A Systematic Review of Factors Associated with Both Bilateral and Recurrent Anterior Cruciate Ligament Disruption

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ABSTRACT:

Background: Numerous studies have reported factors associated with recurrent or subsequent contralateral anterior cruciate ligament disruption, but a comprehensive review of the literature has not been performed.
Purpose: This study attempts to systematically review the literature and provide an overview of the currently reported risk factors for recurrent and subsequent contralateral ACL reconstructions in order to allow for more efficient identification and intervention of high-risk patients.
Study Design: Systematic Review.
Methods: The Pubmed and Embase databases were searched using a combination of keywords such as “ACL reconstruction” and “bilateral or recurrent” and “risk factors” and medical subject headings. All studies were screened by two independent reviewers, and articles that met inclusion criteria (non-contact ACL injury, study analyzed risk factors for contralateral ACL injury or graft rupture) were downloaded and read.
Results: The initial search yielded 129 articles, of which 36 met inclusion criteria. After duplicates were removed, 23 articles remained. The reference lists of included articles were cross-referenced, and an additional 2 articles were included.
Conclusion: Graft harvest site, allograft usage, return to sport, younger age, a positive family history, increased posterior tibial slope, and the number of previous ACL reconstructions are well-reported risk factors for second ACL injury. Recent studies suggest a patients who have negative psychological states in the perioperative periods have worse long-term functional outcomes.

Key Terms*: knee, anterior cruciate ligament, ACL reinjury, knee injury*

1. INTRODUCTION

Tearing the anterior cruciate ligament (ACL) is a common injury among active populations, with re-rupture presenting a devastating complication. Injury to the ACL results in severe instability of the knee joint. Though non-operative management may be an appropriate first-line treatment in older and less active patients, surgical repair or reconstruction is preferred for younger patients or those with high-activity levels. Patients undergo 6-12 months of rehabilitation after surgery to build strength, stability and range-of-motion before returning to activity [1, 2]. The outcomes of initial ACL reconstruction remain excellent; the 5-year survival rate in all patients with autografts is over 95% [3-9]. However, for the unfortunate 5%, re-rupture of the reconstructed ACL can be catastrophic. While primary ACL reconstructions are associated with risk of residual knee pain, recurrent

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instability, and premature osteoarthritis, revision ACL reconstructions are associated with worse clinical outcomes [2].

Some patients who successfully rehabilitate and return to cutting/pivoting activities tear their native contralateral ACL [3, 9]. The rate of contralateral ACL injury following primary ACL reconstruction has been reported between 3.0-20.5% [2, 5, 7-13], increasing risk for bilateral knee pain, instability, and osteoarthritis.

Graft failure and/or contralateral injury is financially, psychologically, and physiologically traumatic for the patient and his family. While prevention of primary ACL injury has been heavily studied, it is of interest to study the factors associated with recurrent and subsequent contralateral ACL reconstructions. A review of the literature reveals numerous reports of associated modifiable and non-modifiable factors [2-3, 5-8, 12-19], but no comprehensive evaluation. Awareness of modifiable and non-modifiable factors allows for intervention to decrease rates of recurring ACL rupture. We aim to provide a comprehensive report of risk factors associated with recurrent and subsequent contralateral ACL reconstructions in the adult population.

2. METHODS

A systematic review of the literature was performed to identify studies which reported risk factors for recurrent or subsequent contralateral ACL reconstruction. The study was registered with the PROSPERO database. The PubMed and Embase databases were searched from January 1, 2010 until December 31, 2017. The search utilized a combination of keywords such as “ACL reconstruction” and “contralateral or recurrent” and “risk factors." Where appropriate, our initial search included medical subject headings (MeSH), to ensure the consideration of all relevant articles.

All study designs were considered, apart from systematic reviews. Two authors independently searched the listed electronic databases for any eligible articles. Abstracts from all search results were reviewed; articles that met inclusion criteria were reviewed. An overview of our search strategy is included (Table 1).

Table 1. Search Strategy

Criteria	Details
Searched databases	PubMed/MEDLINE, Embase
Search string	(“anterior cruciate ligament” OR ACL) AND (lesion OR tear OR rupture OR injury OR reconstruction OR repair) AND (bilateral OR recurrent OR contralateral) AND risk factors
Inclusion criteria	non-contact ACL injury, study analyzed risk factors for contralateral ACL injury or graft rupture
Exclusion criteria	study is a systematic review, study has no data, population studied is skeletally immature or elderly, study is evaluating risk factors for primary ACL injury, study was not published in English, study was not related to the ACL, access to full article was not available
Time filter	2010-2017
Language filter	English
Age filter	19-44, 19+
Other filters	Human studies

3. RESULTS

The initial search yielded one hundred twenty-nine articles, of which thirty-six were deemed relevant once inclusion and exclusion criteria were applied. Once duplicates were removed, twenty-three articles remained. An additional two articles were included, yielding a total of twenty-five articles included in this review.

The included articles had the following designs: five retrospective cohort studies [5,8, 20-22], six prospective cohort studies [2, 23-27], four case series studies [28,-31], five controlled laboratory studies [32-36], three retrospective case control studies [13, 15, 37], and two prospective case control studies [16, 38]. The risk factors catalogued in these studies are grouped into factors the patient can alter against factors the patient has no control over (Table 2).

Table 2. Risk Factors Associated with Graft Rupture and/or Contralateral ACL Rupture

Patient-controlled Factors	Factors Patients Cannot Control
Graft harvest site Allograft vs. autograft Return to activity	Age at index procedure Sex Significant history Rotational asymmetry Neuromuscular asymmetry Strength asymmetry Increased posterior tibial slope Narrow femoral intercondylar notch Technical errors during surgery

4. DISCUSSION

PATIENT-CONTROLLED FACTORS

GRAFT HARVEST SITE

While surgeons offer patients what they deem the most appropriate intervention, patients do have significant input on graft harvest site. Furthermore, if a patient has experienced graft rupture, the patient and surgeon might have limited graft options.

Thompson *et. al* reported a 90% survival rate of the bone-patellar tendon-bone (BPTB) graft at 20-years (average age at surgery 24.6 $\pm$ 9.8 years), which is notably higher than the 67% survival rate of the contralateral ACL [31]. This suggests the BPTB graft may be more durable than the native ACL, though this could be secondary to a variety of other factors such as more dedicated rehabilitation on the operative side or patients favoring their non-operative leg upon return to activity, which could render the non-operative side more susceptible to injury. One obstacle for the BPTB graft is pain upon kneeling; 67% of patients reported kneeling pain at 20 years post-reconstruction [31].

Another study concluded BPTB autografts were associated with an increased risk for contralateral ACL injury [25], noting a trend towards an increased rupture rates with hamstring tendon (HT) autografts [25]. The BPTB autograft carries an increased risk for osteoarthritis,

knee extension deficits, and decreased single-legged hop performance at 15 years post-ACL reconstruction [25]. However, the surgeries were performed in 1993-1994, so these results could be influenced by outdated surgical techniques. Bourke *et. al* reported no significant difference in 15-year rates of graft rupture between BPTB and HT autografts [29]. At 15 years post-reconstruction (average age at surgery 29 years), the odds of contralateral ACL rupture were more than doubled in patients with a BPTB autograft [29], while those with HT autografts experienced similar rates of contralateral ACL injury or primary graft rupture [29], but higher rates of revision [17].

Though HT and BPTB autograft have achieved good long-term results, neither are perfect options. BPTB grafts appear to be more durable and have lower graft rupture rates [17, 25], but may increase the odds of contralateral ACL injury [17, 25, 29], osteoarthritis, anterior knee pain, and kneeling pain [25, 31]. The process of harvesting the BPTB graft may interrupt the afferent signals from the injured knee more than harvesting the hamstring tendon graft, altering central nervous system (CNS) feedback loops and predisposing to contralateral ACL injury [29].

The quadriceps tendon (QT) autograft has become popular because it is easier to harvest, requires a smaller incision, and has comparable strength to the BPTB autograft [39]. Several studies comparing the BPTB and QT autografts found no difference in functional outcomes between the two grafts [40-41]. Similarly, studies comparing the QT and HT autografts have also reported equal outcomes [39, 42-44] . While the outcomes of the QT autograft appear promising, this requires further study with longer follow ups to identify rates of graft rupture and contralateral ACL injury.

AUTOGRAFT VS. ALLOGRAFT

Some studies found allografts carry an increased risk of future injury [2, 8-9, 17, 45], while others have not [46]. Some surgeons believe allograft reconstructions have fewer postoperative complications, a faster rehabilitation, and are better for older patients [8, 55]. Others believe autografts provide fast bone-to-bone healing, encourage return to sport, and are less likely to rupture [27].

Kaeding *et. al* found allografts had 5.2 times greater odds of graft rupture than autografts [2], a finding which is supported by several other studies [17]. A study reported patients who received an autograft were 2.78 times less likely to experience subsequent graft rupture [27]. This study standardized the source of allografts, using grafts with minimal irradiation exposure [27], suggesting graft processing may not cause the higher failure rate. An *in vivo* sheep model concluded allografts took longer to heal than autografts, which could impair graft strength and knee stability [45].

While allografts might be an appropriate choice for older patients, patients who return to a high level of activity should be informed of the associated risks. Though allografts offer shorter rehabilitations, this is inconsequential if the patient requires repeat ACL reconstruction.

RETURN TO ACTIVITY

Returning to high intensity activity is a well-reported risk factor for ensuing ACL injury [13, 21, 23, 26, 26]. Activity level at index surgery is also a risk factor for both graft rupture and contralateral ACL injury [2]. Patients who return to high intensity sports involving cutting, pivoting and jumping movements are especially predisposed to graft and contralateral rupture.

While returning to sports risks future ACL injury, avoiding all athletic activity after surgery is unrealistic. However, the timeline of a patient's return to activity can affect their risk for future ACL injury [23-24, 36]. For each month a patient's return to sport was delayed, up to 9 months postoperative, the reinjury rate was reduced by 51% [23]. Athletes who regained 90% of hamstring, quadriceps, and hopping performance before resuming athletic activities have significantly decreased risk of reinjury [23-24]. *Myer* et. al reported deficits on vertical hop ability on the reconstructed limb up to 11 months post-surgery [36]. Delaying return to sport until after athletes have met specific clinical discharge criteria could decrease the risk of second ACL injury.

Lastly, certain sports such as soccer [2, 28], lacrosse [33], basketball [2], and football [2] carry a higher risk of second injury; identifying high-risk activities allows physicians, patients, and coaches to intervene and decrease the risk for future injury.

FACTORS PATIENTS CAN'T CONTROL

AGE AT INDEX SURGERY

Age at index surgery is a risk factor for secondary ACL injuries [2, 8, 13, 17, 26, 28, 31,38]. Webster *et. al* found 29% of patients younger than 20 experienced a secondary ACL injury within 5 years of their index surgery, compared to 8% of patients older than 20 [13].

Another study concluded patients younger than 18 at index surgery did not have significantly higher rates of graft ruptures, but did have higher rates of contralateral ACL rupture (56%) compared to patients older than 18 (25%) [31]. However, this study had a small sample size (n=90), which could account for the lack of association between age and graft rupture.

It is unclear whether age is a confounding factor, or if there are specific age-related risk factors. Younger persons are more likely to return to pre-injury activity level, risking graft and contralateral injury [13, 23, 26, 29]. Younger patients also engage in more risk-taking behavior and can be less compliant with rehabilitation protocols, which could predispose to future injury.

SEX

Maletis *et. al* reported males had a higher risk of revision ACL reconstruction because males return more often than females to high-level sports involving cutting, pivoting and jumping [17]. Females had a higher risk of contralateral reconstruction [17], which is supported by other studies [29, 47]. This might be due to a larger-sized graft than the native female ACL having a protective effect on the operated leg [17].

An analysis of the Swedish National ACL Register found 22% of female soccer players between ages 15-18 underwent secondary ACL reconstruction, compared to 9.8% of male soccer players [28]. Moreover, female athletes underwent nearly double the ACL reconstructions (11.8% vs. 5.4%) [28], which suggests sex-specific characteristics may predispose female athletes to future ACL injuries. Females have larger quadriceps femoral angles (Q angle), hormonal fluctuations, more joint laxity, are more likely to have valgus knees, and are more prone to lower extremity neuromuscular imbalances than males [48-51].

Webster *et. al* and Sato *et. al* found no relationship between patient sex and the risk of graft rupture [26,52]. It is worth noting that these studies report rates of rupture, not reconstruction, which might affect the statistical analysis.

There is currently no definitive relationship between sex and rates of revision or contralateral ACL reconstruction. All studies were retrospective, and included patient populations from over a decade ago. As the number of female athletes increases yearly, these populations likely represent an outdated demographic.

SIGNIFICANT HISTORY

Several studies reported the number of previous revision surgeries or a positive family history as risk factors for revision or contralateral ACL reconstruction [13, 27, 29]. Wright *et. al* found patients who underwent more than 3 revisions were 25.8 times more likely to sustain graft rupture within 2 years [9]. Surgeons operating on patients after multiple ACL reconstructions are limited in graft selection, which might compromise the surgical outcome. Additionally, repeat operations induce joint trauma and complications such as bone tunnel widening or compromised secondary stabilizers. Moreover, re-injury is an overwhelming experience, which might offset the patient's ability to rehabilitate their injury.

Webster *et. al* and Bourke *et. al* concluded ACL injury in a first-degree relative doubles the odds of graft rupture or a contralateral ACL [13], which is also a risk factor for index ACL injury [52-54]. Certain collagen and proteoglycan polymorphisms (COL1A1, COL5A1, and COL12A1, chromosome 11 MMP gene cluster) have been proposed to be associated with these injuries [55-56, 58], but it is possible body morphology, activity level, hobbies, etc. predispose patients to ACL injuries.

ROTATIONAL, STRENGTH, AND NEUROMUSCULAR ASYMMETRIES

Two controlled laboratory studies demonstrated that athletes who underwent ACL reconstruction had asymmetries in force generation and absorption on their injured leg [36,57]. Another study compared the performance of ACL-reconstructed patients to healthy controls and concluded ACL-reconstructed patients showed reduced range-of-motion (ROM), single-leg jumping distance, and hamstring strength on their operated leg 18-30 months post-reconstruction [35]. Kyritsis *et. al* concluded reduced hamstring strength is a risk factor for future injury [24]. The hamstring muscles impart strength on the knee joint, resist anterior tibial translation, and protect the ACL; weak hamstring muscles are a reported risk factor for injury [58, 59], and reduced hamstring strength is associated with lower Lysholm knee function scores [60].

A study found limiting femoral internal rotation incites earlier ACL failure [32]. Improving internal rotation on patients with limited hip mobility may decrease ACL load, reducing ligament failure [32, 61-62].

Dai *et. al* suggested restoring strength and ROM symmetry in a clinical setting does not translate to kinetic knee symmetry, and found significant asymmetry between surgical and non-surgical limbs in patients returning to activity [34]. Future research should focus on low-cost methods to identify kinetic knee asymmetries.

Patients might overcompensate if the strength and ROM of one leg is reduced, and could predispose patients to injury. Additionally, because asymmetries were observed over one year post-ACL reconstruction, the injured leg may never recover to its pre-operative state.

POSTERIOR TIBIAL SLOPE

Posterior tibial slope (PTS) is most often measured on lateral radiograph with specialized software [38]. An increased PTS is a reported risk factor for index and recurrent ACL injury [20, 30, 38], resulting in an increased anterior tibial translation, which strains the ACL [30, 63-65]. Hendrix *et. al* used lateral radiographs to compare the PTS of 50 patients who had either unilateral, bilateral, or no ACL injury [20]. The mean PTS of the healthy group was significantly lower than the mean PTS of both ACL-deficient groups [20]. Moreover, the study reported a 1^{o} increase in PTS was associated with 20% increase in the odds of unilateral ACL injury and a 34% increase in the odds of bilateral ACL injury [20]. Webb *et. al* reported patients with PTS over 12^{o} had 5 times higher odds of sustaining a subsequent ACL injury [38]. A finite element computer model found PTS was related to anterior tibial translation and ACL stress in both active and passive gait models [66].

Patients with increased PTS should be counseled regarding predisposition for future ACL injury. Moreover, performing a tibial wedge osteotomy could restore knee stability [30, 63]. Sonnery-Cottet *et. al* performed proximal tibial anterior closing wedge osteotomies during ACL re-revision on 5 patients who had "pathological PTS" over 12^{o} and reported no further injury on patients who returned to sport [30]. Arun *et. al* performed open wedge high-tibial osteotomy during primary ACL reconstruction on 30 patients with osteoarthritis and reported improved functional outcomes [67]. Another study performed anterior closing wedge tibial osteotomies on 9 patients with increased PTS during ACL re-revision and reported no graft ruptures or recurrent instability at 2 years post-op [14, 67]. Using tibial osteotomies to decrease pathologic PTS and reduce stress on ACL grafts requires further study with larger sample sizes.

NARROW FEMORAL INTERCONDYLAR NOTCH WIDTH

Femoral intercondylar notch width can be measured on radiograph or intra-operatively, and is often reported as the notch width index (NWI), the ratio of intercondylar notch width to femoral condylar width.

A radiographic study reported significantly smaller NWIs in patients with bilateral ACL injury compared to patients with unilateral injury and healthy volunteers [15]. Another compared several factors between an injured and uninjured group and reported a significantly more narrow intercondylar notch in injured patients [37]. Levins *et. al* reported a 28% decrease in graft rupture in females for every 1-millimeter increase in femoral intercondylar notch, but no significant association between graft rupture and intercondylar notch width in males [16].

Wolf *et. al* intraoperatively measured the femoral intercondylar notch and concluded a smaller intercondylar notch was not a risk factor for graft rupture [22]. The authors proposed the NWI is unreliable, and accredited discrepancies in the literature to different measurement tools [22]. However, this study utilized arthroscopic measurements, which are more variable than radiographic measurements.

The relationship between femoral intercondylar notch width and graft rupture or contralateral ACL injury requires further study utilizing standardized measurements.

MISCELLANEOUS FACTORS

Thompson *et. al* found patients with non-ideal tunnel position were more likely to rupture their graft [31]. Ideal tunnel position was quantified as 80% along the Blumensaat line, a graft inclination angle of greater than 17^{o} from vertical, and tibial tunnel 40-50% along the tibial

plateau [31]. Though the literature poorly defines ideal tunnel position, various surgical techniques can affect knee stability [68-70]. Anterior tibial tunnel placement decreases anterior tibial translation [68], while increasing sagittal and coronal obliquity decreases anterior tibial translation and rotary motion [68, 70].

A study found index surgeries performed in a teaching hospital were associated with higher rates of revision ACL reconstructions (3.6%) compared to those performed in a non-academic institution (2.1%), with surgeon volume having no significant impact on reoperation rates [8]. Residents and medical students are trained in academic institutions, which might contribute to the observed trend. However, the author proposes higher revision rates in academic settings reflects that academic hospital surgeons are more willing to perform revision ACL reconstruction, instead of an increased failure rate [8]. The study reported an overall revision rate of 3%, indicating ACL reconstructions performed at both academic and nonacademic centers are successful [8], but patients and providers should be aware of all contributing factors to graft failure to accurately assess risks of revision surgery.

PSYCHOLOGICAL IMPACT

Almost all studies regarding rehabilitation and prevention of ACL injuries focus on tangible factors. Low confidence, fear of re-injury and low perioperative self-efficacy are associated with performance years after surgery [71-72], which could affect rehabilitation adherence. Athletes who suffered a second ACL rupture had a higher fear of re-injury in the 5 weeks before and after index ACL reconstruction [73].

It is important to counsel patients and attempt to improve self-efficacy and confidence. In a randomized controlled trial, patients underwent nine guided imagery sessions to improve coping skills, simulate motor activities, and improve self-confidence [74]. When compared to controls, the treatment group had less knee laxity, lower noradrenaline levels, and lower dopamine levels, which may improve healing [74]. The treatment group experienced a smaller reduction in self-efficacy [74]. After a severe, painful injury, patients may be apprehensive to fully utilize the leg with the injured ACL, encouraging injury-predisposing neuromuscular imbalances. Guided imagery and relaxation sessions may alleviate patients' fears and allow equal employment of their lower limbs. Another study found motor imagery increased muscle activation, enabling a more complete strength rehabilitation [75]. The relationship between psychology and recovery requires further study; it is important to correct anatomic imbalances, but it is also important to intervene if a patient is mentally predisposed to suboptimal rehabilitation or poor functional outcomes.

LIMITATIONS

This study was not without limitations. The reviewers were not blinded to authors, institutions, or journals during the review process, which introduces the possibility for bias. Moreover, the strength of evidence of systematic reviews is limited by the quality of publications it contains, and there was a significant heterogeneity amongst included studies. Nonetheless, an extensive search of published literature was conducted with strict inclusion and exclusion criteria to minimize the potential for bias .

5. CONCLUSION

The literature demonstrates predisposition to second ACL injury is indeed multifactorial. Because many of these factors cannot be controlled, responsibility lies on the medical profession to assess risk factors and find appropriate interventions so patients can return to

the lifestyle they enjoy. Graft harvest site, allograft usage, return to sport, younger age, a positive family history, increased posterior tibial slope (PTS) and the number of previous ACL reconstructions were predictors for second ACL injury. It is crucial for healthcare professionals to address any neuromuscular, rotational or strength asymmetries between the injured and uninjured leg before the patient returns to sport because these are well-reported risk factors for contralateral ACL rupture and graft rupture. There was some debate in the literature whether narrow femoral intercondylar notch predicts future ACL injury, which can be attributed to a variety of measurement tools used in different studies. This area of research requires further study with a unified method of measurement. The association between sex and future ACL injury was widely debated in the literature, and requires prospective study to represent a current patient demographic. Lastly, it appears that a patient's psychological state throughout rehabilitation is associated with long-term functional outcomes, which requires future study to prove a definitive relationship and examine possible interventions for improved outcomes.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

AUTHORS' CONTRIBUTIONS

Author A designed the study, performed the literature search, and wrote the first draft of the manuscript. Author B performed an independent literature search and edited the first draft of the manuscript. Author C designed the study protocol and oversaw the literature searches. All authors read and approved the final manuscript.

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