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Systematic Selection of Key Logistic Regression Variables for Risk Prediction Analyses: A Five Factor Maximum Model

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Abstract

General and Critical Review format—The evolution of clinical practice and medical technology has yielded an increasing number of clinical measures and tests to assess a patient’s progression and return to sport readiness after injury. The plethora of available tests may be burdensome to clinicians in absence of evidence that demonstrates the utility of a given measurement.

Objective—Thus, there is a critical need to identify a discrete number of metrics to capture during clinical assessment to effectively and concisely guide patient care.

Data Sources—The data sources included Pubmed and PMC Pubmed Central articles on the topic. Therefore we present a systematic approach to injury risk analyses and how this concept may be used in algorithms for risk analyses for primary ACL injury in healthy athletes and patients after ACL reconstruction.

Main Results—In this article we present the Five Factor Maximum Model, which states in any predictive model a maximum of five variables will contribute in a meaningful manner to any risk factor analysis.

Conclusions—We demonstrate how this model already exists for prevention of primary ACL injury, how this model may guide development of second ACL injury risk analysis, and how the Five Factor Maximum Model may be applied across the injury spectrum for development of injury risk analysis.

Background

Prediction of a healthy subject’s or a patient’s injury risk or outcome after treatment is useful to aide in the development of clinical interventions. Risk profiles are derived using

A laboratory-based ACL injury risk prediction algorithm has been developed. Our Research team⁵⁰ prospectively tested 744 uninjured female athletes (basketball and soccer) to determine predictive mechanisms underlying increased KAM during three drop vertical jump (DVJ) tasks. Measures of interest included anthropometrics, maturation, laxity/flexibility, strength and landing biomechanics. Linear regression was used to model KAM, and logistic regression was used to examine high (>25.25 Nm of KAM) versus low KAM as a surrogate for ACL injury risk. The final model identified *five* independent variables that predicted KAM, which included three movement biomechanical variables (peak knee abduction angle, peak knee extensor moment, knee flexion range of motion) as well as body mass index and tibia length (Table 1). Collectively these variables accounted for 78% of the variance in KAM during landing. The logistic regression model that employed these same variables predicted high KAM status with 85% sensitivity and 94% specificity.⁵⁰ Subsequently, clinical correlates of these laboratory measures were validated and predicted a high KAM moment with 73% sensitivity and 70% specificity (Table 2).⁴⁸ The development of accessible, low-cost clinical tools to identify those at risk for future injury is important for developing injury prevention programs at a population level.⁴⁸

Clinical trials have demonstrated that preventive neuromuscular training programs designed to correct neuromuscular and biomechanical risk factors can be effective in reduction of ACL injury in young female athletes. Our research group⁵¹ performed a meta-analysis to determine the effectiveness of neuromuscular training on knee injury prevention in female athletes. A total of 14 studies were included in the analysis and results showed that there was a significantly greater knee injury reduction in females who participated in a preventive neuromuscular training program compared to those who were in a control group.⁵¹ In a separate meta-analysis, Sugimoto et al⁷² evaluated published clinical trials to evaluate types of exercise that best support ACL injury reduction in young females. A total of 14 clinical trials met the inclusion criteria and it was shown that there were fewer ACL injuries among participants who completed injury prevention training that focused on strengthening, proximal control exercises, and multi-exercise genres. The authors hypothesized the design of these training programs ameliorated biomechanical and neuromuscular characteristics contributing to an increased KAM and ACL injury risk.

The primary ACL injury prevention model highlights the process of identification of a narrow range of variables that contribute to injury risk prediction using a multivariable regression analysis. The five factor model is illustrated in the framework for a clinical screening algorithm to identify at risk individuals (Table 1). Furthermore, identification of key risk factors has aided in the development of focused injury prevention training programs. Prior success using an injury prevention model to decrease the rate of primary ACL injury may have important applications in prevention of second injury.⁵⁸

Second and Multiple ACL Injury Prevention

Second or multiple ACL injury, whether it is an insult to the ipsilateral graft or the contralateral ligament, is a growing problem after reconstruction. Besides missing an additional year of athletic participation, increasing health care costs, and increased psychological distress, re-injury and subsequent revision surgery have significantly worse

outcomes compared with those after initial reconstruction.^{12, 17, 81} Among young athletic individuals, a second tear prevalence of 29% has been reported.^{60, 62, 74} This is substantially higher than initial ACL injuries, reported to occur at a rate of 1 in 60 to 100.^{19, 45} Younger athletes⁷⁴ who return to high-level sporting activities early represent the most vulnerable population.^{34, 60} Both sexes are at risk for second ACL injury, with women reported as having higher risk of contralateral injury,^{61, 80} and men having an increased risk of ipsilateral injury.^{6, 12, 70} Despite high second injury rates in ACLR, there is a lack of consensus regarding the underlying mechanism placing these athletes at increased risk for future injury.⁵⁹ The primary ACL injury prevention approach including identification of risk factors that serve as a basis for an injury prevention program is an ideal model for prevention of second injury. The challenge is identification of meaningful risk factors from the plethora of demographic data, clinical tests, movement assessment variables, and self-report questionnaires that have the potential to provide insight to risk for second ACL injury (Table 3).

Risk Factor Categories

a. Patient and Surgical Variables—Multiple surgical and patient factors have been identified as potential contributors to second ACL injury. Patient risk factors for graft rupture include being young,^{38, 39, 70} early return to sport,³⁴ a familial history of ACL injury,⁶ and an index injury sustained via contact mechanism.⁶⁵ Surgical risk factors include a vertical graft position,^{5, 29, 37} small graft,^{39, 57} lax graft^{5, 63} and hamstring graft.⁴⁰ A second ACL injury sustained in the contralateral knee is associated with a young age,^{29, 37, 63} returning to cutting/pivoting sports^{6, 65} and a family history of ACL injury.⁶ The use of patellar tendon grafts has also been shown to be associated with higher rates of contralateral ACL injury than hamstring grafts.^{37, 63} While it is encouraging that so many potential risk factors have been identified, there is considerable inconsistency in the published literature regarding association with second injury.⁷⁴ Furthermore, patient and surgical variables are not modifiable through training interventions. As with primary ACL injury prevention, there should be an emphasis on modifiable factors that may be mitigated with non-invasive intervention strategies, with the additional goal of returning the athlete to their pre-injury activity level.

b. Strength and Power—Deficits in the hamstrings-quadriceps torque production ratio have been established as a key variable in the primary ACL injury risk model.^{47, 49, 50} Factors that have been identified as placing an individual at risk for primary ACL injury provide an important window into underlying deficits that may persist after reconstruction.¹⁰ Dynamic muscular control is necessary for joint stability during dynamic loading conditions such as jump landing and pivoting. Incompetent or unbalanced dynamic elements during these activities may place stress on the passive ligament structures that exceed the tissue failure point. Quadriceps dominance, which is often observed in female athletes,^{23, 25} may contribute to an increase in ACL stress, as unopposed quadriceps muscle activity combined with a knee positioned near full extension may contribute to anterior tibia translation and ligament rupture.^{13, 44, 52} A corresponding increase in hamstring muscle force production can counter the deleterious effects of an unbalanced quadriceps contraction by promoting joint compression and limiting anterior tibia translation,¹³ and frontal plane tibia motion.⁴¹

For individuals who have undergone ACLR, muscle weakness may persist for years after surgery. This weakness, although not definitively related to a second ACL tear, may increase injury vulnerability. Additionally, quadriceps strength deficits have been linked with decreased function, altered performance, and persistent movement asymmetries after ACLR.^{46, 56, 66, 67} Ithurnburn et al³⁰ evaluated three-dimensional lower extremity biomechanics in female athletes after ACLR during single leg drop jump maneuvers. The authors reported individuals with low quadriceps strength exhibited more pronounced lower extremity asymmetries during landing compared to individuals with high quadriceps strength. The authors speculated compromised strength and the resultant movement asymmetries may be a significant risk factor for second ACL injury.³⁰ Despite the absence of a direct link to re-injury, the broad contribution of muscle strength to lower extremity movement patterns, loading, and function necessitates inclusion in the analysis of risk factors contributing to second ACL injury.

c. Movement Biomechanics—Few investigators have reported lower extremity biomechanics predictive of second injury. Paterno et al⁶¹ conducted a prospective, cohort study of fifty-six athletes who had undergone ACLR. Bilateral, three-dimensional lower extremity biomechanics and postural stability were assessed during a drop vertical jump maneuver before the individuals returned to sports activities that included jumping, cutting and pivoting activities. Within one year of returning to sports, thirteen individuals sustained a second ACL injury. Logistic regression identified four variables that predicted second injury with excellent sensitivity (0.92) and specificity (0.88). These variables included uninvolved limb transverse plane hip net moment impulse, the 2-dimensional frontal plane knee joint range of motion, asymmetries in sagittal plane knee moments at initial contact, and involved limb postural stability.⁶¹

The strongest predictor of second ACL injury was uninvolved limb transverse plane hip net moment impulse during the initial 10% of landing, with an area under the ROC of 0.81 and both high sensitivity (0.77) and specificity (0.81).⁶¹ The impulse during the initial 10% of stance was representative of a net hip internal rotator moment in the participants who sustained a second ACL injury compared with a net external rotator moment on the uninvolved limb of participants who did not incur a second ACL injury. Greater hip external rotator moments may act to restrain hip internal rotation motion during this phase of landing.⁶¹ Proximal hip control is critical for promotion of optimal knee position. Although ‘dynamic knee valgus has been identified as a strong predictor of ACL injury,²⁴ this position represents a multi-segment, multi-planar combination of rotations and translations that include hip adduction, hip internal rotation, knee flexion, knee abduction, and tibial rotation.^{24, 32, 68} In cadaveric models this knee position has been shown to increase ACL strain.^{16, 41} It is therefore not surprising that compromised proximal hip control in the transverse plane was the strongest predictor of second injury. Paterno et al stated their findings were consistent with previous studies describing altered movement patterns and impairments either predictive of initial ACL injury in an uninjured population or demonstrated by patients after initial ACLR.²⁴ The authors did caution however, that future investigations would be necessary to determine independent risk factors for both ipsilateral graft failure and contralateral ACL injury, as different factors may contribute to each of these injuries.

d. Proprioception, Kinesthesia and Balance—Injury to the ACL has been shown to lead to deficits in proprioception. Attempts to establish whether restoration of the ACL by surgical reconstruction can reverse such deficits have led to conflicting results. In general, longitudinal studies of ACL reconstructed patients tend to show improvements in joint position sense and the threshold to detect passive movement over time.^{1, 15, 31, 64} However, as it is difficult to relate such findings to a sporting context, another approach to evaluate proprioception has been to use tests of neuromuscular function which test not only proprioception but also the muscular response. These measures have tended to show that ACL reconstructed patients have deficits in proprioception and postural control that persist over time. A systematic review that attempted to summarize the evidence determined that there are subtle, yet significant, impairments in postural control in patients following ACL reconstruction when compared to healthy controls.²⁸ The deficits appeared to be greater when the postural task used was more dynamic or challenging i.e. using unstable platforms or perturbations. This is relevant for the prevention of second ACL injury as most secondary injuries occur during sports participation in a setting of dynamic movement. Research which further shows postural stability to be a contributing risk factor for second ACL injury further supports its inclusion in the analysis of risk factors contributing to second ACL injury.⁶¹

Rehabilitation programs for patients who have undergone ACL reconstruction typically include exercises that are directed towards improving neuromuscular function and coordination and are often loosely referred to as “proprioceptive training” exercises. Overall there are mixed results of programs which incorporate such exercise compared to those which don't with some showing improvements in outcomes⁵⁵ and others showing they have limited effectiveness.⁷

e. Psychosocial Status—Mental status is gaining increased attention as a significant variable that influences an athlete's ability to return to pre-injury sports activities after ACLR. The Tampa Scale for Kinesiophobia (TSK-11) is an eleven item questionnaire designed to capture an individual's pain-related fear of movement/re-injury. This psychosocial measurement instrument has been widely used to capture mental status after ACLR in an attempt to identify barriers to a return to pre-injury sports participation. Lentz et al³⁶ captured physical impairment, self-reported function, and psychosocial status in 46 patients at 6 months and one year after surgery. These authors reported elevated pain related fear of movement/re-injury, quadriceps weakness, and reduced IKDC scores distinguished patients who were unable to return to preinjury sports participation because of fear of re-injury/lack of confidence. Lentz et al³⁶ proposed that these measures may be useful for identification of patients at risk for poor sports participation outcomes after ACLR.

The Anterior Cruciate Ligament Return to Sport after Injury (ACL-RSI) scale measures psychological readiness to return to sport after ACLR. Two large scale studies have shown that the ACL-RSI scale can be used to predict return to sport outcomes. The first enrolled 100 athletes who completed the ACL-RSI at 3, 6 and 12 months after undergoing ACL reconstruction surgery.³⁵ Scores on the ACL-RSI at 6 months were significantly lower in the athletes who did not successfully return to their competition sport at 12 months compared to the athletes who did return to sport (RTS). Therefore, an athlete's readiness to return to sport at 6 month post ACL reconstruction surgery was related to whether or not they actually

returned at 12 months. This result suggests that it may be possible to identify athletes at risk of not returning to competitive sport due to psychological reasons.

The second and larger study of 187 patients administered a battery of psychological assessments, including the ACL-RSI scale, before ACL reconstruction surgery, as well as 4 and 12 months after surgery.² Three variables; psychological readiness to return to sport, the participant's estimate of the number of months it would take to return to sport, and locus of control predicted returning to sport by 12 months after surgery. Psychological readiness, as measured by the ACL-RSI, was the only variable to be predictive of return to sport at both preoperative and 4 month measurements. Therefore this study showed that even before the participants underwent surgery, their psychological responses were associated with their chances of returning to the pre-injury level 12 months later.

It is unclear how psychosocial status may influence second ACL injury. One possibility is individuals may be overly confident in their physical abilities at the time of return to sport. However, despite growing awareness for the importance of fear of re-injury and lack of confidence on return to sport outcomes, psychosocial status is not routinely included in the return to sport decision making process. Assessment of this metric may provide insight to identification of individuals at risk for a second ACL injury.

Return to sport criteria and testing to prevent second injury

Within these risk factor categories there are a multitude of variables and test measures that may identify individuals at risk for second ACL injury. Focusing on the goal of returning athletes to their pre-injury activity level and prevention of second injury, the clinical challenge is applying the five factor model to guide patient management. There has been a rapid growth in the number of studies that document 'return to sport (RTS) criteria' following ACL reconstruction. Within this group of studies it is possible to draw a distinction between those which incorporate such criteria into phased rehabilitation programs that aim to specifically target deficits known to be associated with second ACL injury compared to those which employ a test battery in order to 'clear' the athlete for return to sport.

Phased rehabilitation programs aim to incorporate many of the above discussed risk factors which are thought to contribute to second ACL injury. Neuromuscular impairments have tended to be a large focus of these programs that emphasize the importance of achievement of limb symmetry before a RTS is allowed. Such programs have clearly defined criteria both in terms of the criteria used and the minimum level of performance required for the patient to move between phases and ultimately resume sports participation.⁷⁶ Overall, criterion based phased rehabilitation programs for return sport after ACL reconstruction surgery have good face validity as they are based on sound theoretical underpinnings and have clear performance criteria. They do however require resources and as yet there is little evidence to show that they mitigate against second ACL injury, such evidence is of course challenging to obtain.

There has been a noticeable growth in the number of studies that published a test battery of return to sport criteria over recent years. Such criteria are typically employed at the final

phase of rehabilitation with the notion that athletes who ‘pass’ are ‘cleared’ to return to sport participation. Whilst the use of a test battery of return to sport criteria can be seen as an important step in the attempt to reduce the risk of second ACL injury, it is not clear whether such criteria are designed to determine whether the athlete is capable of returning to play or whether they are designed to determine whether it is safe. Strength and hop tests have been common tests of function which have been used to assess an athlete’s readiness to return to sport after ACL reconstruction surgery. A good argument can be made for such functional tests to aid in the return to sport decision making process based on recent data which show that clinical examination results do not appear to be related to functional ability. Specifically, patients who were cleared to return to sport based on examination findings were still at significant risk of lower limb injury based on results from functional testing.⁴² This mismatch is important to decide on what criteria and which tests to utilize.

Perhaps due to a lack of clear evidence as to what the most salient risk factors are for second ACL injury, the most recent studies attempt to cover a broad range of risk factors and propose a substantial battery of tests with up to 15 to 20 different tasks.¹¹ Of relevance is that few patients actually pass such a test battery. Hebst et al.²² reported that only 17% of their patient group passed all criteria to return to non-competitive sports, and only one patient passed the criteria for return to competitive sport at approximately 9 months after ACL reconstruction surgery. Gokeler et al.¹⁸ similarly showed that only 2 of their 28 patients passed all the criteria of their test battery at 6 months post-surgery. Perhaps data such as this indicate that test batteries have become too broad and that we should focus on fewer but key risk factors for re-injury, anything great than 4–5 factors is likely unnecessary.

It is worth noting that whilst the term criteria are typically used, many studies suggest return to sport tests without reference to specific cut-off values to denote pass or fail. Indeed setting cut-off values for return to sport criteria is somewhat subjective and there is relatively little data to indicate whether those who do not meet criteria actually fare worse. Two recent studies have attempted to address this. The Delaware-Oslo research group²⁰ used a return to sport test battery that consisted of isokinetic quadriceps strength testing, 4 single-limb hop tests and 2 self-report measures to assess the association of these measures with subsequent knee injury. Whilst not specific to second ACL injury, two relevant findings emerged. First, only one in four patients passed the return to sport criteria and second, those patients who passed the criteria had fewer reinjuries than those who failed the criteria. Of the various return to sport criteria that were used having regained more symmetrical quadriceps strength was associated with a reduction in re-injury risk.

In a recent cohort of professional male athletes six return to sport tests (isokinetic quadriceps strength, 3 hop tests, timed running T-test, on-field sport specific rehabilitation) were used to clear the athlete to return to team training.³³ Results showed that not passing all the 6 criteria was associated with a four times greater risk of ACL graft rupture. Hamstring to quadriceps strength ratio deficits were also associated with an increased risk of graft rupture, with a ten times greater risk for every 10% difference in strength. Whilst these studies show some promise in using return to sport criteria to reduce the risk of both an ACL graft rupture and knee injury in general, there is clearly a need for additional data to establish whether the ability to resume sport, either effectively or safely, reflects having met the various return to

sport criteria which have been proposed and whether such criteria can be consistently applied to reduce the risk of second ACL injury.

CONCLUSIONS

Current primary ACL injury prevention models illustrate utilization of five variables to predict injury risk. Development of second ACL injury risk models is underway. Despite the plethora of clinical tests that have been developed to assess patient progress and return to sport readiness, preliminary studies have identified four variables from a finite pool of measures associated that are associated with second injury. Thus, the data indicates a *maximum* of five variables should be used to develop a risk profile based on the proposed *five factor maximum model*. This model will provide a guideline for future investigations in development of injury prediction.

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'What are the new findings'**Model development of logistic regression prediction:**

A *maximum* of five variables should be used to develop a risk profile based on the proposed *five factor maximum model*.

This novel approach will provide a guideline for future investigations in development of injury prediction.

MCQ (applies only to Review papers)

- 1 Female athletes are at greater risk for primary ACL injury. There are modifiable and non-modifiable risk factors that may contribute to this increased risk. What are the proposed modifiable risk factors?
 - a. Knee laxity, poor posterior chain activation, poor trunk control, knee valgus
 - b. Poor posterior chain activation, knee valgus, limb dominance muscle activation asymmetries, poor trunk control**
 - c. Poor posterior chain activation, age, knee valgus, limb dominance muscle activation asymmetries
 - d. Type of athlete, knee valgus, poor trunk control, knee laxity

- 2 Drop vertical jump is used to assess both primary and secondary ACL injury risk factors. The following factors are common to both primary and second injury risk models:
 - a. Knee abduction angle, knee external rotation moment, and side-to-side difference in mechanics during landing
 - b. Knee flexion angle, knee external rotation moment, and side-to-side difference in mechanics during landing
 - c. Knee flexion angle, knee abduction moment, and side-to-side difference in mechanics during landing
 - d. Knee abduction angle, knee abduction moment, and side-to-side difference in mechanics during landing**

The following 3 questions refer to the case below:

A 16-year-old female athlete had ACLR surgery on her right knee 8 months ago. She injured her knee while playing soccer. This was her first major injury and it was non-contact. Her surgeon cleared her to return to sport at her 6-month follow-up appointment. She has been running and working out with her soccer team, but has been hesitant to practice.

- 3 Most ACL injuries are non-contact. What was the most likely position of her body at the time of injury?
 - a. Medial collapse of the knee, a planted foot, straight (or nearly straight) knees, and being off balance**
 - b. Neutral rotation of the hips, a planted foot, straight (or nearly straight) knees, and being off balance
 - c. Medial collapse of the knee, a planted foot, deep bend in the knees, and being off balance

- d. Neutral rotation of the hips, a planted foot, deep bend in the knees, and being off balance
- 4 Her parents sign her up for a Secondary Prevention Program. At initial testing, she demonstrates right quadriceps strength 76% of her uninjured leg. Which of the following is the best option to proceed?
- a. She is within 25% of her uninjured leg, proceed with training at her next visit
- b. **Educate athlete and parent about quadriceps strengthening exercises and discuss the patient's status with the referring surgeon; retest at a later date**
- c. Nearly 50% of athletes after ACLR have decreased quadriceps strength; it is safe to begin unrestricted impact plyometrics next session
- d. She is past the timeframe when she is most at risk for re-injury. Begin plyometrics, but do not progress to single leg activities
- 5 The athlete's mom asks you about risk of ACL injury in females. The most appropriate response is:
- a. Approximately 10–12× greater risk than males in the same sport. Risk for a second injury is about 25%
- b. Approximately 10–12× greater risk than males in the same sport. Risk for a second injury is about 50%
- c. **Approximately 4–6× greater risk than males in the same sport. Risk for second injury is about 25–35%**
- d. Approximately 4–6× greater risk than males in the same sport. Risk for a second injury is about 50%

Table 1
Primary ACL injury Risk Factors

Laboratory and clinical models for primary ACL risk factors. The final laboratory model identified *five* independent variables which accounted for 78% of the variance in the knee abduction moment (KAM) (ACL injury surrogate) during landing. The logistic regression model that employed these same variables predicted high KAM status with 85% sensitivity and 94% specificity. Clinical correlates of these laboratory measures were validated and predicted a high KAM moment with 73% sensitivity and 70% specificity.⁴⁸

Primary ACL Injury Prevention	
<u>Laboratory Model</u>	<u>Clinical Model</u>
Anthropometrics	Anthropometrics
<i>Body mass</i>	<i>Body mass</i>
<i>Tibia length</i>	<i>Tibia length</i>
Movement Biomechanics	Movement Biomechanics
<i>Peak knee abduction angle</i>	<i>Peak knee abduction angle</i>
<i>Peak knee extensor moment</i>	<i>Knee flexion excursion</i>
<i>Knee flexion excursion</i>	
	Strength
	<i>Peak hamstring/quadriceps ratio</i>

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Table 2

Second ACL injury risk factors. Logistic regression identified four variables that predicted second ACL injury with excellent sensitivity (0.92) and specificity (0.88).⁶¹

Movement Biomechanics*Transverse plane hip net moment impulse**Asymmetrical sagittal plane knee moment at initial contact**2-dimensional frontal plane knee excursion***Proprioception, Kinesthesia and Balance***Involved limb postural stability deficits*

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Table 3

Proposed ‘Generalized’ five factor model. Categories from which a maximum of five variables have the potential to predict injury risk.

Anthropometrics
Strength
Movement Biomechanics
Proprioception, Kinesthesia and Balance
Psychological

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