The Impact of Delay to Anterior Cruciate Ligament Reconstruction on Patient-Reported Outcomes and Concurrent Knee Injuries

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science
Institute of Medical Science
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ABSTRACT
The ideal timing of anterior cruciate ligament reconstruction is debatable after ligament tear.

**Purpose:** To investigate the effects of delay from time of injury to reconstruction, on the cost-effectiveness, the incidence of concurrent knee pathology, and the patients’ quality of life.

**Methods:** We performed 2 systematic reviews and 1 multicenter cohort study, looking at the effects of delay, from injury to surgery, on the cost-effectiveness, concurrent knee injuries, and on quality of life, respectively.

**Results:** Despite substantial heterogeneity, ligament reconstruction was cost-effective in each study. A significant increase in medial meniscal and cartilage pathology was found as of 3 months’ post-injury, at which point, a decline in quality of life was also detected, 2 years post-operatively.

**Conclusion:** An increase in delay from time of injury to surgery can lead to an increase in cost, medial meniscal and cartilage pathology, and a potential decline of quality of life.
STATEMENT OF CONTRIBUTIONS

I, Danny Arora, solely prepared this thesis. I was involved in all aspects of this work, including the planning, conceptualization, execution, analysis, and writing of all original research. The following contributions by other individuals are formally and inclusively acknowledged:

Dr. Jay Wunder (Primary Supervisor): Mentorship, guidance and assistance in planning, execution, and discussion of manuscript and thesis preparation.

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Denise Chan: Collection of the data, obtaining and managing clinical information (Study #3).
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ABOS</td>
<td>American Board of Orthopaedic Surgeons</td>
</tr>
<tr>
<td>ACL</td>
<td>Anterior cruciate ligament</td>
</tr>
<tr>
<td>ACL-QoL</td>
<td>Anterior cruciate ligament quality of life</td>
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<tr>
<td>ACLR</td>
<td>Anterior cruciate ligament reconstruction</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>BPTB</td>
<td>Bone patella tendon bone</td>
</tr>
<tr>
<td>CDCP</td>
<td>Centers for Disease Control and Prevention</td>
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<tr>
<td>CE</td>
<td>Cost-effectiveness</td>
</tr>
<tr>
<td>CEA</td>
<td>Cost-effectiveness analysis</td>
</tr>
<tr>
<td>CEAR</td>
<td>Cost-effectiveness analysis Registry</td>
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<tr>
<td>CER</td>
<td>Cost-effectiveness ratio</td>
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<tr>
<td>CI</td>
<td>Cartilage injury</td>
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<tr>
<td>CIHR</td>
<td>Canadian Institutes of Health Research</td>
</tr>
<tr>
<td>CPI</td>
<td>Consumer price index</td>
</tr>
<tr>
<td>CUA</td>
<td>Cost-utility analysis</td>
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<tr>
<td>DR</td>
<td>Delayed Anterior cruciate ligament reconstruction</td>
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<tr>
<td>ER</td>
<td>Early Anterior cruciate ligament reconstruction</td>
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<td>ESRD</td>
<td>End stage renal disease</td>
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<tr>
<td>HGCI</td>
<td>High-grade cartilage injury</td>
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<tr>
<td>HT</td>
<td>Hamstring tendon</td>
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<tr>
<td>HUI</td>
<td>Health Utilities Index</td>
</tr>
<tr>
<td>ICER</td>
<td>Incremental cost-effectiveness ratio</td>
</tr>
<tr>
<td>ICRS</td>
<td>International Cartilage Repair Society</td>
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<tr>
<td>IKDC</td>
<td>International Knee Documentation Committee</td>
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<tr>
<td>ITS</td>
<td>Injury to surgery</td>
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<tr>
<td>KOOS</td>
<td>Knee Injury and Osteoarthritis Outcome Score</td>
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<tr>
<td>KT-1000</td>
<td>KT-1000 knee arthrometer</td>
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<tr>
<td>LCL</td>
<td>Lateral collateral ligament</td>
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<tr>
<td>LM</td>
<td>Lateral meniscus</td>
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<tr>
<td>LMT</td>
<td>Lateral meniscal tear</td>
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<tr>
<td>MCL</td>
<td>Medial collateral ligament</td>
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<tr>
<td>MeSH</td>
<td>Medical subject heading</td>
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<tr>
<td>MM</td>
<td>Medial meniscus</td>
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<tr>
<td>MMT</td>
<td>Medial meniscal tear</td>
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<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>NOQAS</td>
<td>Newcastle-Ottawa Quality Assessment Scale</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>OA</td>
<td>Osteoarthritis</td>
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<tr>
<td>PCL</td>
<td>Posterior cruciate ligament</td>
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<tr>
<td>PLC</td>
<td>Posterior lateral corner</td>
</tr>
<tr>
<td>PMC</td>
<td>Posterior medial corner</td>
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<tr>
<td>QALY</td>
<td>Quality-adjusted life-year</td>
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<tr>
<td>QHES</td>
<td>Quality of Health Economics Studies</td>
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<tr>
<td>QoL</td>
<td>Quality of Life</td>
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<td>QWB</td>
<td>Quality of Well Being Index</td>
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<td>SD</td>
<td>Standard deviation</td>
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<tr>
<td>SF-36</td>
<td>Short Form 36 questionnaire</td>
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<tr>
<td>SHSC</td>
<td>Sunnybrook Health Science Centre</td>
</tr>
<tr>
<td>TTS</td>
<td>Time to surgery</td>
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<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>WORMS</td>
<td>Whole-organ magnetic resonance imaging score</td>
</tr>
<tr>
<td>WTP</td>
<td>Willingness to pay</td>
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CHAPTER 1 - LITERATURE REVIEW

1.1. Introduction

Anterior cruciate ligament (ACL) injuries are a frequent source of disability and health resource utilization. Close to a quarter million ACL injuries occur annually in North America \(^1\), with approximately 50% being treated with an ACL reconstruction (ACLR), a commonly performed procedure, each year \(^2\). The total number of ACLRs performed in the United States increased from 33.0 per 100,000 capita in 1994 to 45.1 per 100,000 capita in 2006. The number of procedures performed in the ambulatory setting increased from 14 per 100,000 capita in 1994 to 43 per 100,000 capita in 2006, whereas the number of inpatient ACLRs decreased from 18 to 1 per 100,000 capita between 1990 and 2007. The total number of ACLRs (inpatient and ambulatory) increased from 86,837 (33 per 100,000 capita) in 1994 to 134,421 (45 per 100,000 capita) in 2006 \(^3\). The Centers for Disease Control and Prevention (CDC) has reported that about 100,000 ACLRs are performed annually \(^4\). Data collected by the American Board of Orthopaedic Surgeons (ABOS) for part II of the Certification Examination reveal that in 2004, ACLR ranked sixth among the most common surgical procedures performed by all sports medicine fellows and third among those surgeons identified as generalists \(^5\).

The age category varies greatly, from pediatric to adult populations, given the active lifestyle and predominance in sport participation, and is becoming more and more frequent in the young adolescent population \(^6\), with the annual incidence estimated at 16 per 1,000 high school students \(^7\). More than 50% of all those sustaining ACL injuries, occur in young athletes (15 to 25 years of age) \(^8\).
1.2. **ACL Anatomy and Kinematic Function**

Ligaments around the knee resist tensile forces in line with their functional axis. In the knee, multiple axes of rotation are in play, which are constantly changing under physiologic loads. Therefore, forces across the knee are absorbed and counterbalanced by the various ligaments in response to the load applied, acting as primary or secondary stabilizers depending upon the position of the limb in space.

The anterior cruciate ligament (ACL) plays an important role in maintaining human knee joint stability not only by limiting anterior tibial translation but also by maintaining axial and transverse rotation of the knee. Anterior tibial translation is the greatest between 20 and 45 degrees of knee flexion. It has been shown that sectioning the ACL results in a significant increase of internal tibial rotation near extension, while additional sectioning of the collateral ligaments did not change the instability pattern, indicating that the ACL is also an important restraint against internal rotation moments during flexion-extension.

During normal gait, the tibia internally rotates during swing phase and external rotation occurs during terminal extension due to the difference in the radius of curvature of the medial and smaller lateral condyle. This allows tightening of both cruciate ligaments, which lock the knee with the tibia in a position of maximal stability with respect to the femur. Between 20 degrees of flexion and full extension, the cruciate ligaments contribute to rotation between the tibia and femur known as the “screw home” mechanism, which is a key for standing upright.
1.3. Disease Burden of an ACL Tear

Abnormal joint forces in an ACL-deficient knee are associated with increased risk of injury to menisci, which normally serves as shock absorbers and transmit loads between the femur and tibia\(^1\). The overall disease burden of an ACL tear has been theorized to increase in complexity with the addition of other associated injuries, such as meniscal or cartilage pathology\(^2\). After an ACL rupture, knee instability can occur, causing the knee joint to give way and buckle. With each episode of knee buckling or giving way, meniscal tears can become more severe and less amenable to repair\(^3\). In a large level 1 prognostic study, it was shown that meniscal and articular cartilage injuries were found, in approximately 67% and 50% of ACLR patients, respectively\(^4\), with poorer two- and six-year functional outcomes\(^5\). A higher prevalence of chondral injury with chronicity has also been reported in prior single surgeon series, although with variable definitions of ‘delayed/ chronic’ from more than 6 weeks\(^6\) to more than 2 years\(^7\), and in one ACLR Norwegian Registry\(^8\). In the latter registry study, of the 3,475 patients, looking at the interaction between timing of ACLR and associated pathology, 26% had articular cartilage lesions, 47% meniscal tears and 15% had both. They demonstrated that adults <40 years of age had a nearly 1% increase odds of articular cartilage injury for each month from injury to surgery, and that cartilage lesions were almost twice as frequent when associated with a meniscal tear, and vice-versa.

An ACL injury can drastically impact normal knee kinematics, making it highly susceptible to concurrent injury, chronic instability, and long-term degenerative changes. While concomitant knee injuries (menisci, cartilage, and/or other ligaments) is thought to contribute to the development of OA in the ACL-deficient knee, ongoing instability and abnormal knee kinematics can also contribute\(^9\).
In some studies, it is thought that adolescents and young adults who sustain an ACL injury are at a significantly increased risk for the development of degenerative changes in the knee \textsuperscript{27-32}. In as many as 80% of ACL injured knees, radiographic evidence of osteoarthritis (OA) can be seen, at 5 to 15 years after initial injury, especially with concomitant meniscal damage \textsuperscript{31-34}. Patients with severe radiographic OA tend to have poorer health-related quality of life \textsuperscript{35}. In the athletic population, it has been shown that the risk of developing OA increased 100 times in athletes who have sustained a knee injury \textsuperscript{36,37}. In their meta-analysis, Ajuied et al. \textsuperscript{38} reported an incidence of 20% (121 of 596) of ACL-injured knees showed moderate or severe radiologic changes (grade III or IV) compared to only 5% (23 of 465) of contralateral uninjured knees; with relative risks of 3.89 and 3.84 to develop minimal and moderate OA changes post-ACL injury, respectively \textsuperscript{38}. In a cross-sectional study by Roos et al. \textsuperscript{39}, patients with injury to the ACL showed the first radiologic signs of OA (joint space narrowing) at an average age of about 40 years \textsuperscript{40}. Barenius et al. \textsuperscript{41} reported an incidence of 57% of OA was significantly greater than the 18% of OA cases in the contralateral knee at 14-year follow-up from ACLR, with OA most frequently found in the medial compartment. For that reason, ACL reconstructive surgery aims to recreate the normal native ACL anatomy.

\textbf{1.4. Timing of ACL Reconstruction}

Different schools of thought come into play when deciding the optimal time for treating ACL tears with a reconstruction. Some advocate for early surgery, others prefer to start the rehabilitation process preoperatively with focused physiotherapy and delayed ACLR, speculating that this will diminish the risk of arthrofibrosis \textsuperscript{42}, and increase preoperative knee range of motion and strength \textsuperscript{21,43}. In comparison to other Orthopaedic surgeries, such as joint replacements, delay to surgery has
been well documented to result in increased morbidity 44-47.

In their attempt to determine the influence of patient-reported outcomes on the chronicity of ACL tears, Nguyen et al. 48 found that patients undergoing ACLR after 6 months from original injury participated in less pivoting and cutting sports but reported better pain and function scores than those who were treated within 3 months from injury. Sernert et al. 49 found an increase in meniscal tears combined with poorer outcome in patients who underwent delayed ACLR compared to those who were reconstructed subacutely.

In the pediatric literature, early ACLR is favoured over the approach of rehabilitation with delayed ACLR. In their meta-analysis, Ramski et al. showed multiple trends favoring early reconstruction over nonoperative or delayed ACLR, as the latter experienced more instability or pathological laxity and an inability to return to previous levels of activity 50.

1.5. Cost-Effectiveness

Cost-effectiveness research has emerged as an increasingly used tool in evaluating health care services and treatments as it considers both the cost of care as well as clinical effectiveness 51. As pressures continue to increase in proving cost-effectiveness of particular treatments in health care, its research may aid in helping payers, providers, and policymakers invest in healthcare treatments that are more cost-effective than other potential interventions. In this era of increasing cost-consciousness, health economic analyses have become more common in the medical 52, and Orthopaedic surgery literature 53.
Some reviews have concluded that many operative interventions in Orthopaedic surgery are cost effective \(^{54,55}\), while another questioned the cost-effectiveness of certain procedures \(^{56}\). In response to this trend toward value-based health care, policy experts and leaders in the field have begun to encourage the publication of high-level evidence-based cost-effectiveness analyses (CEAs) \(^{53,57,58}\). As such, technological advances in the field and the increasing utilization of sports procedures will likely focus a value-based and cost-conscious policy lens onto the field \(^{59}\).

In terms of cost-analysis, ACL tears have been shown to have a significant societal and economic impact \(^{60}\). From a treatment perspective, ACLR has been shown to be a more a cost-effective strategy when compared to rehabilitation \(^{61}\). Furthermore, an early ACLR was shown to be more cost-effective when compared to a delayed reconstruction \(^{62}\).
CHAPTER 2 - RESEARCH FRAMEWORK

The central focus of this thesis will touch upon three (3) key components pertaining to the effects of delay from the time of injury to the time of surgery after an anterior cruciate ligament rupture of the knee. Those components are investigated in their respective research study, and pertain to the following: 1) the cost-effectiveness, 2) the incidence of concurrent knee injuries, and 3) the quality of life. The overall framework of the thesis can be found below.

2.1 RESEARCH QUESTIONS

1. What is the cost-effectiveness of anterior cruciate ligament reconstruction across the literature?

2. How does the delay from time of injury to surgery affect the incidence of concurrent cartilage and/or meniscal pathology at the time of anterior cruciate ligament reconstruction?

3. How does delay from time of injury to surgery affect quality of life after anterior cruciate ligament reconstruction?
2.2 RESEARCH HYPOTHESES

1. Anterior cruciate ligament reconstruction is a cost-effective treatment for anterior cruciate ligament tears.

2. Delay from time of injury to surgery increases the incidence of concurrent injuries, meniscal and/or cartilaginous, associated with anterior cruciate ligament tears.

3. Increased delay from time of injury to surgery negatively affects quality of life after an anterior cruciate ligament reconstruction.

2.3 THESIS COMPONENTS


2. Systematic review on concurrent injuries associated with anterior cruciate ligament tears in terms of delay from time of injury to surgery.

CHAPTER 3 - STUDY #1:

Cost-Effectiveness of Anterior Cruciate Ligament Reconstruction: A Systematic Descriptive Review of the Literature.
3.1. ABSTRACT

**Background:** The anterior cruciate ligament (ACL) is one of the most commonly injured knee ligaments, particularly in young and active individuals. Given the increasing incidence of surgical management and questions regarding natural history, there is increasing interest regarding the cost-effectiveness of operative vs. nonoperative management.

**Purpose:** The objective of this systematic review was to evaluate the literature, specifically on the cost-effectiveness of anterior cruciate ligament reconstruction.

**Study design:** Systematic descriptive review

**Methods:** We conducted a systematic review of published cost-effectiveness analyses of anterior cruciate ligament reconstruction included in electronic databases, PUBMED, MEDLINE, EMBASE and the Cost-Effectiveness Analysis Registry. The data abstracted included cost per anterior cruciate ligament reconstruction, quality-adjusted life years gained, cost-effectiveness ratios, time frame, and utility assessment.

**Results:** Six included studies focused on the economic analysis and cost-effectiveness of ACLR (dates published 1999 to 2014). One study looked at early anterior cruciate ligament reconstruction versus rehabilitation and optional delayed anterior cruciate ligament reconstruction from a societal perspective. One study looked at ACLR alone from an individual perspective [Lubowitz, 2009], two studies looked at ACLR compared to rehabilitation alone, from a societal perspective. Two studies evaluated various modes of anterior cruciate ligament reconstruction from a societal perspective. In 3 of the 6 studies (50%), ACLR has been shown to reduce societal costs relative to rehabilitation alone.

**Conclusion:** Overall, anterior cruciate ligament reconstruction was shown to be a cost-effective treatment for anterior cruciate ligament tears in each respective
study. However, given the heterogeneity across included studies, we cannot make any definitive conclusions. Setting standards for procedural cost and identifying which patients are most likely to benefit from surgery are two methods that must be pursued in order to enhance the healthcare value of anterior cruciate ligament reconstruction in a restricted resource environment.
3.2. INTRODUCTION
There has been an increasing attention to defining and measuring the “value-for-money” associated with interventions in Orthopaedic surgery. Cost-effectiveness research has emerged as an increasingly used tool in evaluating health care services and treatments as it considers both the cost of care as well as clinical effectiveness. In this era of increasing cost-consciousness, health economic analyses have become more common in the medical and Orthopaedic surgery literature. As pressures continue to increase in proving cost-effectiveness of particular treatments in health care, its research may aid in helping payers, providers, and policymakers invest in healthcare treatments that are more cost-effective than other potential interventions.

Some reviews have concluded that many operative interventions in Orthopaedic surgery are cost effective, while another questioned the cost-effectiveness of certain procedures. In response to this trend toward value-based health care, policy experts and leaders in the field have begun to encourage the publication of high-level evidence-based cost-effectiveness analyses (CEAs). As such, technological advances in the field and the increasing utilization of sports procedures will likely focus a value-based and cost-conscious policy lens onto the field.

In the realm of Orthopaedic sports medicine, the anterior cruciate ligament (ACL) is one of the most commonly injured knee ligaments. There are two primary treatments that exist for ACL tears: non-operative treatment with a structure rehabilitation program and surgical reconstruction. Surgical reconstruction is being used more often to facilitate return to activity, and to protect the menisci and
The annual incidence of ACL reconstruction (ACLR) is increasing. In 2006, 129,836 ACLRs were performed in the United States (43.48 per 100,000 person-years) \(^6^8\). The non-operative treatment approach is generally reserved for lower-demand and older patients, however, in their randomized controlled trial, Frobell et al. \(^4^3\) suggest that this approach may also be appropriate for younger patients. Short to intermediate-term outcomes for both treatments are well documented with Level-I and II evidence \(^4^3,^6^9\).

In terms of cost-analysis, ACL tears have been shown to have a significant societal and economic impact \(^6^0\). From a treatment perspective, ACLR has been shown to be a more a cost-effective strategy when compared to rehabilitation \(^6^1\). Furthermore, an early ACLR was shown to be more cost-effective when compared to a delayed reconstruction \(^6^2\).

The goal of this review was to synthesize the existing literature to evaluate the cost-effectiveness of anterior cruciate ligament reconstruction. As per the literature, we hypothesize that ACLR is a cost-effective treatment for ACL tears.

### 3.3. METHODS

#### 3.3.1. Cost-Effectiveness Analysis Tutorial

A thorough review of cost analyses and their application within Orthopaedics have been previously published \(^5^3,^5^8,^7^0\). Below is a brief summary of pertinent definitions:

#### 3.3.1.1. Definitions

*Cost-effectiveness analysis (CEA)*: Economic study design that compares the costs and health effects of an intervention to assess the extent to which it can be regarded
as providing value for money. It is expressed in ratio of costs per unit health gained. From this analysis, an incremental cost-effectiveness ratio (ICER) is calculated by measuring the incremental costs and incremental health benefits for an intervention against an alternative(s). Based on their ICERs, decision-makers can compare and determine where to allocate limited healthcare resources. A strategy is termed ‘dominant’ when an intervention is both less costly and more effective than the alternative.

*Incremental costs:* Difference between the cost of an intervention and the cost of an alternative with which it is being compared.

*Incremental cost-effectiveness ratio (ICER):* Incremental cost associated with an additional quality-adjusted life-year (QALY). It incorporates both increases in survival times (extra life-years) and changes in the quality of life (with or without increased survival) into a single measure.

\[
\text{ICER} = \frac{\text{Cost}_{\text{Intervention}} - \text{Cost}_{\text{Alternative}}}{\text{QALY}_{\text{Intervention}} - \text{QALY}_{\text{Alternative}}}
\]

*Cost-utility analysis (CUA):* Economic analysis that assesses the value of an intervention in terms of its impact on both changes in the quality and quantity of life. This analysis is more patient-centric and subjective (as it required the health effects to be valued) than the CEA.

*Incremental cost-utility ratio:* The difference in intervention costs and those of its alternative divided by the difference in the benefits of the intervention and the benefit of its alternative, where benefits are measured in terms of changes to both
life expectancy and the quality of life. A lower incremental cost-utility ratio translates into a better value.

Sensitivity analysis: Determines the impact of various form of uncertainty on the results.

Quality-adjusted life years (QALY): Measure of disease burden by extra years of life provided by therapy. Those additional years of life are weighted by the quality of life, as measured by social or societal preferences or utilities associated with various health states.

Utilities (aka “preference weights”): Measure of an individual’s or a society’s preference for a particular set of health outcomes. Many generic health tools (e.g., the Quality of Well Being [QWB] Index, the EQ-5D, the Health Utilities Index [HUI] and the SF-6D have been used to link information from these questionnaires to aid researchers in estimating a patient’s preference for a specific health state, which is then used to calculate quality of life, useful in cost-utility analyses.

Direct costs: The costs of labour, supplies, and equipment to provide direct patient care services. E.g. hospitalization costs, outpatient follow-up, rehabilitation costs, imaging costs, etc.

Indirect costs: The costs in relation to an individual’s loss of productivity, probability of being employed, lower productivity while at work, number of missed workdays, and the value of household work and leisure time foregone.
To summarize, when performing a CEA, Cost-effectiveness ratios (CER) must be interpreted to decide whether an intervention yields good value for money, cost-effective or economically attractive. In terms of changing health policy, many factors come into play that are far more complex than what's being described in this review.

3.3.1.2. Cost-Effectiveness Threshold

In cost-effectiveness analyses, the incremental cost-effectiveness ratio (ICER) is represented by the ratio of the incremental cost and the incremental effectiveness of the intervention under review and the next best alternative. Traditionally, $50,000 per QALY gained, has been used in the literature as a cost-effectiveness threshold. This translates to an intervention or surgical strategy being deemed “cost-effective” if the ICER is below this threshold, and deemed of lower value if it above the threshold. This threshold has been globally applied in Health Economics research throughout medicine and surgery for decades. Only a few economic thought leaders have questioned its validity and applicability. Neumann et al. explain the origin of this threshold value, in their New England Journal of Medicine perspective article. It stems back to the 1970s health state preferences for patients with end stage renal disease (ESRD) on dialysis to assist Medicare in coverage decisions for these patients. Neumann and colleagues state that this threshold is in fact too low and should be representative of the lower end of the spectrum. There has been an increasing number of studies also using $100,000 as their threshold. In Orthopaedic surgery, the majority of studies still use the $50,000 per QALY threshold. In their systematic review, Nwachukwu et al. identified 23 cost-utility analyses (CUA) in total joint arthroplasty, 16 (70%) used a $50,000 per QALY, two studies used $100,000, one study used both $50,000 and $100,000, and one study
used $150,000; three studies did not define a cost effectiveness threshold.

A set $50,000 cost-effectiveness threshold cannot be systematically applied; as different surgical procedures have different cost implications even within the same surgical sub-specialty. For example, in the cost-utility analysis of the Spine Patient Outcomes Research Trial (SPORT), Tosteson et al.\(^8^2\) found that spinal decompression alone had an ICER of $38,900/QALY, and for spinal fusion it was $120,200 per QALY gained. If one were to use the $50,000 threshold, that would lead to various interpretations of their findings given the large ICER difference between both procedures.

Neumann and colleagues\(^8^1\) state that a tiered cost-effectiveness threshold approach ($50,000, $100,000 and $150,000) would be more appropriate on a surgery-specific approach. Nwachukwu et al.\(^8^3\) also suggest the use of a tiered cost-effectiveness threshold but with a modification to tailor these thresholds to the perspective from which the analysis is undertaken.

### 3.3.2. Overview and Eligibility Criteria for Review

We conducted a systematic review in accordance using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines with a PRISMA checklist\(^8^4\).

#### 3.3.2.1. Search Methodology

A systematic literature search was performed by both the lead author (Danny Arora) and a second author (Jas Chahal), to make sure there was agreement with respect to the search and validating its methodology, as per the Cochrane Handbook
guidelines\textsuperscript{101}. All disagreements were resolved with a discussion. Studies collected were restricted to English language literature, using electronic databases PUBMED, EMBASE, MEDLINE and the Cost-Effectiveness Analysis Registry (CEAR) (created by Center for the Evaluation of Value and Risk in Health at Tufts University)\textsuperscript{85}. The timeline of the search was from database inception to December 10\textsuperscript{th}, 2015. The search was conducted using medical subject headings (MeSH) and/or text keywords: ‘anterior cruciate ligament’, ‘ACL’, ‘surg*’ (to include variations such as surgery or surgical), ‘reconstruct*’ (to include variations such as reconstructed or reconstruction), ‘QALY’, ‘quality-adjusted life-year’, ‘cost*’ (to include all cost-effectiveness, cost-utility, cost-analysis studies), combined using the Boolean operators “AND” and “OR”. The reference lists of eligible studies were searched for additional papers. The final search function built was used for all four databases:

\begin{verbatim}
(ACL or anterior cruciate ligament) AND (Surg* OR reconstruct*) AND (QALY OR quality-adjusted life-year) AND (cost* OR cost-effect* OR cost-utility)
\end{verbatim}

3.3.2.2. Eligibility Criteria
The studies were retained further if they met the following inclusion criteria: 1) cost-effectiveness papers of ACLR, 2) arthroscopic surgical technique, 3) studies that were looking at cost/QALY as their outcome, 4) English language studies, 5) United States (US)-based studies only, in order to keep the healthcare cost representation uniform (studies were deemed as US-based after a careful review of the affiliation of the corresponding author, journal of publication, patient cohort location, and currency of the cost analysis), and 6) Studies published as of 1999. The exclusion criteria were comprised of: 1) all studies not looking at cost-effectiveness analysis as a primary outcome, 2) non-clinical studies (defined as review articles, opinion articles, and non-operative studies without a surgical comparator), 3) open surgery,
4) meta-analyses, 5) non-English language studies, 6) non-US studies, and 7) studies published prior to 1999.

3.3.2.3. Data Extraction
The data from all studies were extracted by the lead author, and entered using a spreadsheet software. Information regarding the study characteristics (first author, year of publication, study design, level of evidence), area of analysis, cost representation (direct costs, indirect costs, patient versus societal perspective), cost logistics (time horizon, currency, and annual discount rate) and the variables analyzed (cost/ ACLR, QALYs gained, cost/QALYs (ICER)) were recorded.

3.3.3. Quality Scoring Assessment
Identified studies were retrieved, independently reviewed and scored by two authors (Danny Arora and Jas Chahal), validating the assessment, to answer the Quality of Health Economics Studies (QHES) instrument. Both reviewers convened to further evaluate areas of scoring discrepancy and arrive at a consensus score. The QHES is a questionnaire used to evaluate the quality of economic studies. It was designed to evaluate all 3 common types of health economic analyses: cost-minimization, cost-effectiveness, and cost-utility. The instrument emphasizes appropriate methods, valid and transparent results, and comprehensive reporting of results in each study (Figure 3-1). Its 16 criteria were selected by a panel of 8 health economics experts with experience conducting these analyses. Criteria are framed as “yes” or “no” questions, weighted with values ranging from 1 to 9. A “yes” answer receives full point value, whereas, a “no” answer receives zero points. Total scores for the QHES instrument range from 0 to 100. Standardized interpretation of the scores is not yet defined, however, scores ranging between 80
to 100 are considered ‘high quality’, and scores below 50 are typically not deemed worthy of publication. For ease of use, we deemed studies to be of ‘high quality’ for scores between 80-100, ‘moderate quality’ for 50-79, and ‘low quality’ for <50. This QHES was subsequently validated in a survey including 60 experts (30 clinicians and 30 health economists) in 6 disease categories. The experts were asked, by using their judgment (global assessment) and then by using the QHES instrument, to rate 3 health economic evaluation articles in their disease category. It was assumed that the global assessment of the experts was the “gold standard” and they found in their validity analysis that the QHES instrument had good convergent validity (Spearman’s rho test; coefficient=0.78, p<0.0001 and Wilcoxon test; p=0.53). The result of analysis of covariance (ANCOVA, F3, 146=5.97, p=0.001) implied that the instrument has good discriminant validity. The findings of both good construct and discriminant validity indicate that the QHES has good overall construct validity. The QHES will be used to assess each included study.
Figure 3-1: Quality Assessment - QHES Instrument.

3.3.4. Cost Forecasting

After extracting the data from all 6 included studies, the currencies were all in U.S. dollars (USD). However, as expected, there was a large discrepancy in the value of the currency year, ranging from 1999 to 2012, given the different publication period for each study. In order to ensure equivalent in adjustment for inflation was
undertaken, using the consumer price index (CPI) for medical care, with all US dollar costs converted to a common base year of 2016.

The CPI in any year is the cost in that year for a bundle of goods and services purchased by a typical urban consumer compared to the cost of that bundle of goods and services in a base period.

3.4. RESULTS

3.4.1. Overview of Eligible Studies

Our search revealed 30 studies, PUBMED (8), EMBASE + MEDLINE (16), CEAR (6) (Figure 3-2).

**Figure 3-2: Study Flow Diagram**

Study selection log and the number of studies excluded at each stage. Out of the 30 studies, there were 20 duplicates (67.7%), which were removed. From
the remaining 10 studies, 4 studies had irrelevant titles or abstracts (50%) and 1 study was from outside the U.S., a Swiss-based study\(^9\), leaving 5 studies for review. Only one additional study from the reference lists, met the inclusion criteria and was added, and thus, there were six resulting identified studies (Table 3-1).

<table>
<thead>
<tr>
<th>Study</th>
<th>Area of Analysis</th>
<th>Time Horizon (years)</th>
<th>Currency</th>
<th>Annual Discount Rate</th>
<th>Cost Perspective</th>
<th>Major Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genuario et al. (^65) (2012)</td>
<td>ACLR using BTB autograft vs. hamstring autograft vs. allograft</td>
<td>1</td>
<td>2012 USD$</td>
<td>Nil (1 year cycle only)</td>
<td>Societal (Indirect costs partially included)</td>
<td>HT autograft = least costly ($5375/surgery) and most effective (0.912 QALY gained) graft choice compared to both BTB autograft ($5580 per 0.906 QALY gained) and allograft ($6958 per 0.904 QALY gained).</td>
</tr>
<tr>
<td>Gottlob et al. (^61) (1999)</td>
<td>ACLR vs. rehab only in young adults</td>
<td>7</td>
<td>1999 USD$ (estimate)</td>
<td>3%</td>
<td>Societal (Indirect costs NOT included)</td>
<td>ACLR in young adults = $5857 per QALY gained.</td>
</tr>
<tr>
<td>Lubowitz et al. (^57) (2011)</td>
<td>ACLR and knee arthroscopy alone</td>
<td>2</td>
<td>2009 USD$ (inflation adjusted)</td>
<td>/</td>
<td>Patient (Indirect costs NOT included)</td>
<td>Knee arthroscopy = $5783 per QALY gained. ACLR = $10,326 per QALY gained.</td>
</tr>
<tr>
<td>Study</td>
<td>Comparison</td>
<td>Duration</td>
<td>Year</td>
<td>Discount Rate</td>
<td>Type of Cost</td>
<td>Comment</td>
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</tr>
<tr>
<td>Mather et al. 62 (2014)</td>
<td>Early ACLR vs. rehab + delayed ACLR.</td>
<td>6</td>
<td>2012</td>
<td>3%</td>
<td>Societal (Indirect costs NOT included)</td>
<td>Early ACLR = both less costly ($19,883/surgery) and more effective (5.12 QALY gained) compared to rehabilitation plus optional delayed ACLR ($21,454 per 4.84 QALY gained).</td>
</tr>
<tr>
<td>Mather et al. 60 (2013)</td>
<td>ACLR vs. rehabilitation only</td>
<td>ST: 6, LT: Lifetime</td>
<td>2012</td>
<td>3%</td>
<td>Societal (Indirect costs included)</td>
<td>Up to 6 years postoperatively, ACLR = cost savings of $4503 and 0.18 QALY gained. For the lifetime, ACLR = incremental cost savings of $50,417 and 0.72 QALY gained.</td>
</tr>
<tr>
<td>Paxton et al. 66 (2010)</td>
<td>DB vs. SB ACLR</td>
<td>12</td>
<td>2009</td>
<td>3%</td>
<td>Societal (Indirect costs NOT included)</td>
<td>Base case: DB ACLR = $6416 per QALY gained; however, with alternate scenario assumptions = $64,371 per QALY.</td>
</tr>
</tbody>
</table>

**Table 3-1: Identified Studies and Major Findings**

### 3.4.2. Conversion of Costs to 2016 USD$

The average costs for ACLR, as reported across each respective study, have risen from $15,716 to $17,672, when converting from their respective year of currency to 2016 USD$. Please refer to Table 3-2 for all inflated costs of each study, and to Figure 3-3 for the Summary of ACLR Cost/ QALY (Reported vs. Inflated).

<table>
<thead>
<tr>
<th>Study</th>
<th>Area of Analysis</th>
<th>Time Horizon</th>
<th>Currency</th>
<th>Cost (USD$)/ ACLR</th>
<th>Cost (2016 USD$)/ ACLR</th>
<th>Cost (USD$)/ QALY</th>
<th>Cost (2016 USD$)/ QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genuario et al. 65 (2012)</td>
<td>ACLR using BTB autograft vs. hamstring autograft vs. allograft</td>
<td>1 year</td>
<td>2012 USD$</td>
<td>5970$</td>
<td>6240$</td>
<td>6581$</td>
<td>6879$</td>
</tr>
<tr>
<td>Gottlob et al. 61 (1999)</td>
<td>ACLR vs. rehab only in young adults</td>
<td>7 years</td>
<td>1999 USD$ (estimate)</td>
<td>11768</td>
<td>16969</td>
<td>2307</td>
<td>3327</td>
</tr>
<tr>
<td>Lubowitz et al. 57 (2011)</td>
<td>ACLR and knee arthroscopy alone</td>
<td>2 years</td>
<td>2009 USD$ (inflation adjusted)</td>
<td>12740</td>
<td>14295</td>
<td>10326</td>
<td>11586</td>
</tr>
<tr>
<td>Mather et al. 62 (2014)</td>
<td>Early ACLR vs rehab + delayed ACLR. MOON + KANON groups</td>
<td>6 years</td>
<td>2012 USD$</td>
<td>20669</td>
<td>21604</td>
<td>4159$</td>
<td>4347</td>
</tr>
<tr>
<td>Mather et al. 60 (2013)</td>
<td>ACLR vs. rehabilitation only</td>
<td>ST: 6 years, LT: Lifetime</td>
<td>2012 USD$</td>
<td>27433</td>
<td>28674</td>
<td>5422</td>
<td>5667</td>
</tr>
<tr>
<td>Paxton et al. 66 (2010)</td>
<td>DB vs. SB ACLR</td>
<td>12 years</td>
<td>2009 USD$ (inflation adjusted)</td>
<td>/</td>
<td>/</td>
<td>6416$</td>
<td>7199$</td>
</tr>
</tbody>
</table>
Table 3-2: Cost Inflation Summary

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD; range)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>a: Average of all 3 graft</td>
<td>15,716</td>
</tr>
<tr>
<td>types (hamstring tendon</td>
<td>(8385; 5970-27,433)</td>
</tr>
<tr>
<td>and bone-patella-tendon-</td>
<td></td>
</tr>
<tr>
<td>bone autografts, allograft</td>
<td>17,556</td>
</tr>
<tr>
<td>b: Average of early ACLR</td>
<td>5869</td>
</tr>
<tr>
<td>and delayed ACLR; c:</td>
<td>(2701; 2307-10,326)</td>
</tr>
<tr>
<td>Represented by double</td>
<td>6501</td>
</tr>
<tr>
<td>bundle ACLR only.</td>
<td>(2895; 3327-11,635)</td>
</tr>
</tbody>
</table>

*Figure 3-3: Summary of ACLR Cost/QALY (Reported versus Inflated)*

Values for ‘Genuario et al. 2012’ represent the mean of the cost/QALY of all 3 graft types (hamstring tendon and bone-patella-tendon-bone autografts, allograft); for ‘Mather et al. 2014’, the values represent the mean of early ACLR and delayed ACLR; and for ‘Paxton et al. 2010’, the values represent double bundle ACLR only.

3.4.3. Heterogeneity Among Identified Studies

The studies were heterogeneous in terms of the cost perspective, time horizon and type of cost comparisons (direct and/or indirect costs), hence the variability in the reported costs per ACLR and subsequent ICERs.
In 5 of the 6 studies (83.3%), the costs were analyzed from a societal perspective, utilizing decision analytic models\textsuperscript{60,62,65}. In one of the studies, costs were calculated from a patient or health system perspective [Lubowitz, 2011] calculating costs from a prospective cohort of 128 patients or health service.

Only 2 studies (33.3%) included or attempted to include indirect costs in their analysis\textsuperscript{60,65}. Indirect costs are represented by work days lost, and other forms of productivity costs. The remaining 4 studies mentioned that indirect costs were not included in their cost calculations.

Across the studies, the direct costs calculated were variable. Gottlob et al.\textsuperscript{61} added costs for outpatient clinic visits, initial surgery, rehabilitation, and also factored in if a reoperation was needed in each of his operative versus nonoperative arms. Genuario et al.\textsuperscript{65} derived costs from direct operative costs, additional direct postoperative rehabilitation or indirect societal or patient costs. Their costs were estimated from multiple sources in the literature. In their prospective cohort analysis, Lubowitz et al.\textsuperscript{57} direct costs were represented by facility costs and surgical professional fees specific to the author’s home hospital cost data. Paxton et al.\textsuperscript{66} utilized literature-derived costs and calculated using a gross-estimation method, an approach in which the estimation is based on “economically significant” events, such as, costs of acute care hospitalization, outpatient-based care, surgeon and anesthesia fees, physical therapy and durable medical equipment\textsuperscript{91}. In his societal and economic impact of ACL tears study, Mather et al.\textsuperscript{60} calculated estimates from the national mean Medicare reimbursements for the procedures, estimates of direct medical costs as a percentage of the Medicare rate and then weighted by the national distribution of payers for the treatment of ACLR. Indirect costs
estimates were also calculated; in the short to intermediate term estimated by the effects of functional limitations due to ACL tear on work status, earnings, and for the long-term calculation, costs were associated with knee osteoarthritis and total knee arthroplasty (TKA). In their more recent study, Mather et al. 62, did not calculate indirect costs, as they looked into the cost-analysis of timing of ACLR (early versus delayed surgery).

3.4.4. Economic Findings in Identified Studies

From the 6 selected studies on the cost-effectiveness of ACLR, there were 3 areas of investigation: 1) treatment methods for an ACL tear, 2) modes of ACLR, and 3) timing of ACLR.

3.4.4.1. Cost-Effectiveness of Operative versus Nonoperative Management of Anterior Cruciate Ligament Tears

One study (16.7%) analyzed the cost-effectiveness of knee arthroscopy alone and of ACLR 57 on institutional and cohort data. In their non-comparative analysis, Lubowitz et al. 57 found both procedures to be cost-effective, with a cost-effectiveness ratio (CER) of $5,783 for knee arthroscopy alone and $10,326 for ACLR. The cost differences between both knee arthroscopy and ACLR, were partially due to the hospital costs ($1,060 versus $1,740, respectively), but mostly due to the higher professional fees ($5,250 versus $11,000, respectively).

Two studies (33.3%) compared ACLR alone versus rehabilitation only 60, 61. In their study, Gottlob et al. 61 evaluated the cost-effectiveness of ACLR in a young adult population. After the first 7 years after an ACL tear, they found that the resultant cost-effectiveness ratio for ACLR was $9,435 per 1.61 QALYs, leading to an CER for
the base case analysis of $5,857 per QALY. In their comparison of operative versus non-operative treatment of ACL tears, Mather et al. 60 found that in the first 6 years after an ACL tear (short-term analysis), ACLR yielded mean incremental cost savings of $4,503 compared to that of rehabilitation, while providing an incremental QALY gain of 0.18 compared to rehabilitation. In their long-term analysis, the mean lifetime cost to society for a typical patient undergoing an ACLR was $38,121 compared to $88,538 for rehabilitation. This lead to mean incremental cost savings of $50,417, while providing an incremental QALY gain of 0.72.

3.4.4.2. Cost-Effectiveness of Various Modes of Anterior Cruciate Ligament Reconstruction

Two other studies (33.3%) evaluated various modes of ACLR. Paxton et al. 66 evaluated the cost-effectiveness between a double bundle (DB) versus a single bundle (SB) ACLR technique. They found that in the reference case, the DB technique, although costlier by $3,362 compared to the SB technique, it was more effective by 0.52 QALY. The incremental cost-effectiveness ratio (ICER) of DB ACLR compared to SB ACLR was $6,416 per QALY, a short-term finding. However, when alternative scenarios were proposed this finding did not hold up. Genuario et al. 65 evaluated the cost-effectiveness of ACLR with hamstring tendon (HT) autograft versus bone-patella-tendon-bone (BPTB or BTB) autograft versus allograft. The authors found that all 3 methods were cost-effective. The HT autograft proved to be most cost-effective at with a cost-effectiveness ratio (CER) $5,892 per QALY compared to the BTB autograft ($6,157 per QALY) and allograft ($7,694 per QALY).
3.4.4.3. Cost-Effectiveness of Anterior Cruciate Ligament Reconstruction in Relation to Timing of Surgery

One study (13.7%) compared the cost-effectiveness of early ACLR (ER) compared to rehabilitation with optional delayed ACLR (DR) \(^{62}\). The authors found that in the base case, over 6 years after an ACL tear, the CERs were $3,881 per QALY and $4,434 per QALY for the ER and DR groups, respectively. The ICER for the DR group was deemed ‘dominated’ by the ER group, as the latter had a lower average cost to society by $1,572 with an incremental gain of 0.28 QALYs. The effectiveness gains were attributed by the low utility of an unstable knee and the resultant lower utility for the DR group as a whole. The cost of rehabilitation and the rate of additional surgery drove the increased cost of the DR group.

3.4.5. Quality of Identified Studies

Using the Quality of Health Economics Studies (QHES) Instrument (refer to Section 3.2.3. Quality Scoring Assessment for details on the method of calculations), the mean score of all 6 studies was 81.0 (SD = 12.4; range = 61.0 to 94.0). Three studies were judged to be ‘high quality’ papers quality’ (QHES score 80-100) and the three other studies were deemed to be of ‘moderate quality’ (QHES score 50-79). As restated by \(^{59}\) and consistent with prior methods for reporting author-derived quality scores of published CEA evidence in Orthopaedics, the quality of all 6 studies is presented in aggregate and not presented for each individual study \(^{92}\). The breakdown of how frequently each criterion from the QHES Instrument was met by all the studies can be viewed on Figure 3-4.
**3.5. DISCUSSION**

In Orthopaedic surgery, cost-effectiveness studies unfortunately trail behind other specialties in terms of number and quality of studies that are published. Brauer et al. \(^{92}\) recently reported that up until 2003 there were only 62 cost-effectiveness studies (52 cost-utility studies) published focusing on interventions dealing with the musculoskeletal system and Orthopaedic surgery. Our goal was to review and evaluate the literature, specifically looking at the cost-effectiveness of anterior cruciate ligament reconstruction.

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**Figure 3-4: QHES Instrument Breakdown Information**
Frequency of criterion met by all included studies.
Based on the identified studies, anterior cruciate ligament reconstruction (ACLR) has been shown to be a cost-effective surgical procedure, when compared to rehabilitation alone (non-operative treatment) \(^{60,61}\), or when performed early versus rehabilitation with an optional delayed ACLR \(^62\). Based on only 1 study, various modes of ACLR were found to be cost-effective. Using a HT autograft was proven to be less costly and more effective compared to the BTB autograft or the allograft \(^{65}\). The double bundle ACLR technique was also thought to be a potentially more cost-effective (as the reference case) when compared to the single bundle technique in the short-term \(^{66}\). In contrast, Mohtadi et al. \(^{93}\) found no difference in disease-specific quality of life in their randomized controlled trial comparing ACLR with different graft types (HT versus BTB versus DB). Given the added cost, time of surgery, extra training required, they could not recommend at DB ACLR over the other graft types.

Our study is the first descriptive review of the cost-effectiveness of ACLR specifically. Previous reviews on cost-effectiveness analyses in Orthopaedic surgery have been reported. In particular, two previous studies by Brauer et al. \(^{53,92}\) reviewed the quality and trends of cost-effectiveness analysis (CEA) in the Orthopaedic literature. Although, very heterogeneous, there has been an increase in publications with 45 articles (73%) after 1998. In the total joint arthroplasty literature, Daigle et al. \(^{54}\) and Nwachukwu et al. \(^{55}\) have conducted reviews on CEAs and cost-utility analyses (CUAs), and concluded that both total knee arthroplasty (TKA) and total hip arthroplasty (THA) are both cost-effective, despite the paucity of the literature. Kepler et al. \(^{94}\) found that certain aspects of spinal care were cost-effective based on their systematic review, but that there needed to be better definition of value given the wide variations between studies.
As per Nwachukwu et al.\textsuperscript{59}, we also applied the QHES Instrument to assess the value and quality of the cost-effectiveness analysis studies included in our study. Although, not readily used in Orthopaedics, the QHES has been proven to be a simple, consistent, and suitable scale to measure the quality of health economic evaluation studies, especially cost-effectiveness studies\textsuperscript{95}. The lack of literature on the topic was quite apparent. Our hypothesis, that there’s a great deal of heterogeneity and poor quality reporting in the literature, was confirmed. With respect to the poor quality reporting, based on our evaluation with the QHES Instrument, 3 out of the 6 studies (50\%) could be considered high-quality. This seems to be in keeping with the literature, as Nwachukwu et al.’s systematic review showed that there seems to be good quality representation in Sports Medicine specifically\textsuperscript{59}.

This review has a number of limitations. First, in order to keep the healthcare cost representation uniform, only US-based studies were included. For the sake of completeness, we did run the search without this exclusion criteria, and identified one extra study that was Swiss-based [Farshad, 2011], where the authors also found that ACLR had an ICER of $4,890 USD/QALY over conservative treatment within their healthcare system. Conversely, in limiting our search to English-speaking studies only, we create a language bias. Although, there have been studies that have looked into the impact of this type of bias, the problem of language bias may therefore be becoming less significant, but is still one to be aware of\textsuperscript{96, 97}. Additionally, a small number of articles were identified from our search. This relates to the paucity of research related to cost-effectiveness with respect to ACLR. Inherently, the results this review should be taken with caution and inadvertently, further analysis would be necessary. Finally, the heterogeneity in methods and
reporting between studies made head to head comparison difficult across all parameters.

Unfortunately, we were unable to come to a definitive conclusion in terms of the cost-effectiveness of ACLR. Future studies are required. More importantly, a Canadian-based prospective study, whereby direct and indirect costs are calculated with respect to both ACLR and non-operative treatment, would be useful in order to calculate the ICER, and determine whether or not ACLR is the most cost-effective treatment strategy.

3.6. CONCLUSION

Across all the literature, irrespective of how they defined their respective costs, whether it was compared to rehabilitation or knee arthroscopy, to early ACLR versus delayed ACLR, or even to itself in various modes of reconstructions, each study found that ACLR was a cost-effective surgical procedure. However, we found significant heterogeneity across studies in terms of the evaluation methods employed, the way costs were reported, and most importantly, the cost perspective and follow-up time horizon employed. Nonetheless, it is important to undertake cost-effectiveness analyses in medicine, even if a perfect model cannot be constructed. These analyses enable health care policy makers to identify both clinical and cost-effective treatment options, guide future research, and motivate surgeons to practice fiscally responsible medicine.
CHAPTER 4 - STUDY #2:

Systematic Review on the Concurrent Knee Injuries with Anterior Cruciate Ligament Tears in Terms of Delay from Injury to Surgery.
4.1. ABSTRACT

Anterior cruciate ligament (ACL) injuries are very common. The majority of these injuries tend to occur during sports, specifically with mechanisms of injury involving deceleration, cutting or twisting. Studies have supported the theory that ACL injuries increase the risk of concomitant knee injuries and development of premature osteoarthritis. The treatment of choice remains to be an ACL reconstruction (ACLR). There are nearly 200,000 ACLRs performed annually in the United States. The ideal timing of an ACLR, with respect to the injury date, is still a debatable. Some authors advocate that delaying surgery by 3 weeks in the setting of an acute ACL tear is advantageous to minimize postoperative motion, while others feel that, as time elapsed from injury to surgery, the odds of a cartilage injury increased by 1% for every month of delay.

**Hypothesis/Purpose**: To perform a systematic review of the literature looking at the effects of delay from time of injury to time of surgery on concurrent: 1) meniscal injuries and/or 2) chondral injuries, at the time of an ACLR. We hypothesize that as the time from injury to surgery increases, after an ACL tear, there is an increased incidence of meniscal and/or cartilage pathology.

**Study design**: Systematic review

**Methods**: We conducted a systematic review, according to the PRISMA guidelines, of published studies looking into the effects of delay on concurrent knee injuries from time of ACL injury to surgery, included in electronic databases, PUBMED, MEDLINE, EMBASE. The data abstracted included study characteristics, patient demographics, time from injury to surgery (in months), timing breakdown utilized in the study, number medial meniscal tears (MMT), lateral meniscal tears (LMT), and cartilage injuries. Studies were also subdivided in ACLR timing breakdowns from injury: 1) less or more than 3 months, 2) less or more than 6 months, and 3) less or
more than 12 months, when data was available. In groups of studies deemed to be clinically homogenous, data from these studies were pooled and a meta-analysis was conducted. Outcomes were reported as odds ratios. All tests were considered significant at \( p \leq 0.05 \).

**Results**: From the 4613 initial pulled studies, 30 studies met our inclusion criteria. There was a total of 22,113 patients with a frequency weighted age of 21.95 years. The average time to surgery (TTS) was 12.3 months. In terms of concurrent injuries, there were 5,588 MMTs, 5,324 LMTs, and 6,862 cartilage injuries. The most common (50% of studies) timing breakdown, in terms of delay from injury to surgery, was less or more than 12 months. There was a significant increase in odds of MMTs \( (p<0.0003) \) and of cartilage injuries \( (p<0.00001) \), at time of ACLR, when surgery performed after 3 months from injury. An association existed with increased odds of LMTs when ACLR was performed less than 3 months \( (p=0.86) \), but no significance was found.

**Conclusion**: Our findings show that an increase in delay from time of injury (ACL tear) to time of surgery (ACLR) is associated with increased odds of medial meniscal tears (MMTs) and cartilage injuries, and a potential decreasing odds of lateral meniscal tears (LMTs). However, based on this data, we could not show independent risk factors to predict an increase odds of concurrent injuries in terms of timing.
4.2. INTRODUCTION

Anterior cruciate ligament (ACL) injuries are very common. The majority of these injuries tend to occur during sports, specifically with mechanisms of injury involving deceleration, cutting or twisting \(^{98,99}\). Studies have supported the theory that ACL injuries increase the risk of concomitant knee injuries and development of premature osteoarthritis \(^{100}\). The treatment of choice remains to be an ACL reconstruction (ACLR) \(^{99}\). There are nearly 200,000 ACLRs performed annually in the United States \(^{63,64}\). The ideal timing of an ACLR, with respect to the injury date, is still a debatable. Shelbourne et al. \(^{42}\) advocated that delaying surgery by 3 weeks in the setting of an acute ACL tear was advantageous to minimize postoperative motion. In their Scandinavian Registry study, Granan et al. \(^{21}\) showed that as time elapsed from injury to surgery, the odds of a cartilage injury increased by 1\% for every month of delay. As more and more studies are surfacing on this topic, the goal of this study was to perform a systematic review of the literature looking at the effects of delay from time of injury to time of surgery on concurrent: 1) meniscal injuries and/ or 2) chondral injuries, at the time of an ACLR. We hypothesize that as the time from injury to surgery increases, after an ACL tear, there is an increased incidence of meniscal and/ or cartilage pathology.

4.3. METHODS

We conducted a systematic review in accordance using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines with a PRISMA checklist \(^{84}\).
4.3.1. Search Methodology

A systematic literature search was performed by both the lead author (Danny Arora) and a second author (Jas Chahal), to make sure there was agreement with respect to the search and validating its methodology, as per the Cochrane Handbook guidelines. All disagreements were resolved with a discussion. Studies collected were restricted to English language literature, using electronic databases PUBMED, EMBASE and MEDLINE. The timeline of the search was from database inception to October 14th, 2015. The search was conducted using medical subject headings (MeSH) and/or text keywords: ‘anterior cruciate ligament’, ‘ACL’, ‘surg*' (to include variations such as surgery or surgical), ‘reconstruct*' (to include variations such as reconstructed or reconstruction), ‘menisc*' (to include meniscal or meniscus), ‘cart*' or ‘chondr' (to include cartilage and chondral), ‘Tim*' (to include time or timing), ‘acute’, ‘early’, ‘chronic’, and ‘delay’, combined using the Boolean operators “AND” and “OR”. The reference lists of eligible studies were searched for additional papers. The following final search function was used for all four databases:

(Tim* OR acute OR early OR chronic OR Delay*) AND (ACL or anterior cruciate ligament) AND (Surg* OR reconstruct*) AND (menisc* OR cart* or chondr*)

4.3.2. Eligibility Criteria

The studies were retained further if they met the following inclusion criteria: 1) human studies, 2) ACLR, 3) reporting of time from injury to surgery (ITS), 4) prevalence of meniscal pathology, 5) prevalence of chondral pathology, 6) level of evidence I-IV.

The exclusion criteria were comprised of: 1) all studies not reporting or analyzing in terms of ‘delay’ from time of ITS, 2) all studies not reporting concurrent injuries
(meniscal and/or chondral), 3) level of evidence V, 4) Meta-analyses or systematic reviews.

4.3.3. Data Extraction
The data from all studies were extracted, by the lead author (Danny Arora), and entered using a spreadsheet software. Information regarding the study characteristics (first author, year of publication, study design, level of evidence), patient demographics (number, pediatric or adult cohorts, age, gender, BMI), the time from injury to surgery (reported in months), and the timing breakdown utilized in the study. Given the variability in the timing breakdown across all studies, we decided to utilize the three most common time classifications for the analysis portion of this study: 1) ≤ or > 3 months, 2) ≤ or > 6 months, and 3) ≤ or > 12 months. For each of these timing breakdowns, the data from the studies were entered, in an attempt to pool the results on concurrent knee injuries when ACLR is performed at 1) ≤ or > 3 months, 2) ≤ or > 6 months, and 3) ≤ or > 12 months.

4.3.4. Outcomes
In this review, we wanted to analyze the effects of delay on outcomes related to concurrent knee injuries (outcome) after an ACL tear. Those outcomes were as follows: 1) medial meniscal tear (MMT), 2) lateral meniscal tear (LMT), 3) cartilage injury (CI), and 4) ‘high-grade’ cartilage injury (HGCI). For each study, the number of MMTs, LMTs, and CIs were reported. Given the variability in how these injuries were reported, all grades were taken into account, and the presence of any injury (binary method; yes = presence of injury, no = absence of injury) was included.
In addition, when reported in the study, the incidence of HGCIs was also collected. These were defined as a grade 3 or 4 cartilage injury according to the International Cartilage Rating Society (ICRS) scale \(^{102}\) or equivalent according to other scoring methods used.

4.3.5. Quality Scoring Assessment

Identified studies were retrieved, independently reviewed and scored by two authors (Danny Arora and Jas Chahal), validating the assessment, to answer the Newcastle-Ottawa Quality Assessment Scale (NOQAS) \(^{103}\). Both reviewers convened to further evaluate areas of scoring discrepancy and arrive at a consensus score. The NOQAS (Figure 4-1) is a tool used to assess non-randomized studies. It consists of 8 items, categorized into 3 groups: 1) the selection of the study groups; 2) the comparability of the groups; and 3) the ascertainment of either the outcome of interest. Visual interpretation of the scores makes for a quick visual assessment, as stars are awarded for each item, up to 2 stars for ‘comparability’ items. Highest quality studies are awarded up to 9 stars. The scale was developed as a collaboration between the Universities of Newcastle, Australia and Ottawa, Canada using a Delphi process to define variables for data extraction \(^{103}\).
Figure 4-1: The Newcastle-Ottawa Quality Assessment Scale.

Three categories: 1) Selection, 2) Comparability, 3) Outcome. A maximum of 1 star can be awarded to each numbered item within the ‘selection’ and ‘outcome’ categories; whereas, a maximum of 2 stars can be awarded within the ‘comparability’ category.
4.3.6. Statistical Analysis

Data on our outcomes (MMTs, LMTs, CIs, HGCIs) were collected from each study as proportion (number of patients having a particular outcome out of total number of patients). We also obtained data on time delay between injury (ACL tear) and surgery (ACLR) as a covariate.

4.3.6.1. Analyses 1

Data on proportions of outcomes from various studies were pooled using Der-Simonian Laird method using random-effects model. We used random-effects model as we expected some degree of heterogeneity between studies with regards to clinical and methodological heterogeneity. Pooled proportion and 95% confidence interval were estimated. Studies in the meta-analyses were weighted using inverse of variance. Statistical heterogeneity was evaluated using $i^2$ statistic. It was defined as low (25%), moderate (50%), and high (75%) as described by Higgins et al. 101.

4.3.6.2. Analyses 2

Our secondary aim was to identify whether timing of surgery was associated with outcome or not. We conducted meta-regression analyses using time of surgery as a covariate. If timing of surgery was identified to be associated with rate of outcomes, then we explored possibility of median age of patients in cohort to understand whether it influences the estimate.

4.3.6.3. Analyses 3

We included prospective and retrospective studies in this meta-analyses. We conducted subgroup analyses using only prospective studies to evaluate whether
estimates were different or not.

4.3.6.4. Analyses

We compared the outcomes in two groups of patients based on timing of surgery (early vs delayed). Early surgery was defined as ≤ 3 months, ≤ 6 months, and ≤ 12 months, respectively, and late surgery was defined as > 3 months, > 6 months, and > 12 months, respectively. Unadjusted odds ratios were calculated for each study and pooled using fixed-effects model as the observed heterogeneity ($I^2$) was < 50%. When the latter was > 50%, a random-effects model was employed.

All analyses were conducted using Open Meta-analyst platform available at (http://www.cebm.brown.edu/openmeta/) and using Review Manager 5.3 (Copenhagen, Denmark).

4.4. RESULTS

4.4.1. Overview of Search Methodology

Our electronic search revealed 4613 studies, PUBMED (1576), EMBASE + MEDLINE (3037) (Figure 4-2). Out of the 4613, 949 studies (20.6%) were non-human studies, and subsequently, there were 1946 duplicates (42.2%), which were removed. From the remaining 1718 studies, 1459 studies had irrelevant titles (85%), and 217 studies (12.6%) had irrelevant abstracts, leaving 42 studies for review. Two additional studies from the reference lists, met the inclusion criteria and were added, and thus, the total number was 44 identified studies that were assessed for eligibility. From these 14 studies (31.8%) were excluded due to: abstracts only (5), ‘delay’ was inconsistently or not reported outcome (4), not
primarily ACLR-based study (2), meta-analyses or systematic reviews (2), and MRI-based study (1); leaving a total of 30 studies included in our systematic review.

Figure 4-2: Flow Diagram.
Study selection log and the number of studies excluded at each stage.

4.4.2. Study Quality of Identified Studies
Quality assessment of all studies was performed using the Newcastle-Ottawa Quality Assessment Scale (NOQAS). Table 4-1 summarizes the breakdown for each study. The average overall score across all 30 studies was 7.2 (SD = 1.5; range = 4 to 9).
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<th>COMPARABILITY (of 2 stars)</th>
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**Table 4.1: The Newcastle-Ottawa Quality Assessment Score Summary**

Scoring breakdown: maximum of 9 stars: 4 stars for ‘Selection’, 2 stars for ‘Comparability’, and 3 stars for ‘Outcome’.
4.4.3. Overview of Eligible Studies

4.4.3.1 Demographic Results

From the 30 included studies, there was a total of 22,113 patients/ACLRs enrolled, with a study sample size range of 39 to 5086 patients/ACLRs (Table 4-2). Some studies reported the number of ACL reconstructions, instead the number of patients. The mean age was 24.09 years (SD: 6.16; range 13 to 33.7). The frequency weighted age was 21.95 years. The mean percentage of males was 68.9% (SD: 15.64; range 23.1 to 93.6). The average time from injury to surgery across all studies was 12.3 months (SD: 8.4; range 0.7 to 27.4). There was a total of 24 studies where the subjects were adults, and 8 studies investigating the pediatric population. Two of the adult studies\(^\text{21,131}\), had pediatric cohorts, explaining why there are seemingly two extra studies (8 + 24 = 32 studies). A total of 7 studies (23%) had prospectively collected data compared to 23 studies which were retrospective in nature (77%). The level of evidence was applied based on how it was reported in the study. In the event that this was not indicated, we applied the guidelines previously published by Guyatt et al.\(^\text{132}\) and Spindler et al.\(^\text{133}\).
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Early: 0-4mos, Late: >6mos

NR: Not Reported

Arastu et al. 2012
Barenus et al. 2015
Chen et al. 2015
Chhadia et al. 2011
Church and Keating 2005
De Roeck and Lang-Steveson 2003
Dumont et al. 2012
Fok and Yau 2013

NR: Not Reported

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<tr>
<td>Arastu et al. 2012</td>
<td>5.60 (39.3%)</td>
</tr>
<tr>
<td>Barenus et al. 2015</td>
<td>NR</td>
</tr>
<tr>
<td>Chen et al. 2015</td>
<td>18.05 (31.4%)</td>
</tr>
<tr>
<td>Chhadia et al. 2011</td>
<td>NR</td>
</tr>
<tr>
<td>Church and Keating 2005</td>
<td>NR</td>
</tr>
<tr>
<td>De Roeck and Lang-Steveson 2003</td>
<td>NR</td>
</tr>
<tr>
<td>Dumont et al. 2012</td>
<td>NR</td>
</tr>
<tr>
<td>Fok and Yau 2013</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR: Not Reported

Arastu et al. 2012
Barenus et al. 2015
Chen et al. 2015
Chhadia et al. 2011
Church and Keating 2005
De Roeck and Lang-Steveson 2003
Dumont et al. 2012
Fok and Yau 2013

NR: Not Reported

<table>
<thead>
<tr>
<th>Study</th>
<th>Delayed: &gt;6mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arastu et al. 2012</td>
<td>46 (30.8%)</td>
</tr>
<tr>
<td>Barenus et al. 2015</td>
<td>850 (23.9%)</td>
</tr>
<tr>
<td>Chen et al. 2015</td>
<td>92 (22.2%)</td>
</tr>
<tr>
<td>Chhadia et al. 2011</td>
<td>850 (23.9%)</td>
</tr>
<tr>
<td>Church and Keating 2005</td>
<td>53 (29.0%)</td>
</tr>
<tr>
<td>De Roeck and Lang-Steveson 2003</td>
<td>23.62 NR</td>
</tr>
<tr>
<td>Dumont et al. 2012</td>
<td>160 (43.2%)</td>
</tr>
<tr>
<td>Fok and Yau 2013</td>
<td>15.31 (32.7%)</td>
</tr>
</tbody>
</table>

NR: Not Reported

Arastu et al. 2012
Barenus et al. 2015
Chen et al. 2015
Chhadia et al. 2011
Church and Keating 2005
De Roeck and Lang-Steveson 2003
Dumont et al. 2012
Fok and Yau 2013

NR: Not Reported
<table>
<thead>
<tr>
<th>Study</th>
<th>A</th>
<th>4</th>
<th>R</th>
<th>75  (81)</th>
<th>26.0 (12-51)</th>
<th>Early:&lt;6m os; Late:&gt;6mo s</th>
<th>NR</th>
<th>NR</th>
<th>NR</th>
<th>NR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foster et al. (2005)</td>
<td>P</td>
<td>3</td>
<td>R</td>
<td>47 (94)</td>
<td>14.8 (NR)</td>
<td>&lt;1 yr vs. &gt;1 yr; &lt;2yrs vs. &gt;2yrs</td>
<td>16.83</td>
<td>13 (27.7%)</td>
<td>16 (34.0%)</td>
<td>27 (57.4%)</td>
</tr>
<tr>
<td>Funahshi et al. (2014)</td>
<td>A</td>
<td>3</td>
<td>R</td>
<td>709 (56)</td>
<td>28.0 (11-61)</td>
<td>Acute: &lt;4wks, Subacute: 4-8wks, Chronic: &gt;8wks</td>
<td>24.20</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Ghodra et al. (2013)</td>
<td>A</td>
<td>3</td>
<td>P</td>
<td>3475 (57) (P:391; A:3084)</td>
<td>27.0 (12-67)</td>
<td>NR</td>
<td>7.10</td>
<td>P: 93 (23.8%); A: 621 (20.1%)</td>
<td>P: 65 (16.6%); A: 456 (14.8%)</td>
<td>63 (16.1%); A: 844 (27.4%)</td>
</tr>
<tr>
<td>Granan et al. (2009)</td>
<td>A</td>
<td>4</td>
<td>R</td>
<td>112 (NR)</td>
<td>15.4 (NR)</td>
<td>0-4 mos, 4-12mos, 1-2yrs</td>
<td>11.40</td>
<td>60 (53.4%)</td>
<td>64 (57.3%)</td>
<td>NR</td>
</tr>
<tr>
<td>Guenther et al. (2014)</td>
<td>A</td>
<td>3</td>
<td>R</td>
<td>1375 (82)</td>
<td>27.6 (16-48)</td>
<td>&lt;3mos, 3-12mos, 1-3yrs, &gt;3yrs</td>
<td>NR</td>
<td>409 (29.7%)</td>
<td>326 (23.7%)</td>
<td>227 (16.5%)</td>
</tr>
<tr>
<td>Joseph et al. (2008)</td>
<td>A</td>
<td>4</td>
<td>R</td>
<td>176 (NR)</td>
<td>NR</td>
<td>Acute: &lt;6wks, Subacute 6wks-12mos, Chronic: &gt;12mos</td>
<td>NR</td>
<td>108 (61.4%)</td>
<td>95 (54%)</td>
<td>NR</td>
</tr>
<tr>
<td>Keeney et al. (1993)</td>
<td>A</td>
<td>4</td>
<td>R</td>
<td>300 (79)</td>
<td>25.6 (23-31)</td>
<td>A: 0-2mos; B: 2-6mos; C: 6-12mos; D: 12-18mos; E: &gt;18mos</td>
<td>9.89</td>
<td>74 (24.7%)</td>
<td>157 (52.3%)</td>
<td>127 (42.3%)</td>
</tr>
<tr>
<td>Kennedy et al. (2010)</td>
<td>A</td>
<td>3</td>
<td>P</td>
<td>541 (58)</td>
<td>25.9 (7-62)</td>
<td>(1) ≤6wks and &gt;6 wks; (2) ≤12 wks and &gt;12 wks</td>
<td>9.03</td>
<td>197 (36.4%)</td>
<td>211 (39%)</td>
<td>82 (15.2%)</td>
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<tr>
<td>Kluczniski et al. (2013)</td>
<td>A</td>
<td>3</td>
<td>P</td>
<td>70 (NR)</td>
<td>13.5 (11-14)</td>
<td>≤12wks, &gt;12wks</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Study</td>
<td>Group</td>
<td>Sample Size</td>
<td>Mean Age (Range)</td>
<td>NR</td>
<td>Percentage</td>
<td>Number of Cases</td>
<td>Percentage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------</td>
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</tr>
<tr>
<td>Maffulli et al. (2003)</td>
<td>A</td>
<td>378 (75)</td>
<td>27.3 (16-50)</td>
<td>NR</td>
<td>(13.5%)</td>
<td>51</td>
<td>(33.4%)</td>
<td></td>
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<tr>
<td>Magnussen et al. (2013)</td>
<td>A</td>
<td>311 (51)</td>
<td>26.8 (13-59)</td>
<td>≤12wks, &gt;12wks</td>
<td>1.40</td>
<td>90</td>
<td>(28.9%)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Michali tsis et al. (2015)</td>
<td>A</td>
<td>109 (88)</td>
<td>26.4 (26-29)</td>
<td>A: 0-3 mos, B: 3-12 mos, C: &gt;12 mos</td>
<td>NR</td>
<td>32</td>
<td>(29.4%)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Millett et al. (2002)</td>
<td>P</td>
<td>39 (23)</td>
<td>13.6 (10-14)</td>
<td>Acute: &lt;6wks, Chronic: &gt;6wks</td>
<td>3.37</td>
<td>10</td>
<td>(25.6%)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Murrell et al. (2001)</td>
<td>A</td>
<td>130 (73)</td>
<td>26.0 (14-67)</td>
<td>&lt;1mo, 1mo-2yrs, &gt;2yrs</td>
<td>5.07</td>
<td>NR</td>
<td>NR</td>
<td></td>
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<tr>
<td>Newman et al. (2015)</td>
<td>P</td>
<td>272 (54)</td>
<td>13.0 (7-19)</td>
<td>&lt;3mos, &gt;3mos</td>
<td>NR</td>
<td>66</td>
<td>(24.3%)</td>
<td></td>
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<tr>
<td>O’Connor et al. (2005)</td>
<td>A</td>
<td>1375 (64)</td>
<td>28.7 (NR)</td>
<td>&gt;2wks, 2-6wks, 6-12wks, 12-26wks, 26wks-1yr, &gt;1yr</td>
<td>0.70</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papastergiou et al. (2007)</td>
<td>A</td>
<td>451 (82)</td>
<td>26.3 (14-52)</td>
<td>a: &lt;1.5mos, b: 1.5-3mos, c: 4-6mos, d: 7-12mos, e: 1-2yrs, f: 2-4yrs</td>
<td>NR</td>
<td>113</td>
<td>(25.1%)</td>
<td></td>
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<tr>
<td>Sri-Ram et al. (2013)</td>
<td>A</td>
<td>5086 (64)</td>
<td>30.0 (9-69)</td>
<td>&lt;5mos; 5-12mos; &gt;12mos</td>
<td>17.24</td>
<td>1381</td>
<td>(27.2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tandon gan et al. (2004)</td>
<td>A</td>
<td>764 (90)</td>
<td>27.0 (14-59)</td>
<td>&lt;1yr, 2-5yrs, and &gt;5yrs</td>
<td>20.08</td>
<td>279</td>
<td>(36.5%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 4-2: Baseline Characteristics Table.**

4.4.3.2. Incidence of Concurrent Injuries at Time of Surgery

Across all studies (N = 22,113), there were a total of 5,588 medial meniscal tears (MMTs) (25.3%), 5,324 lateral meniscal tears (LMTs) (24.1%), and 6,862 cartilage injuries of all grades (31.0%), found at time of surgery.

4.4.3.3. Effects of Delay on Concurrent Injuries (as reported)

Irrespective of how each study defined ‘delay’ from time of injury to surgery (ITS), their general message in terms of the effects of delay on concurrent knee injuries at the time of an ACLR is important to note. These overall findings are summarized in Table 4-3. The graphic distribution of each can be viewed in Figure 4-3.

Twenty-one (21) studies (70%) showed that an increase in delay from injury to ACLR significantly increased the incidence of medial meniscal tears (MMTs). Four (4) studies (13.3%) showed no significant association with delay. Five (5) studies (16.7%) did not report these findings. Only 3 studies (10%) showed that an increase in delay from injury to ACLR significantly increased the incidence of lateral meniscal tears (LMTs), whereas, 22 studies (73.3%) showed no significant association, and 5 studies (16.7%) did not report these findings.

In terms of cartilage pathology incidence found at time of surgery, the association with delay was significantly found in 17 studies (56.7%). Only 7 studies (23.3%) found no significant association and 6 studies (20%) did not report these findings.
<table>
<thead>
<tr>
<th>Author</th>
<th># Pts or # ACLRs</th>
<th>Timing Breakdown</th>
<th>Mean Time from Injury to Surgery (months)</th>
<th>Does Delay ↑ associated MEDIAL Meniscal Pathology? (Y/N)</th>
<th>Does Delay ↑ associated LATERAL Meniscal Pathology? (Y/N)</th>
<th>Does Delay ↑ associated Cartilage Pathology? (Y/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson and Anderson</td>
<td>135</td>
<td>Acute: &lt;6wks, subacute 6-12wks, chronic: &gt;12wks</td>
<td>10.97</td>
<td>Y (p=0.007)</td>
<td>Y (p=0.016)</td>
<td>Y (p=0.005)</td>
</tr>
<tr>
<td>(2015)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anstey et al.</td>
<td>195</td>
<td>Early: /=&lt;6mo, delayed: &gt;6mo</td>
<td>3.50</td>
<td>Y (p=0.012)</td>
<td>N (p=0.85)</td>
<td>N (p=0.37)</td>
</tr>
<tr>
<td>(2012)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arastu et al.</td>
<td>117</td>
<td>Early= 0-4months, Late= &gt;6mo</td>
<td>5.60</td>
<td>Y (p&lt;0.05)</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>(2015)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barenius et al.</td>
<td>3556</td>
<td>&lt;3mo, 3-6mo, 6-12mo, 1-2yrs, 2-4yrs, &gt;4yrs</td>
<td>NR</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>(2013)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chen et al.</td>
<td>292</td>
<td>Acute: /=1mo, subacute: 2-3mo, early: 4-6mo, midterm: 7-12mo, late: &gt;12mo</td>
<td>18.05</td>
<td>Y (p&lt;0.05)</td>
<td>N</td>
<td>Y (p&lt;0.05)</td>
</tr>
<tr>
<td>(2015)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Chhadia et al.</td>
<td>1252</td>
<td>0-3mo; 3-6mo; 6-12mo; &gt;12mo</td>
<td>NR</td>
<td>Y (P&lt;0.001)</td>
<td>N (p=0.643)</td>
<td>Y (p=0.009)</td>
</tr>
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<td>(2011)</td>
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<tr>
<td>Church and Keating</td>
<td>183</td>
<td>Early: &lt;12mo, Delayed: &gt;12mo. (A:0-12mo, B:13-24mo, C:25-36mo, D:37-48mo, E:&gt;48mo)</td>
<td>27.38</td>
<td>Y (p=0.0051)</td>
<td>N (p=0.704)</td>
<td>Y (p=0.0007)</td>
</tr>
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<td>(2005)</td>
<td></td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>Study</td>
<td>n</td>
<td>Injury Type</td>
<td>Injury to ACLR</td>
<td>p-value</td>
<td>p-value</td>
<td>p-value</td>
</tr>
<tr>
<td>------------------------------</td>
<td>-------</td>
<td>---------------------------------</td>
<td>----------------</td>
<td>----------</td>
<td>----------</td>
<td>----------</td>
</tr>
<tr>
<td>De Roeck and Lang-Stevenson</td>
<td>68</td>
<td>1) Injury to scope, 2) Scope to ACLR</td>
<td>23.62</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Dumont et al. (2012)</td>
<td>370</td>
<td>Early: =/≤150days, Late: &gt;150days</td>
<td>NR</td>
<td>Y (p=0.014)</td>
<td>N (p=NS)</td>
<td>NR</td>
</tr>
<tr>
<td>Fok and Yau (2013)</td>
<td>150</td>
<td>Early: 0-12mos, Late: &gt;12mos</td>
<td>15.31</td>
<td>Y (p=0.007)</td>
<td>N (p=NS)</td>
<td>Y (p=0.033)</td>
</tr>
<tr>
<td>Foster et al. (2005)</td>
<td>75</td>
<td>Early:&lt;6mos; Late:&gt;6mos</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Funahashi et al. (2014)</td>
<td>47</td>
<td>&lt;1 year vs. &gt;1 year; &lt;2yrs vs. &gt;2yrs</td>
<td>16.83</td>
<td>N (p=0.11)</td>
<td>N (p=0.93)</td>
<td>N (p=0.53)</td>
</tr>
<tr>
<td>Ghodadra et al. (2013)</td>
<td>709</td>
<td>Acute: &lt;4wks, Subacute: 4-8wks, Chronic &gt;8wks</td>
<td>24.20</td>
<td>NR</td>
<td>NR</td>
<td>Y (p&lt;0.0001)</td>
</tr>
<tr>
<td>Granan et al. (2009)</td>
<td>3475</td>
<td>NR</td>
<td>7.10</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Guenther et al. (2014)</td>
<td>112</td>
<td>0-4 months, 4-12mos, 1-2yrs</td>
<td>11.40</td>
<td>Y (p=0.001)</td>
<td>N (p=0.45)</td>
<td>NR</td>
</tr>
<tr>
<td>Joseph et al. (2008)</td>
<td>1375</td>
<td>&lt;3mos, 3-12mos, 1-3yrs, &gt;3yrs</td>
<td>NR</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Keene et al. (1993)</td>
<td>176</td>
<td>Acute: &lt;6wks, subacute 6wks-12mos, chronic: &gt;12mos</td>
<td>NR</td>
<td>Y (p&lt;0.001)</td>
<td>N (p=NS)</td>
<td>NR</td>
</tr>
<tr>
<td>Study</td>
<td>n</td>
<td>Group 1</td>
<td>Group 2</td>
<td>Group 3</td>
<td>Group 4</td>
<td>Group 5</td>
</tr>
<tr>
<td>--------------------------------------</td>
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<td>-----------------------------------</td>
<td>-----------------------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>Kennedy et al. (2010)</td>
<td>300</td>
<td>A: 0-2mos; B: 2-6mos; C: 6-12mos; D: 12-18mos; E: &gt;18mos</td>
<td>9.89 (P&lt;0.0001)</td>
<td>N (p=0.270)</td>
<td>Y (P&lt;0.0001)</td>
<td></td>
</tr>
<tr>
<td>Kluczynski et al. (2013)</td>
<td>541</td>
<td>(1) =/&gt;6 wks and &gt;6 weeks; (2) =/&gt;12 wks and &gt;12 weeks</td>
<td>NR</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Lawrence et al. (2011)</td>
<td>70</td>
<td>=or&lt;12 weeks; &gt;12 weeks</td>
<td>NR</td>
<td>Y (p=0.028)</td>
<td>N (p&gt;0.10)</td>
<td>Y (p&lt;0.02)</td>
</tr>
<tr>
<td>Maffulli et al. (2003)</td>
<td>378</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Y (p&lt;0.004)</td>
</tr>
<tr>
<td>Magnussen et al. (2013)</td>
<td>311</td>
<td>&lt;/=12wks, &gt;12wks</td>
<td>1.40 (p = 0.013)</td>
<td>N (p=NS)</td>
<td>Y (P&lt;0.016)</td>
<td></td>
</tr>
<tr>
<td>Michalitsis et al. (2015)</td>
<td>109</td>
<td>A: 0-3 mos, B: 3-12 mos, C: &gt;12 mos</td>
<td>NR</td>
<td>N (p=NS)</td>
<td>N (p=NS)</td>
<td>Y (p&lt;0.001)</td>
</tr>
<tr>
<td>Millett et al. (2002)</td>
<td>39</td>
<td>Acute: &lt;6wks, Chronic: &gt;6wks</td>
<td>3.37 (p = 0.0223)</td>
<td>N (p=NS)</td>
<td>N/A since NONE</td>
<td></td>
</tr>
<tr>
<td>Murrell et al. (2001)</td>
<td>130</td>
<td>&lt;1mo, 1mo-2yrs, &gt;2yrs</td>
<td>5.07 (p&lt;0.05)</td>
<td>N (r /=0.2)</td>
<td>Y (p&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Newman et al. (2015)</td>
<td>272</td>
<td>&lt;3mos, &gt;3mos</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>N</td>
</tr>
<tr>
<td>O'Connor et al. (2005)</td>
<td>1375</td>
<td>&gt;2 weeks, 2-6 weeks, 6-12 weeks, 12-26 weeks, 26 weeks -1 year, &gt;1 year</td>
<td>0.70 (p&lt;0.001)</td>
<td>N (p&gt;0.109)</td>
<td>Y (p&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Papastergiou et al. (2007)</td>
<td>451</td>
<td>a: &lt;1.5mos, b: 1.5-3mos, c: 4-6mos, d: 7-12mos, e:</td>
<td>NR</td>
<td>Y (p=0.001)</td>
<td>N (p=0.90)</td>
<td>NR</td>
</tr>
</tbody>
</table>
### Table 4-3: Summary of Studies Report of Delay on Concurrent Injuries.

d: days, mos: months, yr: year, yrs: years, NR: not reported, Y: yes, N: no.

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Delay Period</th>
<th>Mean Delay</th>
<th>Y</th>
<th>N</th>
<th>NR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sri-Ram et al. (2013)</td>
<td>5086</td>
<td>&lt;5 mos; 5-12 mos; &gt;12 mos</td>
<td>17.24</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Tandogan et al. (2004)</td>
<td>764</td>
<td>&lt;1 year, 2-5 years, and &gt;5 years</td>
<td>20.08</td>
<td>Y (p=0.000)</td>
<td>Y (p=0.000)</td>
<td>Y (p=0.000)</td>
</tr>
</tbody>
</table>

#### Figure 4-3: Effects of Delay on Concurrent Injuries (as reported).

Graphic distribution of studies reporting an increased incidence of concurrent injuries, irrespective of how they defined ‘delay’. MM: medial meniscus, LM: lateral meniscus

#### 4.4.3.4. Timing Breakdown

As depicted in **Table 4-1**, the timing breakdown across all studies is variable. Twelve studies (40%) could be divided into ≤ or > 3 months, 9 studies (30%) into ≤...
or > 6 months, and 16 studies (53%) into ≤ or > 12 months from time of injury to surgery. Those timing breakdowns were the most widely used, with the 12 months’ cut-off being the most common across all the studies.

Not only were the timing breakdowns variable, the terminology used was inconsistent. Five (5) studies (16.7%) divided their cohorts into ‘early’ versus ‘late’ or ‘delayed’. Five (5) other studies (16.7%) utilized the wording ‘acute’, ‘subacute’, and ‘chronic’. Lastly, one study used a different method, combining almost all the terminology, and divided their cohorts into ‘acute’, ‘subacute’, ‘early’, ‘midterm’, and ‘late’.

4.4.4. Statistical Analyses Results
4.4.4.1. Statistical Analysis of Concurrent Knee Injuries - Analysis 1-3
4.4.4.1.1. Medial Meniscal Tears
Twenty-three studies (76.7%) had available MMT data. When pooled, the studies were found to be very heterogeneous with a high $I^2$ (96.4). The pooled estimate of proportions was 32.3%, where approximately 1 in 3 patients had a MMT across studies (Figure 4-4).
**Figure 4-4: Meta-Analysis of Proportions for Medial Meniscal Tears**

Overall pooled estimate proportion rate for MMTs across included studies with available data. C.I. = confidence interval; Ev = event (MMTs); Trt = total events (MMTs)

When time (delay from injury to surgery) was used as a covariate, the model was not found to be significant (p=0.724), showing no association from time of surgery and rate of MMTs (Figure 4-5).
Figure 4-5: Meta-Regression Analysis for Medial Meniscal Tears
Meta-regression analysis for MMTs using time (delay from injury to surgery) as a covariate, across studies with available data. X-axis represents time of surgery. Y-axis represents the proportion of patients having a MMT.

When looking at the data from the prospective studies only (7 of 30 studies), the high heterogeneity remained ($I^2 = 98.5$). The overall pooled estimate rate of MMT was 30.4% (Figure 4-6). The meta-regression model was not significant ($p=0.891$), showing no association between the rate of MMT and timing of surgery.
4.4.4.1.2. Lateral Meniscal Tears

Twenty-three studies (76.7%) had available LMT data. When pooled, the studies were also found to be very heterogeneous with a high $I^2$ (98.6). The pooled estimate of proportions was 34.6%, where approximately one third of patients also had a LMT across the studies (Figure 4-7).
<table>
<thead>
<tr>
<th>Studies</th>
<th>Estimate (95% C.I.)</th>
<th>Ev/Trt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson 2015</td>
<td>0.519 (0.434, 0.603)</td>
<td>78/135</td>
</tr>
<tr>
<td>Jostey 2012</td>
<td>0.651 (0.584, 0.718)</td>
<td>127/195</td>
</tr>
<tr>
<td>Krause 2015</td>
<td>0.308 (0.224, 0.391)</td>
<td>36/117</td>
</tr>
<tr>
<td>Barenius 2013</td>
<td>0.208 (0.195, 0.221)</td>
<td>740/3556</td>
</tr>
<tr>
<td>Chen 2015</td>
<td>0.223 (0.175, 0.279)</td>
<td>65/292</td>
</tr>
<tr>
<td>Chhabra 2011</td>
<td>0.459 (0.432, 0.487)</td>
<td>575/1252</td>
</tr>
<tr>
<td>Church 2005</td>
<td>0.256 (0.229, 0.282)</td>
<td>34/183</td>
</tr>
<tr>
<td>Dumont 2012</td>
<td>0.565 (0.514, 0.615)</td>
<td>209/370</td>
</tr>
<tr>
<td>Fok 2013</td>
<td>0.480 (0.400, 0.569)</td>
<td>72/150</td>
</tr>
<tr>
<td>Funahashi 2014</td>
<td>0.340 (0.205, 0.476)</td>
<td>16/47</td>
</tr>
<tr>
<td>Granan 2009</td>
<td>0.150 (0.138, 0.162)</td>
<td>521/3475</td>
</tr>
<tr>
<td>Guenther 2014</td>
<td>0.571 (0.480, 0.663)</td>
<td>64/112</td>
</tr>
<tr>
<td>Joseph 2008</td>
<td>0.237 (0.215, 0.269)</td>
<td>326/1375</td>
</tr>
<tr>
<td>Keene 1993</td>
<td>0.540 (0.466, 0.613)</td>
<td>95/176</td>
</tr>
<tr>
<td>Kennedy 2010</td>
<td>0.523 (0.467, 0.580)</td>
<td>157/300</td>
</tr>
<tr>
<td>Maffulli 2003</td>
<td>0.058 (0.035, 0.082)</td>
<td>22/378</td>
</tr>
<tr>
<td>Magnusson 2013</td>
<td>0.376 (0.322, 0.430)</td>
<td>117/311</td>
</tr>
<tr>
<td>Michalitis 2015</td>
<td>0.183 (0.111, 0.256)</td>
<td>29/109</td>
</tr>
<tr>
<td>Millett 2002</td>
<td>0.410 (0.256, 0.565)</td>
<td>16/39</td>
</tr>
<tr>
<td>Newman 2015</td>
<td>0.460 (0.400, 0.519)</td>
<td>125/372</td>
</tr>
<tr>
<td>Papastergiou 2007</td>
<td>0.169 (0.134, 0.203)</td>
<td>76/451</td>
</tr>
<tr>
<td>Sri-Ram 2013</td>
<td>0.291 (0.278, 0.303)</td>
<td>1479/5086</td>
</tr>
<tr>
<td>Tandogan 2004</td>
<td>0.158 (0.132, 0.184)</td>
<td>121/764</td>
</tr>
</tbody>
</table>

Overall (*P*=.0055, *P*<.001) **0.346 (0.294, 0.399)** 5062/19145

**Figure 4-7: Meta-Analysis of Proportions for Lateral Meniscal Tears**

Overall pooled estimate proportion rate for LMTs across included studies with available data. C.I. = confidence interval; Ev = event (LMTs); Trt = total events (LMTs)

In our meta-regression analysis, the rate of LMT was significantly associated to the time from injury to surgery, where the rate of LMT was the delay to surgery increased (*p*=0.009). As a part of our third analysis, when using age as a covariate, age was not found to be significant (*p*=0.622), but time remained significant (*p*=0.027). This shows that age is not a variable affecting the rate of LMT (**Figure 4-8**).
Figure 4-8: Meta-Regression Analysis for Lateral Meniscal Tears

Meta-regression analysis for LMTs using time (delay from injury to surgery) as a covariate, across studies with available data. X-axis represents time of surgery. Y-axis represents the proportion of patients having a LMT.

From the selected 7 prospective studies, there was high heterogeneity ($I^2 = 99.3$). The overall pooled estimate rate of LMT was 22.1% (Figure 4-9). In this case, the meta-regression model was not found to be significant ($p=0.497$), indicating no association between the rate of LMT and timing of surgery, when pooling from the prospective studies only.
Figure 4-9: Meta-Analysis of Proportions for Lateral Meniscal Tears (Prospective Studies Only)

Overall pooled estimate proportion rate for LMTs across included prospective studies with available data. C.I. = confidence interval; Ev = event (LMTs); Trt = total events (LMTs)

4.4.4.1.3. Cartilage Injuries

Twenty-six studies (86.7%) had available CI data. When pooled, the studies were found to be very heterogeneous with a high $i^2$ (98.6). The pooled estimate of proportions was approximately 40% (Figure 4-10).
Figure 4-10: Meta-Analysis of Proportions for Cartilage Injuries
Overall pooled estimate proportion rate for CIs across included studies with available data. CI = cartilage injury; C.I. = confidence interval; Ev = event (CIs); Trt = total events (CIs)

In our meta-regression analysis, the rate of CI was not significantly associated to the time from injury to surgery (p=0.769) (Figure 4-11).
Figure 4-11: Meta-Regression Analysis for Cartilage Injuries

Meta-regression analysis for CIs using time (delay from injury to surgery) as a covariate, across studies with available data. X-axis represents time of surgery; Y-axis represents the proportion of patients having a CI.

From the same prospective studies (7 of 30 studies), the high heterogeneity remained ($I^2 = 98.2$). The overall pooled estimate rate of CI was 41.8% (Figure 4-12). The meta-regression model was not significant ($p=0.571$), showing no association between the rate of CI and timing of surgery.
Figure 4.12: Meta-Analysis of Proportions for Cartilage Injuries (Prospective Studies Only)
Overall pooled estimate proportion rate for CIs across included prospective studies with available data. C.I. = confidence interval; Ev = event (MMTs); Trt = total events (CIs)

4.4.4.1.4. High-Grade Cartilage Injuries
Only 7 studies (23.3%) had available reported data specific for high-grade cartilage injuries. When pooled, the studies were found to be very heterogeneous with a high I² (97.3). The pooled estimate of proportions was approximately 20% (Figure 4.13).
**Figure 4-13: Meta-Analysis of Proportions for High-Grade Cartilage Injuries**

Overall pooled estimate proportion rate for HGCIs across included studies with available data. HGCI = high-grade cartilage injury; C.I. = confidence interval; Ev = event (HGCIs); Trt = total events (HGCIs)

In our meta-regression analysis, the rate of HGCI was also not significantly associated to the time from injury to surgery (p=0.524) (**Figure 4-14**).
Figure 4-14: Meta-Regression Analysis for High-Grade Cartilage Injuries
Meta-regression analysis for HGCIs using time (delay from injury to surgery) as a covariate, across studies with available data. X-axis represents time of surgery; Y-axis represents the proportion of patients having a HGCI.

There was not enough available data on HGCIs to run the meta-regression analysis for the prospective studies only.

4.4.4.2. Statistical Analysis of Concurrent Knee Injuries - Analysis 4
For all of the 3 most common time breakdowns (≤ or > 3 months, ≤ or > 6 months, ≤ or > 12 months), a quantitative synthesis was performed for each variable: MMT, LMT, cartilage injuries and high grade (HG) cartilage injuries, using ‘delay’ was as a dichotomous variable

4.4.4.2.1. Medial Meniscal Tears
Statistical significance was found at all time point cut-offs (3, 6, 12 months), suggesting a time dependency in relation to the odds of MMTs when delaying
ACLR (Figure 4-15). These findings suggest that MMTs tend to occur as delay increases, favoring early surgery compared to delayed surgery.

**Figure 4-15: Medial Meniscal Tears Summary**

Pooled results of medial meniscal tears at different time points from injury to time of surgery; A) ≤ 3 months compared to > 3 months, B) ≤ 6 months compared to > 6 months, C) ≤ 12 months compared to > 12 months. (CI: confidence interval).
4.4.4.2.2. Lateral Meniscal Tears

The findings of Figure 4-16 found no significance in the odds of a LMT in terms of delay to ACLR; however, they suggest that an association, but the pattern remains unclear. The odds of having a LMT seems to be more pronounced in the early ACLR groups, with less occurrence when ACLR is delayed.

**Figure 4-16: Lateral Meniscal Tears Summary**

Pooled results of lateral meniscal tears at different time points from injury to time of surgery; A) \( \leq 3 \) months compared to \( > 3 \) months, B) \( \leq 6 \) months compared to \( > 6 \) months, C) \( \leq 12 \) months compared to \( > 12 \) months. (CI: confidence interval).
4.4.4.2.3. Cartilage Injuries

With respect to cartilage injuries, there also seems to be significance at all time point cutoffs (3, 6, 12 months), suggesting a time dependency in relation to the odds of cartilage injuries when delaying ACLR, and favouring early ACLR (Figure 4-17). In addition, this may suggest that the threshold point may in fact be earlier than 3 months from injury to surgery.

![Cartilage Injuries Summary](image)

**Figure 4-17: Cartilage Injuries Summary**

Pooled results of cartilage injuries (all grades) at different time points from injury to time of surgery; A) ≤ 3 months compared to > 3 months, B) ≤ 6 months compared to > 6 months, C) ≤ 12 months compared to > 12 months. (CI: confidence interval).
4.4.4.2.4. High Grade Cartilage Injuries

Significance was also found at all time point cutoffs (3, 6 and 12 months), where early ACLR was favoured uniformly in relation to occurrences of higher grade cartilage injuries (grades 3-4 as per ICRS grading scale) (Figure 4-18). This may also suggest an earlier than 3 months’ threshold point from injury to surgery, similarly found when cartilage injuries of all grades were analyzed (see Figure 4-17).

**Figure 4-18: High Grade Cartilage Injuries Summary**

Poled results of high-grade cartilage injuries at different time points from injury to time of surgery; A) ≤ 3 months compared to > 3 months, B) ≤ 6 months compared to > 6 months, C) ≤ 12 months compared to > 12 months. (CI: confidence interval).
4.5. DISCUSSION

The goal of this systematic review was to review the literature on the effects of delay from injury to surgery after an anterior cruciate ligament tear (ACL) on concurrent knee injuries, specifically medial and lateral meniscal tears, and cartilage injuries of all grades and more specifically of high grade. Our review yielded a few key findings.

First off, a delay of more than 3 months was found to increase the odds of a medial meniscal tear. Secondly, a delay of greater than 3 months was found to increase the odds of a cartilage injury, irrespective of the grade, and more specifically for higher grade cartilage injuries. Thirdly, no significance was found with respect to timing of ACL reconstruction (ACLR) and the odds of lateral meniscal tears, however an association was found.

Our review, has depicted the heterogeneity between studies and the variability in defining delay in the literature. It was quite apparent that in all our meta-regression analyses, the $I^2$ was considered to be high (75% as per Higgins et al.\textsuperscript{101}) for all outcomes measured. This is a major flaw in our analyses findings, however; this remains to be what is available in our literature to date. The reason for this heterogeneity can be very easily attributed to a selection bias between studies, as different patients are selected for each study. This can be even more pronounced in the retrospective studies, as the studies' become either less powered or their inclusion criteria become less refined.

Irrespective of how ‘delay’ was defined, 21 studies (70%) and 17 studies (56.7%) showed that an increase in delay from injury to ACLR significantly increased the
incidence of medial meniscal tears (MMTs) and cartilage injuries, respectively. This information is critical for patient counseling, but also demonstrates the need for future investigators to determine the influence of a surgical delay on patient-reported outcomes and the threshold time point following ACL injury at which patient-reported outcomes and function can be optimized without incurring additional meniscus and cartilage pathology.

The optimum timing of ACL reconstruction is not well established. Shelbourne et al. 42 found a significantly higher rate of arthrofibrosis in patients undergoing ACLR less than 1 week following injury compared to those delayed until 3 weeks’ post-injury. Similar findings were found by Cosgarea et al. 132. Further studies have concluded that when modern techniques are applied success is independent of timing of reconstruction 133, 134. Furthermore, emerging evidence has demonstrated a benefit to preoperative physical therapy, termed ‘prehabilitation’ 135, 136. Despite all of this data suggesting that a delay from injury to reconstruction is beneficial, it is unknown if this has deleterious effects on meniscus and cartilage integrity, which in the long term can potentially influence the risk of osteoarthritis.

In this review, we demonstrate that even a 3-month delay from ACL injury to ACLR can increase the odds of meniscus and cartilage pathology at the time of surgery, and this finding holds true at multiple time points including 6 and 12 months’ time cut-offs.

De Roeck and Lang-Stevenson 23 feel that irrespective of timing, full knee extension must be achievable prior to ACLR and state that 6 weeks’ post-injury is their preferred time for ACLR. Church and Keating 22 have shown that delays of equal or more than 12 months increases the incidence of both meniscal tears and
degenerative change compared to patients who have reconstructive surgery less than 12 months from injury. In their retrospective analysis, O’Connor et al. \(^{127}\) reported an increase in meniscal injuries with a delay of \(\geq 6\) months, and an increase in chondral injuries with a delay of equal or more than \(12\) months. In younger patients, Sri-Ram et al. \(^{129}\) concluded that ACLR should not be delayed more than 5 months from injury, given the increased incidence of secondary knee pathology with increased time from injury to surgery. In their pediatric population study, Millett et al. \(^{124}\) found a similar time-dependent association with concurrent knee injuries with delay to reconstructive surgery. Arastu et al. \(^{107}\) reported the incidence of meniscal injury and chondral damage appeared greater in patients having an ACLR after 6 months following injury compared to those within 4 months following injury.

Historically, patients who are ACL-deficient have increased rates of meniscus and cartilage injury as compared to patients who underwent ACLR. Medial meniscus tears have classically been associated with chronic ACL deficiency \(^{18, 137}\), defined as greater than six months between injury and surgery \(^{138}\). It is believed that in the absence of an ACL, the medial meniscus assumes a larger role in knee stability lending itself to an increased risk for tearing. Given the role of the medial meniscus as a secondary stabilizer in the knee, injury to this structure can be a particularly challenging problem to deal with \(^{139}\). In the present study we demonstrate that the odds of a medial meniscus injury increased with a delay between ACL injury to ACLR. Perhaps the most interesting finding is that a delay as little as three months can make a significant influence in the presence or absence of a MMT, and the antiquated perception that MMTs arise largely in the chronic setting may not be true.
Early ACLR is commonly associated with lateral meniscus and cartilage injury\textsuperscript{18,137}. It is believed that during the initial pivoting event where the ACL was compromised, the lateral meniscus is subject to tearing\textsuperscript{18,137}. Even though this injury has commonly been associated with the initial pivoting event, we demonstrate in this study that ACL deficiency can increase the risk of observing this pathology at the time of ACLR\textsuperscript{25}. The reason for this may be ongoing frank and micro pivoting events in the ACL-deficient knee that leave the lateral meniscus susceptible to injury. Although the medial meniscus has classically been considered the more important meniscus for risk of instability and future development of osteoarthritis, a large lateral meniscus tear requiring near or total removal can also lead to increased stress across the lateral tibiofemoral joint and the onset of post-menisectomy osteoarthritis, which can adversely influence long-term patient outcomes following ACLR\textsuperscript{122,140}.

In this review, we demonstrate that the risk of MMTs, and cartilage injury is increased with a delay to reconstruction. Although this is not necessarily a new concept, the idea that even a delay as little as 3 months can increase this risk is certainly interesting and generates a number of questions, namely how the functional benefits of ‘prehabilitation’ can be balanced with the potential deleterious long term effects of concomitant meniscus and cartilage injury, namely osteoarthritis. At present, there is no study examining long term outcomes (>10-20 years) for patients undergoing ACL reconstruction with and without meniscus injury, so the natural history of having concomitant pathology is unclear at present. Ultimately, our data suggests that the increasingly common belief that the more preoperative physical therapy the better may not be entirely true, as there appears to be a time line for when patients may incur additional injury for which we do not understand the long-term ramifications.
This study has a number of limitations. First, we did not report patient-reported outcomes and it remains unknown how additional meniscus or cartilage injury can influence patient outcome in the short- and long-term. Second, our data was limited to what already existed in the literature, and our findings were the result of combining multiple different studies, each with their own limitations. Third, the data could not be manipulated in a way to determine if there is a threshold time point at which the risk of concomitant meniscus and cartilage pathology outweighs the benefits of prehabilitation. It should be noted that it is our opinion that this is the most important and clinically relevant question. Lastly, based on the nature of this study, we did not have access to patient-specific information such as pre-injury sport type, mechanism of injury, involvement in preoperative physical therapy, pre-operative return to sport (post-injury) or symptoms, all of which are important considerations.

4.6. **CONCLUSION**

In conclusion, our findings show that an increase in delay from time of injury (ACL tear) to time of surgery (ACLR) can increase the risk for concomitant knee injury, specifically associated with increased odds of medial meniscal tears and cartilage injuries, as little as 3 months after injury. However, based on this data, we could not show independent risk factors to predict an increase odds of concurrent injuries in terms of timing, nor were we able to definitely determine an optimal time point for ACLR. Going forward, there is a need to determine the impact of concomitant pathology on long-term patient outcome and to determine the time at which a delay to ACLR can optimize short-term outcomes related to prehabilitation and long-term outcomes related to osteoarthritis.
CHAPTER 5 - STUDY #3:

The Delay of Anterior Cruciate Ligament Reconstruction and its Effect on Quality of Life: A Prospective Cohort Study.
5.1. ABSTRACT

**Background**: Among those who tear their anterior cruciate ligament (ACL), between 20% and 50% will undergo surgical reconstruction (ACLR). Given that the burden of delay prior to ACLR on quality of life (QoL) remains unknown, the objective of this study was to evaluate the effects of delay from injury to surgery following ACL rupture.

**Study design**: Multicenter retrospective study of prospective data

**Methods**: Multicenter retrospective study using prospectively collected data from two Canadian academic centers (Calgary and Toronto). A multivariable linear regression model was used that evaluated the relationship between delay and the difference in ACL-QoL (quality of life) from baseline to 2 years post-operatively. A secondary analysis was performed to look into the incidence of meniscal and chondral pathology and delay to surgery.

**Results**: A cohort of 542 patients was obtained, with a mean time from injury to ACLR of 20.91 months. The median age was 28.7 years (range, 14.6-51), and 57% (309/542) were male. Baseline findings between sites showed significantly different average times from injury to surgery (26.2 versus 2.5 months, p<0.001), presence of meniscal (91% versus 76%, p<0.001), and articular cartilage pathology (72% versus 97%, p<0.001) for Calgary and Toronto cohorts, respectively. A delay of greater than or equal to three months, from time of injury to surgery, was associated with a decline in ACL-QoL from baseline to 2 years post-operatively (p = 0.03). However, when controlling for site, no significance was found between delay and presence of cartilage or meniscal pathology at time of surgery.

**Conclusion**: Our results reveal that delay from injury to surgery following an ACL injury negatively affects ACL-QoL at 2-years post-op when delay is greater than three months. Given these findings, our recommendations to clinicians are to
encourage patients to seek early care following injury, and to work for decreased surgical wait times following patient presentation with an ACL injury.
5.2. Introduction

Almost 250,000 anterior cruciate ligament (ACL) injuries occur annually in North America \(^1\), with approximately half being reconstructed each year \(^2\). This injury is mostly prevalent during sporting activities, varying from non-contact (76%) to direct contact (19%) mechanisms of injury \(^{16}\). Patient age varies greatly, from pediatric to adult populations, given the active lifestyle and predominance in sport participation. The annual incidence estimated at 16 per 1,000 high school students \(^7\), and is becoming more frequent in the young adolescent population \(^6\). More than 50% of all those sustaining ACL injuries are young athletes (15 to 25 years of age) \(^2\), and ACL reconstruction (ACLR) is a commonly performed procedure. Data collected by the American Board of Orthopaedic Surgeons for part II of the Certification Examination reveal that in 2004, ACLR ranked sixth among the most common surgical procedures performed by all sports medicine fellows and third among those surgeons identified as generalists \(^5\). The Centers for Disease Control and Prevention has reported that about 100 000 ACLRs are performed annually \(^4\).

Abnormal joint forces in an ACL-deficient knee are associated with increased risk of injury to menisci, which normally transmit load and absorb shock between the femur and tibia \(^{14}\). The overall disease burden of an ACL tear has been hypothesized to increase in complexity with the addition of other associated injuries, such as meniscal or cartilage injuries \(^{16,17}\). After an ACL rupture, knee instability can occur and with each episode of knee buckling or giving way, meniscal tears may become more complex and less amenable to repair \(^{18}\). In a large level 1 prognostic study, it was shown that meniscal and articular cartilage injuries were found, in approximately 67% and 50% of ACLR patients, respectively \(^{17}\), and these were associated with poorer two- and six-year functional outcomes after ACLR \(^{16}\). A
higher prevalence of chondral injury with chronicity has also been reported in prior single surgeon series, although with variable definitions of ‘delayed/ chronic’ from more than 6 weeks $^{19}$ to more than 2 years $^{20}$. In one ACLR Norwegian registry study $^{21}$ looking at the interaction between timing of ACLR and associated pathology, they demonstrated that the odds for a cartilage lesion in the adult knee increased by nearly 1% for each month that elapsed from the injury date until the surgery date, and the presence of cartilage lesions was associated with an early 2-fold increase in the risk of having meniscal tears, and vice versa, independent of patient age.

Timing of surgery is multifactorial, with both surgeon and patient influences. Some surgeons advocate for early surgery, others prefer to start the rehabilitation process preoperatively with focused physiotherapy and delayed reconstruction theorizing that this will diminish the risk of arthrofibrosis $^{42}$ and increase preoperative knee range of motion and strength $^{21,43}$. In a recent comparative study, it has been shown that additional preoperative rehabilitation (progressing strengthening and neuromuscular training) allowed for greater functional outcomes and return to sport rates at 2 years following ACLR $^{135}$. In comparison to other orthopaedic surgeries, such as joint replacements, where delay has been well documented to result in increased morbidity post-operatively $^{44-47}$, studies examining the burden of delay from injury to ACLR on quality of life (QoL) do not exist. The goal of this study was to investigate the effects of delay from time of injury to surgery on disease-specific (ACL) QoL. Our hypothesis is that an increase in surgical delay will have a negative impact on disease-specific QoL. This is relevant in the context of the Canadian healthcare system, given resource constraints and relatively longer surgical wait times in comparison to the United States $^{141}$. 
5.3. Methods

5.3.1. Study Design and Data Source
This multicenter retrospective study used prospectively collected data from two Canadian academic centers. One hundred and twenty-one (121) patients, consecutively enrolled from April 2005 to June 2007, were collected from a Canadian Institutes of Health Research (CIHR)-funded prospective cohort study based out of Sunnybrook Health Science Centre (SHSC) in Toronto, Ontario, Canada. Four hundred twenty-one (421) patients, consecutively enrolled from October 2007 to December 2010, were collected from a prospective cohort at the University of Calgary Sport Medicine Centre in Calgary, Alberta, Canada. Data collection from both cohorts were originally intended for other studies, but were sub-collected and matched for the purpose of this study. Ethics approval for this data collection was obtained from each hospital. ACLR at each site were performed by a single surgeon.

5.3.1.1. Study Inclusion Criteria – Toronto Cohort
The inclusion criteria comprised, for the Toronto cohort: 1) patients with an isolated ACL tear, 2) age between 16-60 years, 3) a single-bundle, trans-tibial ACLR with bone-patella tendon-bone (BPTB) autograft, 4) minimum of 2 years’ follow-up.

5.3.1.2. Study Inclusion Criteria – Calgary Cohort
For the Calgary cohort, the inclusion criteria comprised: 1) confirmed diagnosis of ACL damage based on the following criteria: i) a history of trauma or injury, ii) increased anterior translation of the tibia on the femur, iii) a positive pivot shift test, 2) age between 14-50 years, 3) patients with an isolated ACL tear, 4) an X-ray confirming skeletal maturity.
5.3.1.3. Study Exclusion Criteria - Toronto Cohort

The exclusion criteria comprised, for the Toronto cohort: 1) patients with pre-existing medial osteoarthritis (OA), osteochondral defect/injury, subtotal/total menisectomy, 2) injury to associated structures (posterolateral corner (PLC), posteromedial corner (PMC) and/or posterior cruciate ligament (PCL)), 3) presence of a varus thrust on gait analysis.

5.3.1.4. Study Exclusion Criteria - Calgary Cohort

For the Calgary cohort, the exclusion criteria were: 1) presence of a combined ligamentous deficiencies (posterior cruciate, medial and/or lateral collateral deficiency) [N.B.: grade 1 side-to-side difference (i.e. <5mm) on valgus/varus or posterior stress test were not excluded]; 2) an intraoperative identification of a grade 4 International Cartilage Research Society (ICRS) lesion of >1 cm²; 3) previous ligamentous surgery on the affected or contralateral knees; 4) cases involving litigation or Worker’s Compensation; 5) diagnosis of a connective tissue disorder (i.e. Ehlers-Danlos disease, Marfan syndrome) and 6) inability to speak, read or understand the English language. Each patient received a primary ACL reconstruction by his or her respective surgeon. Application of these criteria resulted in an analysis data set of 542 unique patients from the two study sites.

5.3.2. Data Abstraction

With the goal of ensuring that similar data points were collected from both cohorts, the following data was assimilated from each enrolled patient: 1) site at which the surgery took place (Calgary or Toronto), 2) age at the time of surgery, 3) gender, 4) body mass index (BMI), 5) operative side (right or left), 5) mechanism of injury (contact vs. non-contact activity), 6) type of ACL reconstruction (bone-patella
tendon-bone (BPTB) vs. hamstring tendon (HT) vs. allograft), 7) presence of associated meniscal pathology (medial and lateral), 8) presence of cartilage pathology, 9) meniscal treatment performed, 10) time from injury to surgery (ITS), and 11) ACL-QoL questionnaire scores measured at baseline and at two years post-operatively. The ACL-QoL disease-specific quality of life questionnaire was the main patient-reported outcome measure used for all patients and has been demonstrated to be reliable, valid and responsive by Mohtadi et al. and Lafave et al. The time to surgery (TTS) was defined as the time from when the injury occurred to the time when the surgery took place. The time when the injury occurred was collected at the first Orthopaedic consultation. Given that the actual delay from time of injury to time of consultation (TTC) is extremely variable and the reasons for which are numerous, we did not record that time interval. The presence of meniscal treatment was variable between both cohorts; therefore, we simplified the reporting to be either no treatment or any treatment (meniscal repair or meniscectomy) performed.

5.3.3. Data Omission

Due to heterogeneity between the two cohorts, the following data points were not collected: 1) preoperative/postoperative MRI findings, 2) objective strength and functional outcome scores (i.e. hop test, KT-1000 knee arthrometer (KT-1000) (MEDmetric, San Diego, CA) measurements, Tegner activity level scores, KOOS scores. The reasons for these omissions were in part due to different scoring systems used for each cohort, data not collected from one of the cohorts or different reporting techniques utilized. In terms of QoL measuring, the Short-Form 36 (SF-36) questionnaire, was only used in the Toronto cohort, compared to the ACL-QoL questionnaire which was used for both Calgary and Toronto cohorts,
hence the choice of using the latter. It also allows for a more disease-specific measuring tool.

5.3.4. Assessment of Cartilage Findings of the Knee

As for associated cartilage knee findings, the whole-organ magnetic resonance imaging scoring method (WORMS)\textsuperscript{150} (Figure 5-1) of knee osteoarthritis (OA) was used in the Toronto cohort, whereas the International Cartilage Repair Society (ICRS)\textsuperscript{102} (Figure 5-2) grading scale was used in the Calgary cohort. The WORMS score (see Figure 1 - simplified from Alizai et al.\textsuperscript{151}) is divided into 6 grades: 0 = normal; 1 = bogginess; 2.0 = partial thickness focal defect <1 cm in greatest width; 2.5 = full thickness focal defect <1 cm in greatest width; 3 = multiple areas of partial thickness defects <75 % of subregion or a single partial thickness defect >1 cm, but <75 % of the subregion; 4 = diffuse (>75 % of the subregion) partial thickness loss; 5 = multiple areas of full thickness loss <75 % of the subregion or a single full thickness lesion >1 cm, but <75 % of the subregion; 6 = diffuse (>75 % of subregion) full thickness loss. The ICRS grading scale (see Figure 2 - adapted from Mainil-Varlet, 2003) is divided into 4 grades: 0 = normal; 1 = Nearly normal (superficial lesions Superficial lesions. Soft indentation (A) and/or superficial fissures and cracks (B)); 2 = Abnormal (lesions extend < 50% of cartilage depth); 3 = Severely abnormal (>50% of cartilage depth. (A) as well as down to calcified layer (B) and down to but not through the subchondral bone (C). Blisters are included in this Grade (D)); 4 = Severely abnormal (full-thickness, through the subchondral bone). Because of the differences between the two grading scales, we wanted to parallel the two, and could not find a correlation analysis in the literature; therefore, we decided to analyze the cartilage pathology in two (2) ways: 1) presence of abnormal cartilage (grades >0 in either WORMS or ICRS scales), and 2) presence
of high-grade cartilage lesions (WORMS grades 2.5, 4, 5, 6 and ICRS grades 3, 4).

**Figure 5-1 - Whole-Organ Magnetic Resonance Imaging Scoring Method (WORMS).** Adapted from Peterfy et al.\(^{150}\) and Alizai et al.\(^{151}\). Grades: 0 = normal; 1 = bogginess; 2.0 = partial thickness focal defect <1 cm in greatest width; 2.5 = full thickness focal defect <1 cm in greatest width; 3 = multiple areas of partial thickness defects <75 % of subregion or a single partial thickness defect >1 cm, but <75 % of the subregion; 4 = diffuse (>75 % of the subregion) partial thickness loss; 5 = multiple areas of full thickness loss <75 % of the subregion or a single full thickness lesion >1 cm, but <75 % of the subregion; 6 = diffuse (>75 % of subregion) full thickness loss.
Figure 5-2 - International Cartilage Rating Society (ICRS) grading scale.  
*Adapted from ICRS © 145*.  
Grades: 0 = normal; 1= Nearly normal (superficial lesions Superficial lesions. Soft indentation (A) and/or superficial fissures and cracks (B)); 2 = Abnormal (lesions extend < 50% of cartilage depth); 3 = Severely abnormal (>50% of cartilage depth. (A) as well as down to calcified layer (B) and down to but not through the subchondral bone (C). Blisters are included in this Grade (D)); 4 = Severely abnormal (full-thickness, through the subchondral bone).
5.3.5. Statistical Analysis

The relationship between delay (as a continuous variable) and ACL-QoL was evaluated with a multivariable linear regression model. All analyses were conducted using SPSS version 21.

5.3.5.1. Primary Analysis

In order to assess for heterogeneity between the two cohorts (Toronto and Calgary), a 1-way ANOVA was conducted in order to analyze the distribution of ACL-QoL scores.

In the first step, after ensuring the absence of co-linearity among the independent variables, bivariate linear regression analysis for each of the independent variables were conducted to identify potential predictors of quality of life, with site of surgery serving as a control. Following this step, independent variables with a p<0.15 from bivariate analyses were carried forward into the multivariate linear regression, where backward elimination was used to identify all factors significantly associated with the outcome of interest. A cutoff of p<0.05 was used to determine significance in the multivariate analysis.

5.3.5.2. Secondary Analysis

In our secondary analysis, ‘delay’ (defined as the time from injury to ACLR) was analyzed as a dichotomous variable for use in multiple multinomial linear regression, where it was analyzed for multiple time points from injury to surgery.
5.3.5.3. Tertiary Analysis

If applicable, an overall model linear regression analysis was performed, dichotomizing delay at the significant time point from injury to surgery found in our secondary analysis and controlling for site.

5.4. Results

5.4.1. Baseline Characteristics

Of the 542 patients who met the inclusion criteria, of which there were 421 patients from the Calgary cohort and 121 patients from the Toronto cohort, thirty-two (32) patients were lost to follow-up at two years (5.9%). The median age was 28.7 years (range, 14.6-51), and n=309 (57%) were male. The mean body mass index (BMI) for the group was 25.1 kg/m^2 (range, 15.8-42.1), where 39% (211/542) were classified as overweight (BMI\geq25 \text{ kg/m}^2) \text{ }^{153}$. Please refer to Table 5-1 for an outline of the baseline characteristics of the included patients.

<table>
<thead>
<tr>
<th>Number (n; %) N = 542</th>
<th>Toronto Cohort</th>
<th>Calgary Cohort</th>
<th>Combined Data</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean; SD)</td>
<td>27.3 (6.1)</td>
<td>29.1 (9.9)</td>
<td>28.7 (9.2)</td>
<td>0.06</td>
</tr>
<tr>
<td>Gender (M/F (n; %)</td>
<td>78 (64%)</td>
<td>232 (55%)</td>
<td>310 (57%)</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>43 (36%)</td>
<td>189 (45%)</td>
<td>232 (43%)</td>
<td></td>
</tr>
<tr>
<td>BMI (mean; SD)</td>
<td>24.9 (3.5)</td>
<td>25.2 (3.7)</td>
<td>25.1 (3.7)</td>
<td>0.43</td>
</tr>
<tr>
<td>Operative Side (n; % Right)</td>
<td>65 (54%)</td>
<td>226 (54%)</td>
<td>291 (54%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Type of ACL Repair (n; %):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT = patella tendon</td>
<td>PT: 121 (100%)</td>
<td>PT: 140 (33%)</td>
<td>PT: 261 (48%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HT = hamstring tendon</td>
<td>PT: 281 (67%)</td>
<td>HT: 281 (52%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>---</td>
</tr>
<tr>
<td>Intraop Presence of Cartilage Injury (n; %)</td>
<td>117 (97%)</td>
<td>296 (72%)</td>
<td>413 (76%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intraop Presence of Associated Meniscal Pathology (n; %)</td>
<td>94 (78%)</td>
<td>396 (94%)</td>
<td>490 (90%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Required Tx for Meniscal Pathology (n; %)</td>
<td>46 (38%)</td>
<td>330 (78%)</td>
<td>376 (69%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean/ Median Delay from Injury to Sx (months) (SD)</td>
<td>2.5/ 2.63 (0.6) Min=0.8 Max=3.8</td>
<td>26.2/ 10.8 (45.4) Min=0.8 Max=339.4</td>
<td>20.91/ 8.2 (41.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td># of Patients ≥3 Months from Injury to Surgery (%)</td>
<td>28 (23%)</td>
<td>401 (95%)</td>
<td>429 (79%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mechanism of Injury Contact vs. Non-Contact (n; % Contact)</td>
<td>14 (12%)</td>
<td>86 (20%)</td>
<td>100 (18%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Quality of Life Score (Baseline)</td>
<td>29.8 (12.7)</td>
<td>28.5 (14.1)</td>
<td>28.7 (13.8)</td>
<td>0.26</td>
</tr>
<tr>
<td>Quality of Life Score (2 year follow-up)</td>
<td>80.8 (16.8)</td>
<td>83.5 (17.1)</td>
<td>83.0 (17.0)</td>
<td>0.62</td>
</tr>
<tr>
<td>Change in Quality of Life Scores (2 years - Baseline)</td>
<td>50.3 (16.8)</td>
<td>54.7 (21.0)</td>
<td>53.8 (20.3)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

**Table 5-1: Baseline Characteristics Table**

Baseline characteristics of patients included in both datasets. Unless otherwise specified, mean (and standard deviation) values are reported for each measurement.
5.4.2. Significant Differences Between Cohorts

A significant difference in wait times between the both cohorts was seen. The Calgary cohort, had a longer average time from injury to surgery compared to the Toronto cohort (26.2 months versus 2.5 months (p<0.001), respectively), whereby 95% of patients in Calgary having had a delay of greater than 3 months from the time of injury to surgery, compared to only 23% in the Toronto cohort.

With respect to the presence of intraoperative concurrent knee pathology, significant differences were identified between the two cohorts, regarding the presence of meniscal pathology (91% versus 76%, p<0.001) and cartilage pathology (72% versus 97%, p<0.001) for Calgary and Toronto cohorts, respectively. Interestingly, significant differences were also found in terms of need for meniscal treatment at the time of ACLR (78% versus 38%, p<0.001), for the Calgary and Toronto cohorts respectively.

Significant differences were also found, in terms of graft choice at ACLR, (33% BPTB/ 67% HT versus 100% BPTB, p<0.001) for Calgary and Toronto cohorts, respectively.

The change in ACL-QoL score from 2-years to baseline was also significant, (54.7 versus 50.3, p=0.05), for the Calgary and Toronto cohorts respectively.

5.4.3. Primary Analysis Results

The result of the 1-way ANOVA (Table 5-2) yielded a p-value of 0.039, thereby allowing us to conclude that the two cohorts were significantly different from one
another. As such, we elected to include the ‘site of surgery’ variable in all our models to ensure that this difference is accounted for.

<table>
<thead>
<tr>
<th></th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Between Groups</strong></td>
<td>1722.635</td>
<td>1</td>
<td>1722.635</td>
<td>4.301</td>
<td>.039</td>
</tr>
<tr>
<td><strong>Within Groups</strong></td>
<td>203084.521</td>
<td>507</td>
<td>400.561</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>204807.156</td>
<td>508</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 5-2: One-Way ANOVA**

One-way ANOVA to evaluate potential heterogeneity between the two cohorts (Toronto and Calgary) for the ‘ACL-QoL Difference’ (variable) proved to be statistically significant, suggesting that the two cohorts are heterogeneous to each other.

Initial bivariate analysis of the independent variables yielded the following variables to be potential predictors of quality of life: 1) delay to surgery, 2) age, 3) presence of medial meniscal tear, and 4) a contact mechanism of injury. Multivariate linear regression with backwards stepwise elimination of these variables, while controlling for site, did not find evidence of a significant relationship between delay and a change in ACL-QoL (Table 5-3).
<table>
<thead>
<tr>
<th></th>
<th>Coefficient</th>
<th>Standard Error</th>
<th>Significance (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant Variable</td>
<td>44.86</td>
<td>3.31</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Injury to Surgery</td>
<td>-0.05</td>
<td>0.02</td>
<td>0.053</td>
</tr>
<tr>
<td>Site of Surgery</td>
<td>5.28</td>
<td>2.24</td>
<td>0.02</td>
</tr>
<tr>
<td>Age at Surgery</td>
<td>0.20</td>
<td>0.01</td>
<td>0.04</td>
</tr>
</tbody>
</table>

**Table 5-3: Linear Regression Analysis (Delay as a Continuous Variable)**

The change in quality of life is a dependent variable and delay is a continuous variable. The model was significantly associated with the change in quality of life (p=0.01, $R^2=0.022$).

5.4.4. Secondary Analysis Results

Conversely, through use of the same model while converting delay into a dichotomous variable in monthly increments from 1 to 12 months, a significant relationship was found between delay and a change in ACL-QoL when dichotomized at 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 months, indicating that delays of 3 months or greater had a negative effect on a patient’s quality of life as measured by the ACL-QoL questionnaire (**Table 5-4**).

<table>
<thead>
<tr>
<th>Delay in months</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.397</td>
</tr>
<tr>
<td>2</td>
<td>0.369</td>
</tr>
<tr>
<td>3</td>
<td>0.040</td>
</tr>
<tr>
<td>4</td>
<td>0.045</td>
</tr>
<tr>
<td>5</td>
<td>0.023</td>
</tr>
<tr>
<td>6</td>
<td>0.049</td>
</tr>
<tr>
<td>7</td>
<td>0.027</td>
</tr>
</tbody>
</table>
Table 5-4: Multinomial Linear Regression Analysis (Delay as a Dichotomous Variable)
Depiction of the significance of the relationship between delay variable when dichotomized and ACL-QoL, controlling for site of surgery and age at surgery. Delay of 3 months or greater was found to be significantly associated with a lower ACL-QoL.

5.4.5. Tertiary Analysis Results
The overall model, with delay dichotomized at 3 months and controlling for site, demonstrated a significant $R^2$ value of 0.022 ($p<0.01$), thereby estimating that the proportion of the variance in quality of life explained by the variables included in our model was 2.2% (Table 5-5).

Table 5-5: Overall Linear Regression Analysis (Delay Dichotomized at 3 Months)
Change in QoL is a dependent variable and delay is dichotomous variable at 3 months, controlling for site. The model was significantly associated with the change in QoL ($p =0.009$, $R^2=0.022$).
5.4.6. Statistically Non-Significant Results

Though we attempted to control for these variables, we were unable to find a significant relationship between change in ACL-QoL and the following variables: 1) age, 2) sex, 3) BMI, 4) operative side, 5) type of activity at the time of injury, 6) mechanism of injury, 7) type of ACLR (HT or BPTB), 8) presence of associated meniscal pathology, 9) meniscal treatment performed, and 10) presence of cartilaginous injuries. As such, these variables were removed from our final regression model as the process of stepwise elimination was performed.

5.5. Discussion

The main finding in this study is that a delay greater than three months from ACL injury to surgery was associated with lower disease-specific QoL, as determined by the ACL-QoL questionnaire, two-years post-operatively. Efforts to minimize delay to surgery following an ACL injury may avoid detrimental effects on quality of life.

Our finding is novel, in that the effects of delay to surgery on quality of life after an ACL tear has yet to be reported. Mohtadi et al. [Mohtadi, 1998] showed, that patients with ACL injuries assess themselves more highly in terms of mental function and that this group of patients is younger and more physically active than other well-studied populations. In the Danish ACL Register, the quality of life dimension of the KOOS was 60 out of 100 one year after ACLR. This result is in line with Kvist et al. who registered 64 out of 100, 3-4 years after ACLR. In amateur football players, Frobell et al. compared those that had any kind of knee injury during their lifetime with those without any such injury. They found that all five dimensions of the KOOS were significantly lower in the group with injuries. Even though the
quality of life in general may be given high scores, an injured knee limits the person’s perceived satisfaction with life.

To our knowledge, our study is the first to analyze the effects of delay from ACL tear to ACLR on quality of life. We found that a delay of $\geq 3$ months to ACLR negatively affected quality of life, as per the ACL-QoL questionnaire. Other strengths of this study include that our data was collected from two different centers (Calgary and Toronto), which is a better representation of the average ACL-injured patient, therefore, increasing the external validity of the study. Additionally, by combining both cohorts, we increased the power of the study, in turn increasing the ability to potentially detect significant findings. Also, in each respective cohort, the data was initially collected in a prospective manner, which decreases the risk of recall bias, when compared to traditional retrospective cohort studies. Lastly, the combined follow-up rate was high at 94.1% (510 of 542 included patients).

Our study did in fact show some interesting difference between both cohorts at the time of ACLR. A higher prevalence of meniscal tears in the Calgary cohort compared to the Toronto cohort (91% versus 76% ($p<0.001$), respectively). In the former cohort, there was a significantly longer average delay from injury to surgery (26.2 months versus 2.5 months ($p<0.001$), respectively). Our study also, showed a significantly higher prevalence of medial meniscal tears in the ‘delayed’ Calgary cohort compared to the ‘early’ Toronto cohort (67% versus 36% ($p<0.001$), respectively). These findings seem to be in keeping with the literature, as a higher prevalence of medial meniscal tears with greater time from ACL injury has been demonstrated previously $^{18,21,25}$. In the KANON study $^{43}$, among patients who did not undergo ACLR, approximately 33% still underwent subsequent meniscectomy.
This finding relates likely to the known function of the posterior horn of the medial meniscus as a dynamic secondary stabilizer to anterior knee translation in the ACL-deficient knee \(^{157, 158}\). Better protection of critical knee structures during rehabilitation or in those awaiting surgery seems warranted, although a ‘safe’ level or type of activity remains unknown.

A higher prevalence of chondral injury with chronicity has been reported in prior single surgeon series, but with variable definitions of ‘chronic’ from >6 weeks \(^{19}\) to >2 years \(^{20}\), and in one ACLR Norwegian registry study \(^{21}\). In the latter registry, of 3,475 patients looking at the interaction between timing of ACLR and associated pathology, 26% had articular cartilage lesions, 47% meniscal tears and 15% had both. They demonstrated that adults <40 years of age had a 3% increased odds of articular cartilage injury for each month from injury to surgery, and 0.4% increase for meniscal tears. Karlsson et al. \(^{15}\) found an increase in meniscal tears combined with poorer outcome in a group of patients who underwent delayed ACLR (between 12-24 months) compared to those who were reconstructed sub-acute (within 2-12 weeks). In addition, Woods et al. \(^{159}\) found that the percentage or repairable meniscal lesions dropped from 50% to 27% in the acute (within ~14 days from injury) versus chronic ACL-deficient knee (mean ~37 months). Our study failed to show the association of chondral pathology with chronicity of an ACL injury. The incidence of cartilage injuries was 72% in the ‘delayed’ Calgary cohort compared to 97% in the ‘early’ Toronto cohort (p<0.001). This discrepancy can likely be attributed to the differences in exclusion criteria, given that for the Calgary cohort, ICRS grade 4 cartilage lesions were excluded, which was not the case for the Toronto cohort. Also, the grading scales used for cartilage injuries differed between sites, as the ICRS classification was used in the Calgary cohort, whereas the WORMS
was used in the Toronto cohort. Another potential reason could be that, since MRIs were obtained more routinely in the Toronto cohort, and known pathology diagnosed preoperatively, perhaps this lead to an internal bias in reporting these injuries, being frequently subtle in nature. Conversely, in the Calgary cohort, the secondary pathology was mainly diagnosed at the time of ACLR. While we observed slightly more meniscal pathology in the delayed cohort (Calgary), which was expected, this did not influence QoL at 2 years post-operatively.

Conversely, the design of the study is not without its limitations. Firstly, heterogeneity existed between the two cohorts, numerous data categories could not be utilized in our analyses, including preoperative/ postoperative MRI findings, intraoperative cartilage findings, and objective strength and functional measures. Some of these factors may confound baseline QoL. Secondly, delay was defined from time of injury to surgery, which includes the time from injury to the first Orthopaedic Surgery consultation, the time to decision to treat surgically, and the scheduled date of surgery. In either case, the reasons for delay can vary greatly. For example, the delay could have been due to a referral time delay, a delay in diagnosis from the family physician or emergency physician, a delay to obtain an MRI if/when needed, a surgeon’s surgical wait list delay, an apprehension by the patient to seek treatment, or even patient’s / surgeon’s decision to delay surgical treatment. Some reasons for delay to surgery may have more influence on QoL than others (i.e. patient’s choice in treatment); however, the reasons for lower QoL are multifactorial. We can only speculate that a patient’s quality of life may be more likely affected, for reasons of direct patient control (i.e. patient’s choice in treatment). Thirdly, as indicated by the low $R^2$ of the multinomial regression models,
there are likely numerous variables associated with QoL that were not detected in our study.

Considering the strengths and limitations of this study, our recommendations for future studies evaluating the effects of delay on quality of life include larger prospective cohorts to collect more information of potential explanatory variables. Additionally, considerations should be made to consider costs, evaluating the effects of the difference in quality of life on the cost burden to society with an increase in delay to surgery. There is data\textsuperscript{60} to support ACLR as the preferred cost-effective treatment strategy for an ACL tear with reduced societal costs compared to rehabilitation, including for early ACLR over rehabilitation with optional delayed ACLR\textsuperscript{62}.

5.6. Conclusion

Delay to surgery after an anterior cruciate ligament rupture has a detrimental effect on disease-specific quality of life. Efforts should be made to ensure that delays between the time of injury to subsequent surgery are minimized.
CHAPTER 6 - GENERAL DISCUSSION

Based on the identified studies in our first systematic review, anterior cruciate ligament reconstruction (ACLR) has been shown to be a cost-effective surgical procedure, when compared to rehabilitation alone (non-operative treatment) \(60, 61\), or when performed early versus rehabilitation with an optional delayed ACLR \(62\). Based on only 1 study, various modes of ACLR were found to be cost-effective. Using a hamstring tendon autograft was proven to be less costly and more effective compared to the bone-patella-tendon-bone autograft or the allograft \(65\). The double bundle ACLR technique was thought to be more cost-effective in the short-term (as the reference case) when compared to the single bundle technique \(66\).

Our study is the first descriptive review of the cost-effectiveness of ACLR specifically. Previous reviews on cost-effectiveness analyses in Orthopaedic surgery have been reported \(53, 92\). Those authors reviewed the quality and trends of cost-effectiveness analysis (CEA) in the Orthopaedic literature and found it to be very heterogeneous, with an increase (~73%) in publications after 1998. Kepler et al \(94\) found that certain aspects of spinal care were cost-effective based on their systematic review, but that there needed to be better definition of value given the wide variations between studies.

As per Nwachukwu et al. \(59\), we also applied the QHES Instrument to assess the value and quality of the cost-effectiveness analysis studies included in our study. Although, not readily used in Orthopaedics, the QHES has been proven to be a simple, consistent, and suitable scale to measure the quality of health economic evaluation studies, especially cost-effectiveness studies \(95\). The lack of literature on
the topic was quite apparent. Our hypothesis, that there’s a great deal of heterogeneity and poor quality reporting in the literature, was confirmed. With respect to the poor quality reporting, based on our evaluation with the QHES Instrument, 4 out of the 6 studies (66.7%) could be considered high-quality. This seems to be in keeping with the literature, as Nwachukwu et al.’s systematic review showed that there seems to be good quality representation in Sports Medicine specifically.\(^5^9\)

Our review had a number of limitations. First, in order to keep the healthcare cost representation uniform, only US-based studies were included. For the sake of completeness, we did run the search without this exclusion criteria, and identified one extra study that was Swiss-based\(^9^0\), where the authors also found that ACLR had an ICER of $4,890 USD/QALY over conservative treatment within their healthcare system. Additionally, a small number of articles were identified from our search. This relates to the paucity of research related to cost-effectiveness with respect to ACLR. Inherently, the results this review should be taken with caution and inadvertently, further analysis would be necessary. Finally, the heterogeneity in methods and reporting between studies made head to head comparison difficult across all parameters.

The goal of our second systematic review was to review the literature on the effects of delay from injury to surgery after an anterior cruciate ligament tear (ACL) on concurrent knee injuries, specifically medial and lateral meniscal tears, and cartilage injuries of all grades and more specifically of high grade. Our review yielded a few key findings.
First off, a delay of more than 3 months was found to increase the odds of a medial meniscal tear and the odds of a cartilage injury, irrespective of the grade, and more specifically for higher grade cartilage injuries. Thirdly, no significance was found with respect to timing of ACL reconstruction (ACLR) and the odds of lateral meniscal tears, however an association was found.

Our review, has depicted the heterogeneity between studies and the variability in defining delay in the literature. However, irrespective of how ‘delay’ was defined, 21 studies (70%) and 17 studies (56.7%) showed that an increase in delay from injury to ACLR significantly increased the incidence of medial meniscal tears (MMTs) and cartilage injuries, respectively. This information is critical for patient counseling, but also demonstrates the need for future investigators to determine the influence of a surgical delay on patient-reported outcomes and the threshold time point following ACL injury at which patient reported outcomes and function can be optimized without incurring additional meniscus and cartilage pathology.

The optimum timing of ACL reconstruction is not well established and we were unable to define a single critical time point for surgery. Shelbourne et al. found a significantly higher rate of arthrofibrosis in patients undergoing ACLR less than 1 week following injury compared to those delayed until 3 weeks’ post-injury. Similar findings were found by Cosgarea et al. Further studies have concluded that when modern techniques are applied success is independent of timing of reconstruction. Furthermore, emerging evidence has demonstrated a benefit to preoperative physical therapy, termed ‘prehabilitation’. Despite all of this data suggesting that a delay from injury to reconstruction is beneficial, it is unknown if this has deleterious effects on meniscus and cartilage integrity, which in the long
term can potentially influence the risk of osteoarthritis. In this review, we demonstrate that even a 3-month delay from ACL injury to ACLR can increase the odds of meniscus and cartilage pathology at the time of surgery, and this finding holds true at multiple time points including 6 and 12 months’ time cut-offs.

De Roeck and Lang-Stevenson\textsuperscript{23} feel that irrespective of timing, full knee extension must be achievable prior to ACLR and state that 6 weeks’ post-injury is their preferred time for ACLR. Church and Keating\textsuperscript{22} have shown that delays of equal or more than 12 months increases the incidence of both meniscal tears and degenerative change compared to patients who have reconstructive surgery less than 12 months from injury. In their retrospective analysis, O’Connor et al.\textsuperscript{127} reported an increase in meniscal injuries with a delay of $\geq 6$ months, and an increase in chondral injuries with a delay of equal or more than 12 months. In younger patients, Sri-Ram et al.\textsuperscript{129} concluded that ACLR should not be delayed more than 5 months from injury, given the increased incidence of secondary knee pathology with increased time from injury to surgery. In their pediatric population study, Millett et al.\textsuperscript{124} found a similar time-dependent association with concurrent knee injuries with delay to reconstructive surgery. Arastu et al.\textsuperscript{107} reported the incidence of meniscal injury and chondral damage appeared greater in patients having an ACLR after 6 months following injury compared to those within 4 months following injury.

Historically, patients who are ACL-deficient have increased rates of meniscus and cartilage injury as compared to patients who underwent ACLR. Medial meniscus tears have classically been associated with chronic ACL deficiency\textsuperscript{18,137}, defined as greater than six months between injury and surgery\textsuperscript{138}. It is believed that in the absence of an ACL, the medial meniscus assumes a larger role in knee stability
lending itself to an increased risk for tearing. Given the role of the medial meniscus as a secondary stabilizer in the knee, injury to this structure can be a particularly challenging problem to deal with\textsuperscript{139}. In the present study we demonstrate that the odds of a medial meniscus injury increased with a delay between ACL injury to ACLR. Perhaps the most interesting finding is that a delay as little as three months can make a significant influence in the presence or absence of a MMT, and the antiquated perception that MMTs arise largely in the chronic setting may not be true.

Early ACLR is commonly associated with lateral meniscus and cartilage injury\textsuperscript{18,137}. It is believed that during the initial pivoting event where the ACL was compromised, the lateral meniscus is subject to tearing\textsuperscript{18,137}. Even though this injury has commonly been associated with the initial pivoting event, we demonstrate in this study that ACL deficiency can increase the risk of observing this pathology at the time of ACLR\textsuperscript{25}. The reason for this may be ongoing frank and micro pivoting events in the ACL-deficient knee that leave the lateral meniscus susceptible to injury. Although the medial meniscus has classically been considered the more important meniscus for risk of instability and future development of osteoarthritis, a large lateral meniscus tear requiring near or total removal can also lead to increased stress across the lateral tibiofemoral joint and the onset of post-menisectomy osteoarthritis, which can adversely influence long-term patient outcomes following ACLR\textsuperscript{122,140}.

In this review, we demonstrate that the risk of MMTs, and cartilage injury is increased with a delay to reconstruction. Although this is not necessarily a new concept, the idea that even a delay as little as 3 months can increase this risk is certainly interesting and generates a number of questions, namely how the
functional benefits of ‘prehabilitation’ can be balanced with the potential deleterious long term effects of concomitant meniscus and cartilage injury, namely osteoarthritis. At present, there is no study examining long term outcomes (>10-20 years) for patients undergoing ACL reconstruction with and without meniscus injury, so the natural history of having concomitant pathology is unclear at present. Ultimately, our data suggests that the increasingly common belief that the more preoperative physical therapy the better may not be entirely true, as there appears to be a time line for when patients may incur additional injury for which we do not understand the long-term ramifications.

Our second review had a number of limitations. First, we did not report patient-reported outcomes and it remains unknown how additional meniscus or cartilage injury can influence patient outcome in the short- and long-term. Second, our data was limited to what already existed in the literature, and our findings were the result of combining multiple different studies, each with their own limitations. Third, the data could not be manipulated in a way to determine if there is a threshold time point at which the risk of concomitant meniscus and cartilage pathology outweighs the benefits of prehabilitation. It should be noted that it is our opinion that this is the most important and clinically relevant question. Lastly, based on the nature of this study, we did not have access to patient-specific information such as pre-injury sport type, mechanism of injury, involvement in preoperative physical therapy, preoperative return to sport (post-injury) or symptoms, all of which are important considerations.

In our third study, the main finding was that a delay greater than 3 months from ACL injury to surgery is associated with lower disease-specific QOL, as determined by the ACL QoL questionnaire, at two-years post-op. This conclusion must be taken in
light of the study limitations, including the major differences in sample size (421 versus 121 patients) and their respective average time from injury to surgery (26.2 versus 2.5 months), for the Calgary and Toronto cohorts, respectively. Efforts to minimize delay to surgery following an ACL injury may avoid detrimental effects on quality of life.

Our finding is novel, in that the effects of delay to surgery on quality of life after an ACL tear has yet to be reported. Mohtadi et al. showed, that patients with ACL injuries assess themselves more highly in terms of mental function and that this group of patients is younger and more physically active than other well-studied populations. In the Danish ACL Register, the quality of life dimension of the KOOS was 60 out of 100 one year after ACLR. This result is in line with Kvist et al. who registered 64 out of 100, 3-4 years after ACLR. In amateur football players, Frobell et al. compared those that had any kind of knee injury during their lifetime with those without any such injury. They found that all five dimensions of the KOOS were significantly lower in the group with injuries. Even though the quality of life in general may be given high scores, an injured knee limits the person’s perceived satisfaction with life.

Our study did in fact show a higher prevalence of meniscal tears in the Calgary cohort compared to the Toronto cohort (91% versus 76% (p<0.001), respectively). In the former cohort, there was a significantly longer average delay from injury to surgery (26.2 months versus 2.5 months (p<0.001), respectively). Our study also, showed a significantly higher prevalence of medial meniscal tears in the ‘delayed’ Calgary cohort compared to the ‘early’ Toronto cohort (67% versus 36% (p<0.001), respectively). These findings seem to be in keeping with the literature, as a higher
prevalence of medial meniscal tears with greater time from ACL injury has been demonstrated previously \(^{18,21,25}\). In the KANON study\(^ {43}\), among patients who did not undergo ACLR, approximately 33% still underwent subsequent menisectomy. This finding relates likely to the known function of the posterior horn of the medial meniscus as a dynamic secondary stabilizer to anterior knee translation in the ACL-deficient knee \(^ {157,158}\). Better protection of critical knee structures during rehabilitation or in those awaiting surgery seems warranted, although a ‘safe’ level or type of activity remains unknown.

A higher prevalence of chondral injury with chronicity has been reported in prior single surgeon series, but with variable definitions of ‘chronic’ from >6 weeks \(^ {19}\) to >2 years \(^ {20}\), and in one ACLR Norwegian registry study\(^ {21}\). In the latter registry, of 3,475 patients looking at the interaction between timing of ACLR and associated pathology, 26% had articular cartilage lesions, 47% meniscal tears and 15% had both. They demonstrated that adults <40 years of age had a 3% increased odds of articular cartilage injury for each month from injury to surgery, and 0.4% increase for meniscal tears. Karlsson et al. \(^ {15}\) found an increase in meniscal tears combined with poorer outcome in a group of patients who underwent delayed ACLR (between 12-24 months) compared to those who were reconstructed sub-acutely (within 2-12 weeks). In addition, Woods et al. \(^ {159}\) found that the percentage or repairable meniscal lesions dropped from 50% to 27% in the acute (within ~14 days from injury) versus chronic ACL-deficient knee (mean ~37 months). Our study failed to show the association of chondral pathology with chronicity of an ACL injury. The incidence of cartilage injuries was 72% in the ‘delayed’ Calgary cohort compared to 97% in the ‘early’ Toronto cohort (\(p<0.001\)). This discrepancy can likely be attributed to the differences in grading scales that were used to report these
injuries, as the ICRS classification was used in the Calgary cohort, whereas the WORMS was used in the Toronto cohort. Another potential reason could be that, since MRIs were obtained more routinely in the Toronto cohort, and known pathology diagnosed preoperatively, perhaps this lead to an internal bias in reporting these injuries, being frequently subtle in nature. Conversely, in the Calgary cohort, the secondary pathology was mainly diagnosed at the time of ACLR.

The need for meniscal treatment (menisectomy or meniscal repair) was found to be significantly different between cohorts, which puts into question the severity of the meniscal injuries and its effect on QoL. We did not find any significance when controlling for meniscal treatment and QoL difference, which is also similar to findings by Paradowski et al.\textsuperscript{160}, who found no differences between patients who received an ACLR alone versus those who also received meniscal treatment.

There were some baseline differences between cohorts with respect to the graft choice used at ACLR, as the Toronto cohort had uniformly all BPTB ACLRs, compared to the Calgary cohort, which had some HT and BPTB ACLRs. However, there was no significance found in association with type of ACLR and QoL. This is in keeping with the literature, as no differences in ACL-QoL were found at two-years in Mohtadi et al.’s randomized control trial, looking at differences on patient-reported outcome measures with HT, BPTB and DB ACLR (p=0.591)\textsuperscript{93}.

To our knowledge, our study is the first to analyze the effects of delay from ACL tear to ACLR on quality of life. We found that a delay of ≥3 months to ACLR negatively effects quality of life, as per the ACL-QoL questionnaire. Other strengths of this
study include that our data was collected from two different centers (Calgary and Toronto), which is a better representation of the average ACL-injured patient; and, that the data was collected prospectively. Lastly, our follow-up rate was 94.1% (510 of 542 included patients).

Conversely, the design of the study is not without its limitations. Firstly, given the heterogeneity that existed between the two cohorts, numerous data categories could not be utilized in our analyses, including preoperative/ postoperative MRI findings, intraoperative cartilage findings, and objective strength and functional measures. Some of these factors may confound baseline QoL. Secondly, delay was defined from time of injury to surgery, which includes the time from injury to the first Orthopaedic Surgery consultation, the time to decision to treat surgically, and the scheduled date of surgery. In either case, the reasons for delay can vary greatly. For example, the delay could have been due to a referral time delay, a delay in diagnosis from the family physician or emergency physician, a delay to obtain an MRI if/when needed, a surgeon’s surgical wait list delay, an apprehension by the patient to seek treatment, or even patient’s / surgeon’s decision to delay surgical treatment. Some reasons for delay to surgery may have more influence on QoL than others (i.e. patient’s choice in treatment); however, the reasons for lower QoL are multifactorial. We can only speculate that a patient’s quality of life may be more likely affected, for reasons of direct patient control (i.e. patient’s choice in treatment). Thirdly, as indicated by the low $R^2$ of the multinomial regression models, there are likely numerous variables associated with QoL that were not detected in our study.
Considering the strengths and limitations of this study, our recommendations for future studies evaluating the effects of delay on quality of life include larger prospective cohorts to collect more information of potential explanatory variables. Additionally, considerations should be made to consider costs, evaluating the effects of the difference in quality of life on the cost burden to society with an increase in delay to surgery. There is data\textsuperscript{60} to support ACLR as the preferred cost-effective treatment strategy for an ACL tear with reduced societal costs compared to rehabilitation, including for early ACLR over rehabilitation with optional delayed ACLR\textsuperscript{62}. 
CHAPTER 7 - CONCLUSIONS

This project allowed us to review the literature in great depth pertaining to the effects of delay from injury to surgery after an anterior cruciate ligament (ACL) tear, from 3 different angles: 1) cost, 2) concurrent knee injuries, and 3) quality of life.

**Hypothesis #1:** *Anterior cruciate ligament reconstruction is a cost-effective treatment for anterior cruciate ligament tears.*

First off, we wanted to determine whether ACL reconstruction (ACLR) was a cost-effective treatment option, as the ongoing argument on the ideal timing of surgery is still debatable. From our review, there were 6 relevant studies included that investigated the cost-effectiveness of ACLR. Two studies compared ACLR to rehabilitation alone, two studies studied various modes of ACLR, 1 study analyzed both knee arthroscopy alone and ACLR, and 1 study compared early versus delayed ACLR. There was no common denominator across the studies in terms of cost perspective (individual or societal), time horizon, and cost comparisons (direct and/or indirect costs). Also, despite each study claiming ACLR was a cost-effective treatment strategy, we were unable to draw any generalized conclusions to this effect given the significant amount of heterogeneity across all studies. This lead us only to provide a thorough descriptive analysis of the literature, for which we can conclude it’s quite heterogeneous and poor quality reporting.
Hypothesis #2: Delay from time of injury to surgery increases the incidence of concurrent injuries, meniscal and/or cartilaginous, associated with anterior cruciate ligament tears.

In our second study, we performed a systematic review looking at the effects of delay from ACL injury to ligament reconstruction on concurrent knee injuries at time of ACLR, specifically looking at the rate of medial meniscal tears (MMTs), lateral meniscal tears (LMTs), cartilage injuries (all grades) and high grade cartilage injuries (grades 3-4). From our review, there were 30 studies that met our inclusion criteria. The average time to surgery was 12.3 months. In terms of concurrent injuries, there were 5,588 MMTs, 5,324 LMTs, and 6,862 cartilage injuries. There was a significant increase in odds of MMTs (p<0.0003) and of all grade cartilages injuries (p<0.00001) and high grade cartilage injuries (p=0.0003), at time of ACLR, when surgery performed after 3 months from injury. An association existed with increased odds of LMTs when ACLR was performed less than 3 months (p=0.86), but no significance was found. Our findings show that an increase in delay from time of injury (ACL tear) to time of surgery (ACLR) can increase the risk for concomitant knee injury, specifically associated with increased odds of medial meniscal tears (MMTs) and cartilage injuries, as little as 3 months after an ACL tear. However, based on this data, we could not show independent risk factors to predict an increase odds of concurrent injuries in terms of timing.
**Hypothesis #3:** *Increased delay from time of injury to surgery negatively affects quality of life after an anterior cruciate ligament reconstruction.*

In our third study, we conducted a multicenter retrospective review of prospectively collected data, looking at 542 patients who underwent a primary ACLR and assessing the effects of delay, from time of ACL tear to their reconstruction, on the change in quality of life from baseline to 2 years post-operatively. Quality of life was assessed with the disease-specific ACL-QoL questionnaire. A delay of greater than or equal to 3 months, from time of injury to surgery, was associated with a decline in ACL-QoL from baseline to 2 years post-operatively ($p = 0.03$). Our results reveal that delay from injury to surgery following an ACL injury negatively affects ACL-QoL at 2-years post-operatively when delay is greater than 3 months.
CHAPTER 7 - FUTURE DIRECTIONS

There are many interesting findings from each of the 3 studies, as well as, many improvements that can be made.

From a cost perspective, future goals would be to take our findings from our descriptive review and run a prospective longitudinal cost-analysis here in Canada. In that study where both micro and macro hospital costs are taken into account over a set period of time, we would be able to determine the true cost-effectiveness of ACL reconstruction, and even compare it to rehabilitation with delayed surgery. This can be analyzed from both the patient and societal perspective. The cost data would be in Canadian dollars (CAD) and then be applicable to our healthcare system.

Additionally, considerations should be made to consider costs, evaluating the effects of the difference in quality of life on the cost burden to society with an increase in delay to surgery. There is data\textsuperscript{60} to support ACLR as the preferred cost-effective treatment strategy for an ACL tear with reduced societal costs compared to rehabilitation, including for early ACLR over rehabilitation with optional delayed ACLR\textsuperscript{62}.

A cost-benefit analysis of early surgery versus late surgery from the perspective of PROMs and the potential risks of increased posttraumatic osteoarthritis are also important areas of future research.
Setting standards for procedural cost and identifying which patients are most likely to benefit from surgery are two methods that must be pursued in order to enhance healthcare value of ACLR in our restricted resource environment.

Future work should be aimed at separating remotely ACLR patients based on nonoperative treatment strategies and patient modifications. As outcomes become available in this cohort, a second significant future endeavor will be to compare intermediate- and long-term outcomes (revision, reoperation, and PROMs) based on chronicity.

Going forward, there is a need to determine the impact of concomitant pathology on long-term patient outcome and to determine the time at which a delay to ACLR can optimize short-term outcomes related to prehabilitation and long-term outcomes related to osteoarthritis.

In terms of quality of life, a larger prospective cohort study, using a more homogenous sample, would carry more weight with our conclusions. Ideally, we would have hoped to collect more information of potential explanatory variables. For example, looking at all primary ACLRs from one Centre within a given region and where there’s no disparity in the timing of surgery. This will allow for more generalizable conclusions, applicable to most Orthopaedic centers. Similar inclusion and exclusion criteria and similar preoperative and intraoperative meniscal and chondral grading schemes would allow for more conclusive findings.

In our study, we did not address the potential effect of concurrent injuries on quality of life, as secondary knee pathology can in turn affect quality of life and potentially
lead to the development of osteoarthritis many years down the road. This would be a great approach to tie in both concepts.

Lastly, given that the delay period from injury to surgery carries a lot of variability, there would be value to investigate the different factors of delay. For example, the time from injury to surgery, inadvertently carries the time from injury to Orthopaedic consultation. Both times are considered to be variable and dependent on their own respective factors. Looking at the time to consultation as well would be quite valuable, as we hope to decrease the overall time to surgery for optimal patient care.
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