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Prediction of Future Injury in Sport: Primary and Secondary Anterior Cruciate Ligament Injury Risk and Return to Sport as a Model

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Can we predict future events? The obvious answer of any rational human being is, "No, certainly not!" However, we keep trying . . . hard! A lot of meteorologists are employed by "rational" television networks and making good money. So maybe we also can make generalized predictions of future occurrences preternaturally. Biostatisticians might answer with an unequivocal yes to this same question and state that logistic regression models do exactly that: they predict the relative risk of an outcome on the basis of logistic regression of multiple independent variables. If this is the case, then which approaches improve predictive capability? We are not attempting to predict individual events in individual athletes. However, certain approaches can improve predictive power.

Primary Anterior Cruciate Ligament Injury Prediction

Our research team uses both a prospective coupled biomechanical-epidemiologic cohort model and a 3-pronged approach to sports injury prediction and prevention. First, we use multiple experimental paradigms to discern the mechanisms of the specific injury. Second, we develop screening tools based on the identified injury mechanisms and reliable and valid screening methods and characteristics. Third, we develop interventions informed by the delineated mechanisms and screening tools.

Confounders in Study Design

Contamination The stated purpose of many studies is to prospectively investigate the association between independent risk factors and outcome variables to determine the risk of future sports injury. However, undetected but major flaws in prospective cohort study design and execution can cast doubt on the authors' conclusions. For example, if a study of a cohort of athletes is confounded by prior interventions relating to a modifiable outcome variable that is used as a risk indicator, a large percentage of subjects may have been unknowingly exposed to outcome-altering interventions. Such major experimental design flaws may cause authors to incorrectly conclude that the variables under study are not predictive of future injury risk. The timing, volume, and duration of interventions before and after screening must be accounted for, quantified, and included in any valid prediction model. For example, Krosshaug et al[7] reported that those who went on to suffer a primary anterior cruciate ligament (ACL) injury had great-

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er medial knee collapse during the drop vertical jump (DVJ) than those who did not suffer a future ACL injury; however, they studied a cohort of athletes in which a large percentage of the sample were contaminated by repeated bouts of neuromuscular training designed to correct this medial knee collapse and a valgus knee position, their outcome measures of choice. They subsequently concluded that valgus knee collapse was not a sufficiently good predictor of primary ACL risk, based on this highly contaminated data set.

Surveillance Another major flaw in many prospective cohort sports injury studies is the use of a flawed injury surveillance system and the extended and varying time between screening and injury. Future authors should analyze their data to determine potential prior contamination, document and quantify the amount and degree of contamination from prior interventions, and estimate the effects of contamination on the modifiable factors (primary and secondary outcome variables) being screened.

Without concerted efforts to reduce and control for contamination, screening tests may be unintentionally designed to fail. For example, imagine a large cohort prospectively undergoing BRCA gene family screening for breast cancer—if an unknown number of subjects had radical mastectomy on the basis of family history alone, the positive and negative predictive values for BRCA genes on the incidence of breast cancer would be invalid. Similarly, injury prediction studies should apply exclusion criteria to remove subjects with prior neuromuscular training, or prior neuromuscular training could be included as a covariate in the analyses. These relatively straightforward alterations would improve the analyses, correct for certain design flaws, and potentially clarify the conclusions drawn.

The Flaw in Normalization

Normalization should be avoided in the development of predictive injury models. In a 2005 study,[6] our research team calculated and analyzed normalized moments, including the knee abduction moment, which was found to be highly predictive of injury risk. However, normalized moments did not predict subsequent ACL injury in mixed-effects logistic regression models, whereas absolute-value moments did predict subsequent ACL injury. These findings should not surprise anyone. Researchers and clinicians alike should be aware that normalized forces and moments are merely derived calculations—they do not occur in nature, nor do they act on the bodies of athletes, so normalized forces and moments do not rupture ligaments. Actual and real (absolute-value) forces and moments do exist in nature; when applied to joints at high rates, they are what actually rupture ligaments. Therefore, absolute-value forces and moments should be expected to be actual predictors of future injury risk. Although it is a good idea to normalize forces and moments so that populations with different anthropometric features (eg, height, weight) can be compared, these normalized forces and moments are likely invalid for prediction of future injury risk and may dilute or wash out potentially significant effects.

The False Assumption of Parametricity

The assumption that classic Gaussian or normal "bell-shaped" data distribution can be used for regression of nonparametric data is a frequent study analysis flaw, and all data should be tested for parametricity. Often, the predictive data used in regression models are not Gaussian in nature. Multiple authors have made this erroneous assumption in their data analyses. These and other authors should assess their data, determine whether they are indeed parametric or nonparametric, and perform analyses with potential confounders included as covariates in their logistic regression analyses.

Injury Prediction and the Second-Injury Dilemma

One clear precept of injury prediction is that the single best predictor of second injury is a prior injury. Young, active athletes have exceedingly high second-injury rates for the ACL, in the range of one quarter to one third.[13,14] This risk level is unacceptably high. Young athletes with multiple serious knee ligament injuries by their early twenties have markedly increased risk of premature knee osteoarthritis, which will have a lifetime impact on their ability to remain active. The high propensity for multiple injuries and osteoarthritis creates grave concern from the perspectives of sport participation and injury prevention. Most second ACL injuries occur within 2 years after the first injury, suggesting a too-early return to activity, or rehabilitation protocols that may be insufficiently based on evidence and not objectively implemented. Numerous studies[4,5,8-10,12] have shown biomechanical and neuromuscular deficits in both limbs after ACL reconstruction and that these modifiable deficits accurately predict second ACL injury. Recently, rehabilitation programs have been urged to target modifiable risk factors for second ACL injury, particularly for younger athletes, who are likely to have the greatest benefit.

This Viewpoint brings together current approaches for reducing the rate of second ACL injuries. Objective criteria that enable screening for such deficits are presented, along with objectively targeted intervention programs designed to prevent second ACL injury. The translational aspect of injury prediction modeling is addressed in terms of providing accurate advice and counseling to athletes with ACL injuries. Such multidisciplinary knowledge is essential to achieve the critical goal of markedly reducing the rate of second ACL injuries. Next, we discuss the highest-level approach to the prospective coupled biomechanical-epidemiologic cohort model and explain this important approach in detail.

Our 3-Pronged Approach and Relative Injury Risk Stratification

The neuromuscular characteristics that

make an individual vulnerable to a noncontact injury may persist after the injury and after surgical stabilization. Across patient populations, whether they are managed nonoperatively or surgically, clear and distinct subgroups of patients unable to maintain dynamic knee stability have been identified. This differential patient response after ACL reconstruction necessitates distinct rehabilitation approaches to optimize outcomes. Future investigations should determine how to prospectively identify vulnerable patients and determine what rehabilitation interventions are most effective in enhancing outcomes and preventing subsequent injuries.

How to Build Optimal Logistical Regression Models

Predictive models with high sensitivities, specificities, and *c* statistics in the range of 70% to 100% can be built, but the goal should be a maximum of 5 variables, with each variable accounting for at least 20% of the variation. A high level of consilience and corroboration is evident among multiple studies[1,2,7,12,13] and in our 2005 study[6] that examined a much greater number of biomechanical and neuromuscular variables as potential risk factors for 205 athletes performing the DVJ. Although a recent study[3] significantly modified the methodology used for the DVJ (eg, no target set for maximum vertical jump height), the results were quite similar in direction and magnitude. Strikingly, in both studies, stiff landings were predictive of risk for future ACL injury because vertical ground reaction force was 20% versus 24% higher, and knee flexion range of motion was approximately 8° versus 6° lower in the ACL-injured versus uninjured groups, respectively.

The final model in the 2005 study[6] identified multiple combined independent variables that predicted ACL injury, including the "valgus" parameters of peak knee abduction angle, peak knee abduction moment, peak hip adduction moment, and knee flexion and ground reaction force (knee flexion range of motion and vertical ground reaction force); these variables showed similar direction and magnitude to those reported by Leppänen et al.[8] However, the authors may have incorrectly interpreted their findings when they stated, "These measures cannot predict injury with sufficient accuracy." The knee flexion and ground reaction force variables alone may be used to stratify ACL injury risk in this new cohort of athletes. Even stronger models might be built when strong evidence supports the use of DVJ as a stratification tool for ACL injury risk.

Reliability, Reproducibility, and Validity Studies Are Key

Future authors would be well served to test the reliability, reproducibility, and validity (or invalidity) of prior studies by using identical and stringent methodologies, which may lower the marked variation observed in their measures. They could use a more rigorous and inclusive multivariate logistic regression to reanalyze their data; such multivariate models could include different combinations of "stiff landing" and valgus factors that showed similarities to the 2005[6] and 2017[8] studies. The authors would also likely observe higher correlation in these variables if the correlations within the injured and uninjured groups were examined separately.

Summary and Conclusions

Authors of future studies should (1) apply exclusion criteria that address subject selection bias and intervention contamination; (2) analyze their data to determine whether they are parametric or nonparametric; and (3) add all potential confounders as covariates in the analyses and include other covariates as necessary for more appropriate, less biased analyses. Let me close with one final statement from my all-time greatest hero, Abraham Lincoln: "The best way to predict your future is to create it." ◉

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