

3 Materials and methods

3.1 Ethical considerations

All studies were conducted in accordance with the declaration of Helsinki [1]. Ethical permits were granted before the commencement of the studies, either from the regional ethical board of Karolinska university in Stockholm or from the Swedish ethical review board.

Informed consent was obtained from all participants in study IV. In studies I, II and III, the need for informed consent was waived by the ethical review boards. The decision is based on the current regulations in Sweden, which allow the use of registry-based data for research without requiring informed consent from the study participants. The data is anonymized and presented at the group level and the risk of identifying sensitive information for an individual is minimal.

3.2 Identifying the adverse events (Study I)

Study I was designed as a retrospective observational study. the goal was to identify all the patients with an ACL injury between 2005 and 2014 who had filed an ACL-related compensation claim. First, we searched the National Insurance Company's (Löf) database for claims with ICD-10 codes that are associated with anterior cruciate ligament injuries, S83.5, S83.6, S83.7, or M23.5.

Secondly, all patients with an ACL injury between 2005 and 2014 who are registered at SNKLR were cross-matched with data from Löf's database based on the Swedish Personal Identification Number (PIN). A flowchart of patients in study I is presented in figure 3.

734 claims were found. After a thorough review of medical records, 530 eligible claims were identified. 191 claims were excluded as they were not ACL-related. Most of them were patients who had an ACL injury registered in the SNKLR during the study period. Simultaneously they had also filed a compensation claim to Löf for a different matter. Thirteen claims were excluded, as they were not eligible for compensation because their private care provider was not included in the national insurance. These patients were directed by Löf to contact their care provider and file a claim to the private care insurance company.

If the adverse event was deemed to be avoidable according to the medical experts at Löf, then the claim will be accepted and the patient will be compensated. The causes behind accepting or rejecting a compensation claim were studied and the patients were categorized

accordingly. The group with accepted claims was analyzed regarding demographic data, increase in recovery time, increase in disability and the amount of economic compensation.

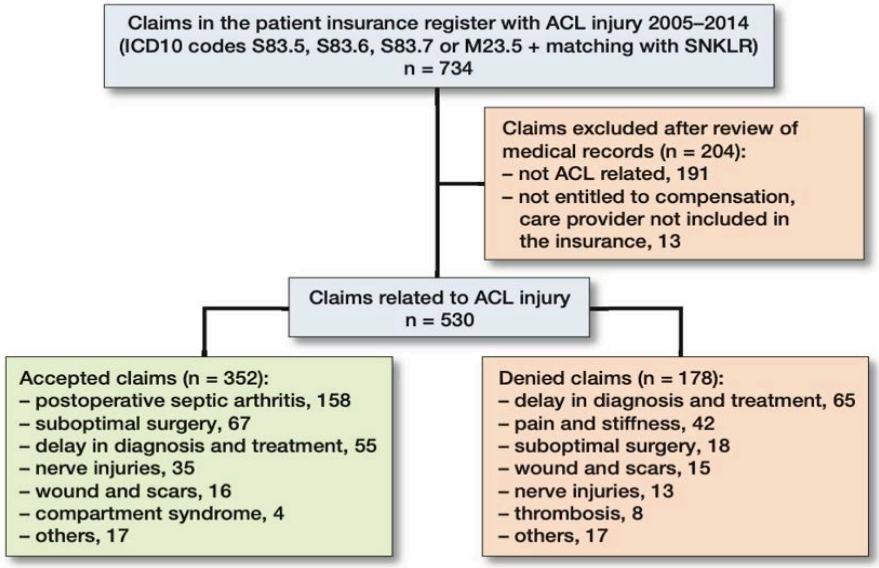

Figure 3. A flowchart of patients in study I

3.3 The consequences of post-operative septic arthritis (Study II)

Post-operative septic arthritis was identified as the most common reason for accepted compensation claims in study I. The outcomes and revision risk of septic arthritis was analyzed in study II. The design is a retrospective analysis of prospectively collected data.

Based on a previously published study by the research group aimed at analyzing the risk factors for septic arthritis following ACLRs [41], all primary ACLRs (n=23,075) performed utilizing a hamstring or patellar autograft in 2006-2013 were identified. This was a subgroup from the original cohort which was a result of a cross-matching process between SNKLR and three registries from Swedish national board of health and welfare, which was then followed by a national medical record review to confirm the diagnosis of septic of arthritis. The flow chart of patients and methods in study II is presented in figure 4.

PROMs (KOOS and EQ-5D index) and revision surgery data was extracted from SNKLR up to five years following ACLR.

The patients were categorized into two groups: with or without septic arthritis. An analysis was performed of the KOOS subscales and EQ-5D index data collected pre-operatively and post operatively at 1-,2- and 5-years follow-ups. PROMs data for patients that underwent revision ACLR was included until the date of the revision surgery. The risk of revision ACLR within 5 years of the index ACLR was calculated.

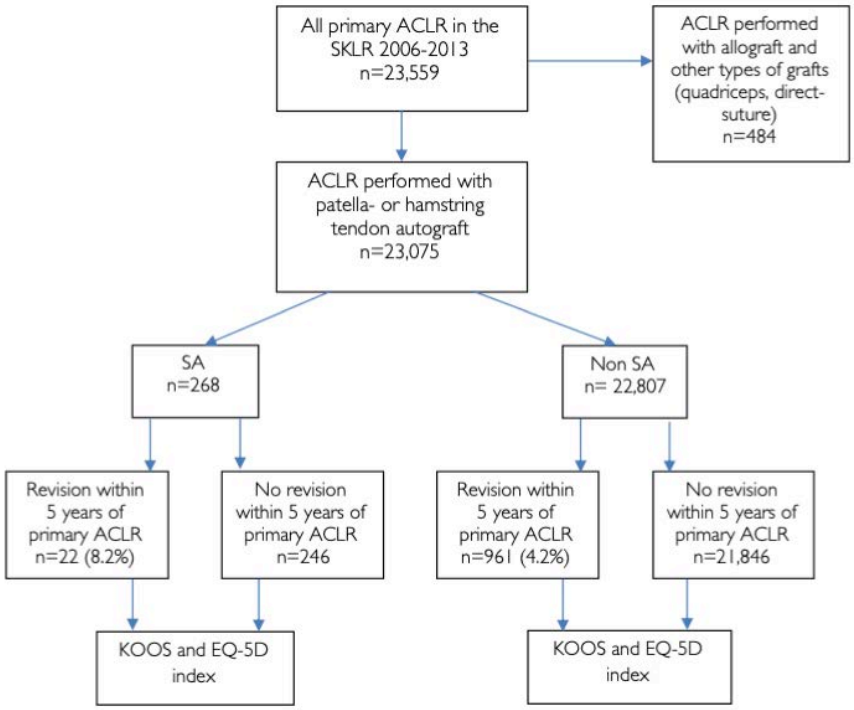

Figure 4. A flowchart of patients in study II

3.4 Microbiology and clinical presentation of septic arthritis (Study III)

Study III is a retrospective observational study. The aim was to describe the variations in the clinical presentation of post-operative septic arthritis based on the causative infectious agent.

In study I, 158 patients with an accepted compensation claim due to post-operative septic arthritis were identified. Löf obtains detailed medical records from the treating hospital in order to make a decision regarding compensation. The medical records include admission notes, follow-up notes, operation notes, lab results and other associated medical records. The medical experts at Löf go through medical records to provide a medical decision to

confirm septic arthritis. The medical experts are experienced orthopedic surgeons specialized in the subject of the claim.

A thorough analysis of the medical records was performed for the study patients. Additionally, data was extracted from SNKLR.

Data collected from the medical records included:

- Causative infectious agent
- Age at the time of surgery
- Sex
- Date of the surgery
- The side of the operation (right or left knee)
- Primary or revision ACLR
- The choice of the graft used in ACLR
- The duration from ACLR to the first I&D (irrigation and debridement) operation
- The number of days of inpatient care
- The number of arthroscopic and open I&D operations
- If the graft was removed during the initial I&D operations or not
- CRP (C-reactive protein) at the time of presentation
- Maximum CRP value during the inpatient period
- WBC (White blood cell) count at the time of presentation
- Temperature at the time of presentation

Data collected from SNKLR included:

- BMI (Body mass index)
- Smoking
- The operating time
- The choice of pre-operative antibiotic prophylaxis

The data was then grouped according to the agent causing the infection.

3.5 The long-term outcome of early ACLR (Study IV)

Study IV was a long-term follow-up of a randomized controlled trial. The patients were consented and clinically assessed, differing in methodology from the other studies which were register-based.

Between 2006 and 2013, patients were recruited at Stockholm South General Hospital (Södersjukhuset) to participate in a randomized controlled trial aimed at investigating the impact of the timing of ACLR on the development of arthrofibrosis and short-term outcomes.

70 patients were randomized to either acute ACLR performed within 8 days after injury or to delayed ACLR performed after recovery of ROM within 6 and 10 weeks after injury. Previous follow-ups were performed at 3,6,12 and 24 months post-operatively. The patients were contacted and invited to participate in a long-term follow-up. The flowchart of patients and methods in study IV is presented in figure 5.

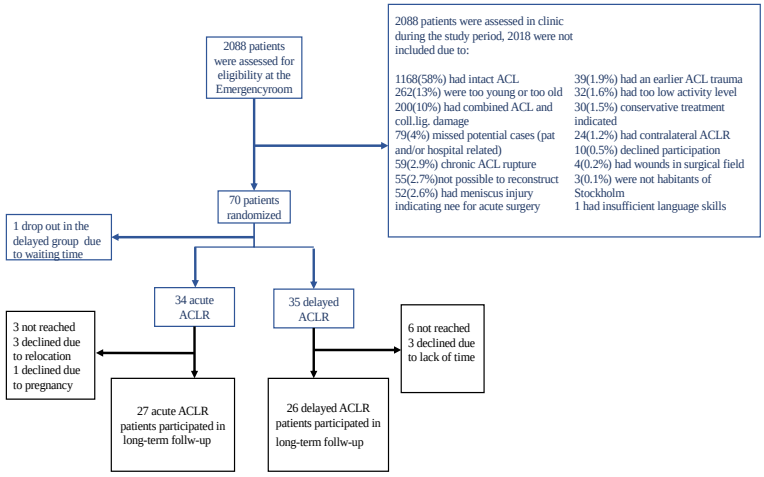

Figure 5. A Flowchart of patients in study IV. Black boxes indicate data concerning the long-term follow-up and blue boxes indicate data published earlier.

The long-term follow-up included 3 parts:

- Clinically-assessed knee function: The patients were assessed by the same experienced physiotherapist. The assessment included ROM measurements using a goniometer, instrumented knee laxity using a Rolimeter and KT-1000 and muscle strength using Biodex, thigh circumference and single leg hop test.
- PROMs: The patients were asked to fill in a questionnaire containing: KOOS, Tegner's activity level and Lysholm's score. Two questions were added "How is your knee functioning?" and "How does your knee affect your activity level?" The patients provided their answers on a visual analogue scale (VAS) ranging from 0 to 100.
- Weight-bearing radiological examination: Both index and contralateral knees were examined with anteroposterior (AP) and lateral view in 30 degrees of flexion. OA was defined as grade ≥2 according to Kellgren-lawrence classification, which is defined as definite osteophyte formation with possible narrowing of the joint space.

3.6 Statistics

All the statistical analyses were performed using IBM SPSS software package for Macintosh or Windows version 26.0, 27.0 or 28.0.

The variables were presented as frequencies and percentages, means and standard deviations (SD) or medians, ranges or interquartile ranges (IQRs) depending on the level of measurement and the normality of distribution.

In study II, Linear mixed models with restricted maximum likelihood method was used to analyze PROMs change over time. Within-subject effects and the between subjects' effect were presented at each time point with 95% confidence interval (CI) and p-value. Proportional Cox regression was used to calculate the risk of revision ACLR within 5 years of the primary ACLR. The hazard ratio with 95% CI is presented.

In study III, Kruskal-Wallis analysis of variance test was used to analyze the distribution of continuous variables across infectious agents. Chi-squared or Fisher's test was used to analyze the association between categorical variables.

In study IV, categorical variables were tested with Chi-squared or Fisher's test. Non-parametric tests were used to compare the non-normally distributed ratio scale variables. The Student t-test was used for independent normally distributed ratio scale variables. To evaluate changes over time for ordinal data, Friedman's test was used. A binary logistical multivariable regression analysis was performed to assess the a-priori defined risk factors for OA (age, BMI, cartilage and meniscus resection) with the randomization variable (Acute or Delay)

4 Results

4.1 Compensation claims related to an ACL injury

In study I, 530 eligible compensation claims related to an ACL injury between 2005 and 2014 were identified. 352 claims were accepted and 178 were rejected. The most common cause for accepting a compensation claim was post-operative septic arthritis followed by suboptimal surgery and delayed in diagnosis and treatment. The number of accepted claims each year in relation to the number of claims due to septic arthritis is presented in figure 6.

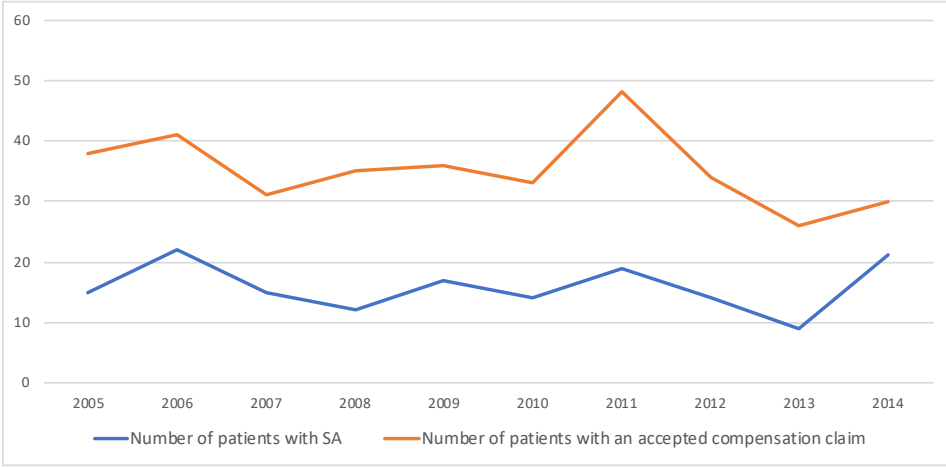

Figure 6. The number of patients with a claim related to post-operative septic arthritis (SA) in comparison to the total number of patients with an accepted ACL-related compensation claim each year during 2005-2014.

50% of the accepted claims were found to have increased disability due to the adverse event. The median increased disability ranged from 2% to 4% depending on the adverse event. The details are described in Table 1.

Type of patient injury	Number of ACLR	Age Median (range)	Sex ♂/♀	Increased disability Median (range)	Prolonged time of recovery In days Median (range)	Economic compensation Median (range) in EUR
Post-Operative Septic arthritis (n=158)	158	25 (14-59)	♂=103 ♀= 55	n=87 3% (1-12%)	n=122 60 (0-480)	n=154 3344 (474–40613)
Suboptimal surgery (n=67)	67	25 (16-49)	♂=32 ♀=35	n=34 2% (1-10%)	n=57 60 (0-300)	n=62 3024 (112-21875)
Delay in diagnosis or treatment (n=55)	45	21 (14-53)	♂=28 ♀=27	n=11 4% (1-17%)	n=47 90 (0-730)	n=55 1628 (183-21957)
Nerve injuries (n=35)	35	24 (13-48)	♂=21 ♀=14	n=32 2% (1-5%)	n=41 0 (0-120)	n=35 2919 (256-12830)
Wounds and scars (n=16)	16	22 (16-50)	♂=11 ♀=5	n=2 3% (1-4%)	n=15 0 (0-90)	n=15 1258 (128-10342)
Compartment syndrome (n=4)	4	21 (18-35)	♂=3 ♀=1	n=4 3% (1-5%)	n=3 30 (14-180)	n=4 6649 (1959-10407)
Others (n=17)	17	28 (14-47)	♂=9 ♀=8	n=6 2% (1-2%)	n=8 15 (0-270)	n=17 2766 (409-6507)

Table 1. Demographics and characteristics of patients with accepted claims categorized by cause. Values are counts or medians (range).

4.2 The impact of septic arthritis on the outcome of ACLR

In study II, a cohort of 23,075 patients who underwent primary ACLR using a hamstring or a patellar autograft in 2006-2013 were analyzed. 268 (1.2%) events of septic arthritis were observed.

Significant differences were observed between the groups with (n=268) and without (n=22,807) septic arthritis for the variables sex, cartilage lesion, operating time, choice of graft, choice of preoperative antibiotic prophylaxis and revision ACLR within 5 years.

Two years after ACLR, patients with septic arthritis had a greater proportion of treatment failures and fewer PASS on all KOOS subscales, compared with patients without septic arthritis (figure 7). Moreover, patients with septic arthritis had poorer scores on KOOS and EQ-5D at 1,2- and 5-years follow-ups. The rate of revision ACLR within five years of the primary ACLR was nearly double for patients with septic arthritis when compared to those without septic arthritis (figure 8).

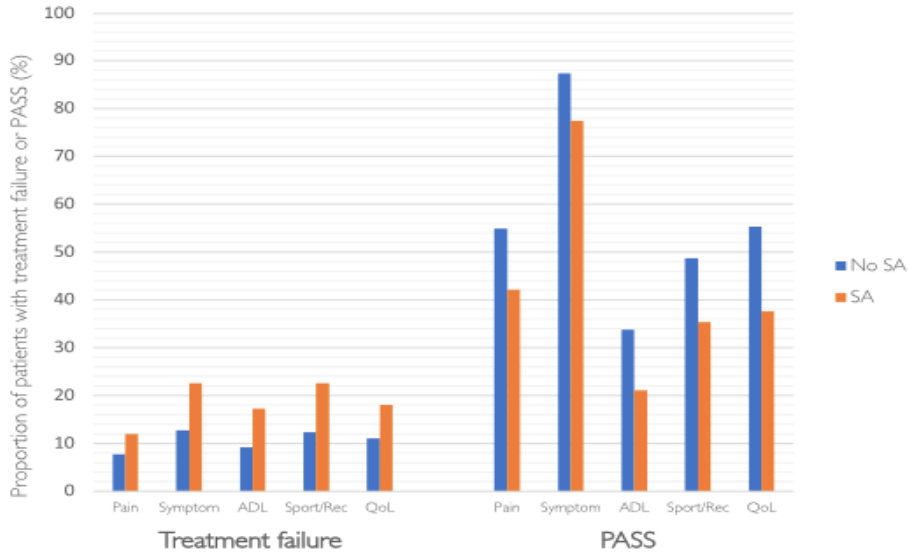

Figure 7. Proportions of patients with Treatment failure and patient's acceptable symptoms state (PASS) in the groups with and without septic arthritis (SA), displayed with the five KOOS subscales; 2 years post-operatively.

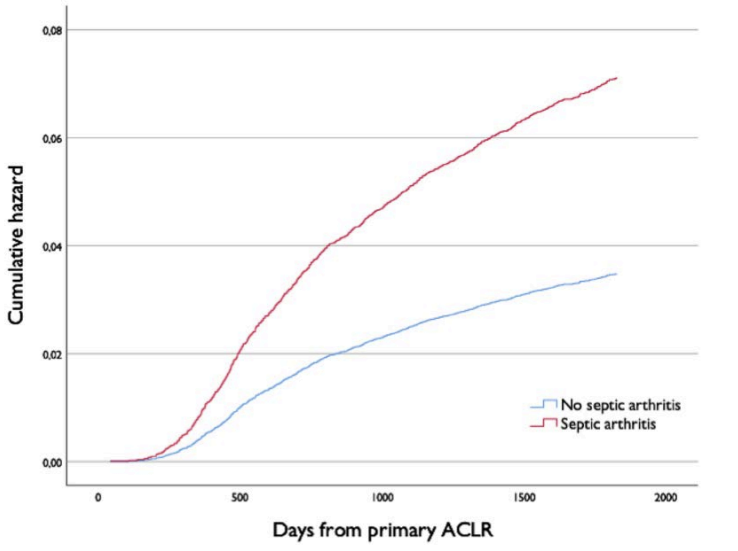

Figure 8. Adjusted, cumulative hazard rate for revision ACLR within 5 years of the primary surgery for patients with and without septic arthritis.

4.3 Clinical characteristics of the infectious agents causing septic arthritis

In study III, a subgroup analysis was performed for 158 patients with septic arthritis identified in Study I. One patient's medical record lacked information regarding the causing infectious agent. The majority (60%) of patients were infected with Coagulase negative staphylococci (CoNS) (figure 9).

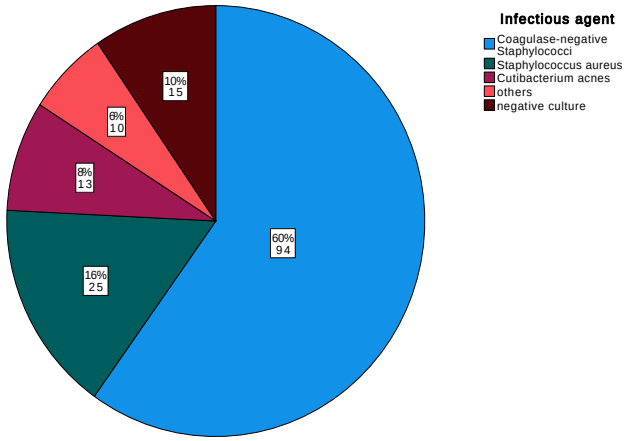

Figure 9. The distribution of infectious agents causing septic arthritis among 157 patients in Sweden from 2005-2014 presented in counts and percentages.

Significant differences were observed across causing infectious agents regarding maximum CRP level (Figure 10), and duration from ACLR to the first irrigation and debridement operation (Figure 11).

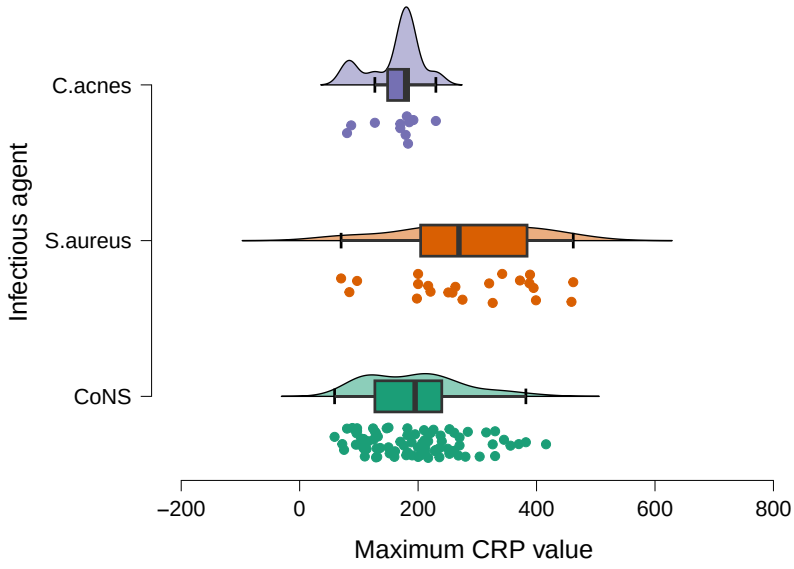

Figure 10. The distribution of maximum CRP levels for patients infected with Coagulase negative staphylococcus (CoNS), Staphylococcus aureus (S.aureus) and Cutibacterium acnes (C.acnes).

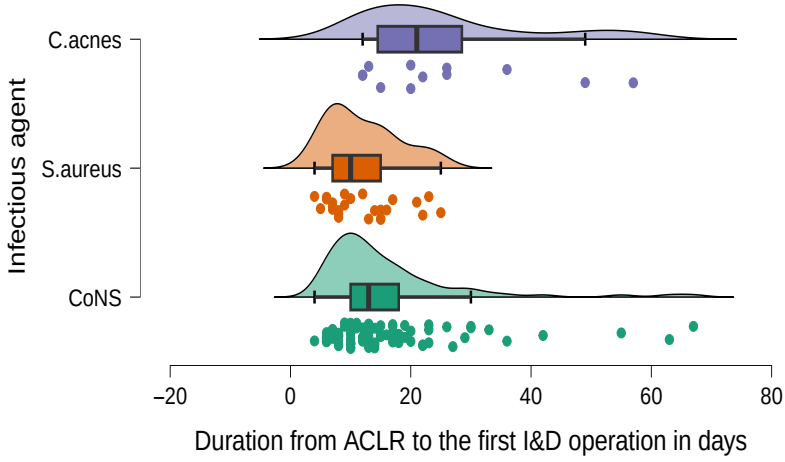

Figure 11. The distribution of the duration from ACLR to the first irrigation and debridement (I&D) operation in days, for patients infected with Coagulase negative staphylococcus (CoNS), Staphylococcus aureus (S.aureus) and Cutibacterium acnes (C.acnes).

4.4 The long-term results and consequences of early ACL reconstructions

In study IV, 53 (76%) patients out of 70 randomized, participated in the long-term follow-up at a mean of 13 years (SD± 1.8) after ACLR. (Table2).

	Acute or Delayed ACLR (n=53)			OA or No OA (n=44)		
	Acute ACLR (n=27)	Delayed ACLR (n=26)	sign.	No OA (n=31)	OA (n=13)	sign.
Time from injury to surgery in days, mean (SD)	5 (2)	54 (8)	< 0.001	24 (26)	39 (20)	n.s
Time to long-term follow-up in years, mean (SD)	13 (1.8)	12.9 (1.9)	n.s	13.2 (1.8)	12.9 (1.8)	n.s
Female sex, n (%)	7 (26)	10 (39)	n.s	8 (26)	5 (39)	n.s
BMI at ACLR, mean (SD)	23.9 (2)	24.8 (2.7)	n.s	23.8 (2.2)	26 (2.1)	0.003
BMI at long-term follow-up, mean (SD)	25.8 (3.6)	26.5 (3)	n.s	25.4 (3.2)	28.1 (3.3)	0.014
Age at long-term follow-up, mean (SD)	40.8 (7.2)	39.2 (6.5)	n.s	40.2 (7)	41.4 (6.2)	n.s
Revision of index ACLR, n (%)	3 (11)	4 (15)	n.s	4 (13)	3 (23)	n.s
Injury to contralateral knee, n (%)	3 (11)	3 (11)	n.s	3 (10)	1 (8)	n.s
Meniscus resection at ACLR or later, n (%)	10 (37)	10 (39)	n.s	9 (29)	8 (62)	n.s
Meniscus resection or cartilage injury debrided at ACLR or later, n (%)	11 (41)	11 (42)	n.s	10 (32)	9 (69)	0.044

Table2. Demographics and clinical characteristics of the study patients categorized by acute versus delayed ACLR and by OA versus No OA on radiographic examination. OA was defined as grade ≥ 2 according to Kellgren-Lawrence classification.

Knee function was clinically assessed in 49 (70%) patients. Satisfactory knee function was observed in both groups. No differences between the groups were found in terms of ROM, anterior knee laxity or knee strength tests.

50 patients (71%) completed a PROMs questionnaire. The median activity level according to Tegner's scale continued to improve until 24 months after ACLR (Figure 12). KOOS subscales pain and symptoms scores were worse (p=0.019, 0.008) for patients in the delayed group.

Figure 12. The distribution of the median scores for Tegner's activity scale through various time points: before the injury, at inclusion after the injury, at 6, 12 and 24 months after reconstruction and at the long-term follow-up (P= <0.01).

44 patients (62%) were assessed with radiological examination. 13 patients (30%) showed signs of OA in the index knee, compared to 4 patients (9%) in the contralateral knee (p=0.037). 10 patients (48%) in the delayed group showed signs of OA, compared to 3 patients (13%) in the acute group (p=0.012) (Figure 13).

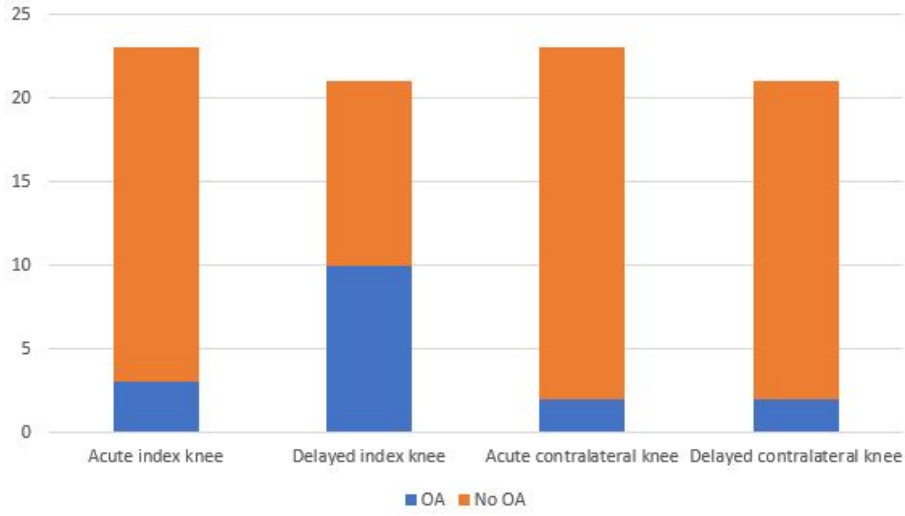

Figure 13. The number of patients with and without radiological signs of OA in the acute (n=23) and delayed (n=21) groups in both the index and contralateral knee for the study patients.

5 Discussion

5.1 Utilizing compensation claims to study the adverse events

In study I, ACL-related compensation claims filed to the national insurance company (Löf) were examined.

There are various alternatives for studying adverse events after a procedure or treatment. The utilization of compensation claims has emerged as a valuable way of gathering information and insights [38, 65, 68]. One of the main advantages is that compensation claims often include detailed records and comprehensive data on the patients that are usually hard to find somewhere else.

The detailed information conveyed through the patient's own narrative enables the researchers to capture a diverse range of problems and circumstances. Moreover, it provides higher levels of participant engagement in the research process. Another benefit is that compensation claims often include documented longitudinal follow-ups which are often essential for filing a claim. Conducting these follow-ups can be technically challenging or comes with a significant financial cost. Therefore, studying compensation claims seems to be a cost-effective alternative. Another advantage of studying compensations claims is that, due to the financial implications, insurance companies tend to perform thorough investigations of the claims conducted through experienced medical consultants, which often provides valuable addition to the information provided by the patient.

ACLR is often considered as a safe procedure [55]. The findings of study I shows that fewer than 1% of ACLRs performed in Sweden was reported to have an avoidable treatment error that merited compensation by the national insurance company (Löf). Previous studies from neighboring countries have shown comparable results [59, 68]. Studying the reasons for compensation claims have been insightful in identifying adverse events that can be avoided. Nonetheless, there is a possibility that the actual number of avoidable treatment errors is higher than what is reported. The discrepancy might be due to some patients with treatment errors may choose not to file a claim or could lack information on the appropriate procedure for doing so.

It is important to emphasize that Löf accepts a compensation claim based on the presence of treatment errors that can be avoided and not based on the severity of the complication. An important illustration is evident in a tragic case where a patient, unfortunately, died due to lung embolism 2 months following ACLR. Despite the severity of the complication, the compensation claim was dismissed by Löf, as their medical consultants could not identify a treatment error. Their assessment concluded that the treating physician acted according to accepted medical practice, particularly considering the prevailing cautious approach among

Swedish surgeons regarding the use of anti-thrombotic agents following ACLR. The patient did not have any known factors such as previous history of thrombosis, use of oral contraceptives or prolonged immobilization. Consequently, despite the devastating nature of this complication, the compensation claim was not accepted.

Post-operative septic arthritis was found to be the most common cause of an accepted claim. The consequences of this complication as well as aspects on the clinical presentation will be discussed in the following chapters.

Suboptimal surgery and technical errors were common causes for accepted compensation claims. A frequent claim was when the graft was placed in a higher position due to the surgeon's lack of updated knowledge on the evolving consensus regarding surgical technique. These findings emphasize the significance of continuous education. During the studied period, there was a shift from trans-tibial to anteromedial femur drilling. Consequently, claims related to graft mispositioning using the trans-tibial technique were more likely to be accepted in the later years of the study period and rejected during the earlier years.

Delays in diagnosis and treatment were as well common reasons for accepted compensation claims. The accuracy in diagnosing the ACL injury primarily is reported to be suboptimal. It has been reported that fewer than one-third of patients with an ACL injury receive an accurate diagnosis during the primary medical consultation [6]. The impact of timing of surgery will be discussed in details in another chapter. But it is worth mentioning that delaying ACLR has been reported to increase the risk of cartilage and meniscus injuries [18, 24]

The study is limited by its retrospective design and that it is limited to patient-reported claims which may introduce potential biases. Consequently, the study is unable to provide an accurate assessment of the true incidence of patient injuries and treatment errors following ACLRs in Sweden. The study reports that ACL-related treatment and patient-injuries are infrequent, yet likely underreported.

5.2 Evaluating the outcome of ACLR complicated by septic arthritis

In study II, PROMs and the risk for revision ACLR for patients with and without septic arthritis were examined.

Various methods are available for assessing the outcome after a surgical procedure, one of which is by using PROMs. KOOS and EQ-5D have been used to evaluate the outcome of ACLR in study II. While KOOS is a comprehensive tool that has been validated for the assessment of knee function, its utility for the ACL injured patient has been questioned [95]. It contains questions that are irrelevant for the ACLR patients, as well as it leaves out important issues such as feeling of instability and return to sport. But KOOS was chosen by

our research group because it is the tool adopted by the Swedish national knee ligament registry (SNKLR) for assessing the outcome of the ACL reconstructed patient.

Based on the findings of Study II, patients with post-operative septic arthritis had worse KOOS scores at one-, two- and five-year follow-ups, compared to patients without septic arthritis. The study also shows that the risk of undergoing revision ACLR within five years of the primary ACLR is nearly double for patients who suffered from septic arthritis after ACLR, compared to patients without septic arthritis.

A major strength of this study is that the findings are based on a valuable large nationwide database and thus it has the ability to identify broader trends. The study presents a much larger patient sample size than previous studies on the subject. Post-operative septic arthritis is a rare complication [3, 7] and therefore large studies on this devastating condition is of great importance, especially when previous studies have been predominantly performed in single institutions with small numbers of patients [2, 14, 52].

The reason behind poorer outcomes for patients with septic arthritis is not fully understood. Many factors may play a role in the course of septic arthritis; patient specific factors and factors associated with the infection. One explanation might be the development of arthrofibrosis due to synovitis [50, 78]. Another explanation might be due to the cartilage damage caused by the toxins of the bacterial infection [75, 80], as it has been reported that patients with cartilage lesions are associated with poorer outcome of ACLR [76]. Another explanation might be that the graft would lose its tension because of the toxins of the bacteria or the washout procedures leading to instability and poorer outcomes.

It is important to mention the limitations of this study. There is no available information regarding the removal of the graft during the washout procedures, which could potentially affect both PROMs and the revision rate. On the other hand, the common practice in Sweden is to retain the graft during the primary washout procedures [14]. Additionally, there is no available information regarding technical errors during the index ACLR or re-trauma which could also affect both PROMs and the revision rate.

The KOOS and EQ-5D data during the time of this investigation include an increasing number of missing data at each subsequent follow-up. The response rate for the two year-follow up stands at 50% [70]. Nonetheless, Reinholdsson et al. [72] showed that PROMs data extracted from SNKLR is valid, in a non-response analysis. Additionally, the use of linear mixed model statistical method in this study is considered a versatile and robust approach to handle missing data in longitudinal or repeated measures studies. By incorporating all available data and making reasonable assumption about the missing data mechanism, it can produce reliable estimates and enhance the validity of the results.

While acknowledging that no study is flawless, the primary merit of this investigation lies in its status as the largest to date in reporting PROMs and risk for revision following ACLR complicated by septic arthritis.

5.3 Variations in the clinical presentation of septic arthritis

In study III, the variations in clinical presentation of septic arthritis depending on the causative infectious agent were examined.

To start, it is important to acknowledge the main limitation of the study which is its reliance on patient claims reported to Löf. As a result, the actual number of infections, during the study period is not available. Over a decade, 158 patients infected with septic arthritis were found. During the same period 32,519 ACL reconstructions were performed, resulting in an incidence rate of 0.5%. Data from a comprehensive register-study has reported an incidence of 1.1% in Sweden [40]. As a result, confirming associations between variables and generalizing outcomes to other populations might not be feasible.

On the other hand, as mentioned previously, septic arthritis is a rare disease, and every large study on this condition is important. This case-series of 158 infected patients is, to my knowledge, the largest study describing detailed insights into the clinical presentation of septic arthritis following ACLR. Moreover, the finding that CoNS is responsible for 60% of the infections, as well as the distribution of the other infectious agents, is comparable to the results reported by a meta-analysis that included 147 infected patients across 16 studies [42]. Therefore, the findings of this study might be applicable to other populations, although it cannot be confirmed.

CoNS are often described as low-virulent agents. The fact that the majority of infections are caused by low-virulent agents has a clinical importance. Many patients seek medical help post-operatively with pain after ACLR. The decision on whether to perform synovial fluid analysis is a clinical decision that is usually based on clinical findings and lab results. Therefore, it is recommended that synovial fluid analysis should be performed even when the symptoms are mild and lab values are not so convincing.

Variations have been found in the duration from ACLR to the first washout procedures with patients with S.aureus (10 days) having the shortest duration and patients with C.acnes (21 days) having the longest. One hypothesis is that the variations in duration maybe due to delays in diagnosis. Previous studies have reported that it is harder to diagnose septic arthritis following ACLR caused by low-virulent agents due to milder symptoms [37].

Knowledge of the clinical characteristics of different causative agents contributes to our understanding of the epidemiology of septic arthritis following ACLR. These findings

emphasize the importance of tailored management strategies in order to be able to detect and treat this devastating complication.

Future research should focus on understanding the underlying mechanisms for the virulence of different causative agents, as well as investigating the variations in the clinical presentation and outcome of septic arthritis based on causative infectious agents in large comprehensive studies.

5.4 The ideal timing to perform ACLR

In study I, delayed diagnosis and treatment was a common reason for filing a compensation claim. The ideal timing of surgery is still a matter of debate.

In study IV, PROMs, clinically-assessed knee function and radiological examinations were evaluated for patients who underwent ACLR within 10 weeks after injury.

The study is a long-term follow-up of a randomized controlled trial comparing acute and delayed ACLR. The acute group underwent ACLR within 8 days after injury and the delayed group underwent surgery after normalized ROM was achieved, 6-10 weeks after injury. Despite these definitions, all study participants underwent ACLR within 10 weeks of the injury. In the Swedish context, this timeframe can be classified as early ACLR, considering that the median waiting duration for ACLR from injury was 264 days between 2005 and 2020 in Sweden [70].

With the aim of facilitating the interpretation of KOOS scores, Muller et al. [56] conducted a study proposing thresholds for the KOOS subscales and defining the patient acceptable symptom state (PASS). The proportions of study patients who achieved PASS at the long-term follow-up 13 years after ACLR were as follows: Symptoms= 98%, Pain 72%, ADL 54%, Sport= 72%, QoL= 82%. To compare, Bergerson et al. [12] conducted a study based on data from SNKLR and reported that patients (n=20,352) who underwent ACLR within a year from injury had superior outcomes and had the following proportions of PASS 10 years after ACLR: Symptoms=90%, Pain=59.5%, ADL=46.8%, Sport=58.9%, QoI=69.4%. Although these studies are not directly comparable, it is an indication that ACLR performed within 10 weeks of the injury is associated with satisfactory patient-reported outcomes.

No indications of persistent arthrofibrosis or higher complications rates were observed when ACLR was performed within 8 days of the injury. As stated previously, the median waiting time in Sweden for ACLR after injury is long. In Sweden, a prevalent treatment approach, especially for patients without high activity demands, involves a period of non-operative treatment for structured physiotherapy. If instability persists, delayed ACLR is then offered to the patient. It is important to acknowledge that the decision-making process

regarding ACL injury treatment is complex [62]. Research conducted by Frobell et al. [28] highlighting the benefits of non-operative treatment has played a role in shaping treatment strategies in Sweden. Moreover, many surgeons are still influenced by a study conducted by Shelbourne et al. [79] reporting a higher risk for arthrofibrosis after acute ACLR. Several other studies have reported an association between acute ACLR and persistent arthrofibrosis [22, 53, 66, 78]. All these studies were retrospective and are susceptible to various biases. Contrary to these studies, our study findings, revealing no differences in terms of ROM between acute and delayed ACLR, challenge the concept of persistent arthrofibrosis.

13 patients (30%) showed signs of OA in the index knee, compared to 4 patients (9%) in the contralateral knee (p=0.037). 10 patients (48%) in the delayed group showed signs of OA, compared to 3 patients (13%) in the acute group (p=0.012). In an older long-term outcome study conducted at our institution [9], the prevalence of OA was compared between patients who underwent ACLR using patellar BTB graft and those using semitendinosus tendon. The study reported an OA prevalence ranging from 55 to 70 % depending on the graft. No differences were observed between the grafts. It is encouraging to see that this more recent cohort reveals considerably lower OA prevalence. However, these studies are not comparable, for example the frequency of meniscus resections in the old study was more than 40%. Interestingly the time between injury and reconstruction in the old study was 14-16 months. Could the variation in OA prevalence be partially attributed to the time between injury and reconstruction? Unfortunately, this study is not capable of answering this question.

As previously stated, the ideal timing to perform ACLR is still a matter of debate. Cristiani et al. [24] argued that ACLR should be performed within 6 months after injury to reduce meniscal loss and the risk jeopardizing knee laxity. Prodromidis et al. [64] recommended that ACLR should be performed within 3 months after injury to decrease the risk of further intraarticular damage. Cance et al. [18] found that delaying ACLR is associated with increased rate and severity of cartilage injuries in a dose-effect fashion.

The findings of this study indicate that ACLR performed within 10 weeks after the injury results in satisfactory long-term outcomes, but with still increased risk of OA compared to the contralateral knee.

This study is limited by the low number of patients that may have restricted the ability of to detect subtle differences between the acute and delayed ACL reconstruction groups. Secondly, the prior power analysis was performed on ROM in the short term, which affects the validity of the results regarding the impact of timing of surgery on the long-term outcomes. Another limitation is the loss of follow-up of some patients which could introduce selection bias and affect the generalizability of the results.

A number of comparisons were made introducing a risk for randomly significant results. However, most of the results align with what is clinically expected and the results correspond well to earlier reported results from larger studies.

6 Conclusions

- The most common reasons for accepted compensation claims following an ACL injury are post-operative septic arthritis, suboptimal surgery and delay in diagnosis and treatment.
  -Study I

- The outcome of ACLR complicated by septic arthritis is worse than without septic arthritis and the risk of revision ACLR is twice as high for patients with septic arthritis compared to patients without septic arthritis.
  -Study II

- Variations were observed in the clinical presentation of septic arthritis after ACLR depending on the causative infectious agent, with low-virulent agents being responsible for the majority of the infections. This hilights the need for larger studies aimed at understaning the differences among these infectious agents.
  -Study III

- Early ACLR within 10 weeks of injury results in satisfactory long-term outcomes, but with increased risk of osteoarthritis compared to the contralateral knee.
  -Study IV

7 Points of perspective

The primary focus of this thesis was to investigate the adverse events and long-term outcomes for patients who have suffered from an ACL injury. However, most of the patients that participated in the studies underwent ACL reconstruction. Consequently, while the intention was to study the adverse events following the ACL injury regardless of treatment choice, the main findings are predominantly associated with the adverse events and outcomes following ACLR.

7.1 Compensation claims and adverse events

In medical school, we were taught the doctors oath "do no harm". That is why it is crucial to study adverse events in order to be able to work towards prevention. An important aspect of my research journey has involved reading hundreds of letters written by the patients describing their injury in details. This has granted me deeper insights into the mistakes we make while treating our patients and the variability of the adverse events based on the reasons behind them.

An important aspect that should be dealt with in the future is the large number of underreporting of adverse events that has been found in study I. A similar problem has been found by Kasina et al. when examining adverse events after hip arthroplasty [38].

7.2 Septic Arthritis

In study II, worse outcome and higher risk for revision was observed for patient with septic arthritis. In study III, variations were observed in the duration from surgery to start of treatment based on the causative agent. These variations may represent delay in diagnosis of this devastating complication. The impact of this delay and the impact of the causative infectious agent on the outcome is unknown, which can be the focus in future large epidemiological studies.

A common practice at our institution and many other institutions is soaking the graft with Vancomycin. There is growing evidence that this practice lowers the rates of septic arthritis

[19]. However, the retrospective design of these studies and the lack of randomized controlled trials raise questions about this practice.

7.3 The ideal timing of ACLR

The findings of study IV showed that long-term results of both acute ACLR and within 10 weeks of the injury provides satisfactory results, but the prevalence of osteoarthritis is still high. A recently published systematic review by Liukkonen et al. [45] concluded that the prevalence of post-traumatic OA after ACLR is still high despite the advances in surgical techniques. The current evidence indicates that the injury itself, whether managed operatively or non-operatively, is the cause of OA. However, the impact of the duration between injury and surgery on the development of OA is not well-studied. Whether acute ACLR can help to lower the prevalence of post-operative OA is an interesting topic for future studies.

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