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Meniscus or cartilage injury at the time of ACL tear are associated with worse prognosis for patient-reported outcome 2 to 10 years after ACL injury – a systematic review

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Abstract

OBJECTIVES: (1) To assess prognostic factors for patient-reported outcome measures (PROMs) and physical activity two to ten years after anterior cruciate ligament reconstruction (ACLR) or injury, and (2) to assess differences in prognostic factors between patients treated with ACLR and with rehabilitation alone.

DESIGN: Prognosis systematic review.

LITERATURE SEARCH: Systematic searches in PubMed, Web of Science and SPORTDiscus.

STUDY SELECTION CRITERIA: We selected prospective cohort studies and randomised clinical trials that included adults/adolescents undergoing either ACLR or rehabilitation alone after ACL rupture. Studies had to assess for a statistical association between potential prognostic factors (factors related to patient characteristics, injury or knee symptoms/function measured at baseline or within one year) and outcomes (PROMS and physical activity).

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Public trials registry: Our study protocol was published in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42018095602) on June 7th 2018.

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DATA SYNTHESIS: Our search yielded 997 references. Twenty studies met inclusion criteria. Seven studies with low or moderate risk of bias remained for data synthesis.

RESULTS: There was moderate certainty evidence that concomitant meniscus and cartilage injuries were prognostic factors for worse PROMs two to ten years after ACLR. There was very low certainty evidence that BMI, smoking and baseline PROMs were prognostic factors for worse outcome. There was very low certainty evidence that female sex and worse baseline Marx Activity Rating Scale (Marx) were prognostic factors for worse Marx two to ten years after ACLR. There was a lack of studies on prognostic factors after rehabilitation alone.

CONCLUSION: Concomitant meniscus and cartilage injuries were prognostic factors for worse long-term PROMs after ACLR. The certainty was very low for other prognostic factors.

Keywords

Prognosis; Ligament; Knee surgery; Sporting injuries

INTRODUCTION

Anterior cruciate ligament (ACL) injuries have serious negative long-term consequences such as lower extremity dysfunction, low levels of physical activity, poor quality of life, and early development of knee osteoarthritis (OA) (1-7). Resolving impairments and returning to sport are often the main short-term goals for patients (1, 8). Clinicians must consider the long-term consequences of ACL injury when providing patient education, and when making decisions about interventions early after injury or reconstruction (9). Hence, high quality studies on prognostic factors for important long-term outcomes such as patient reported outcome measures (PROMs), levels of physical activity and OA are valuable.

A prognosis study can aim to predict the total individual risk given all available information in a prediction model, or to estimate a population average causal effect of an exposure or treatment on an outcome given adjustment for relevant confounders. Both approaches may provide important information on prognostic factors, as a prognostic factor can be either causally or non-causally related to an outcome variable (10-12). Many systematic reviews have evaluated prognostic factors for developing knee OA after ACL injury (5, 13-17). A few systematic reviews have reported prognostic factors for long-term PROMs and level of physical activity (15, 16, 18-21), but most of them are of poor quality due to lack of risk of bias assessments (15, 16, 18). Also, patients treated with rehabilitation alone have not been included in previous systematic reviews.

Consequently, we need a high-quality systematic review on prognostic factors for PROMs and level of physical activity two to ten years after ACL reconstruction (ACLR) or injury, with an appropriate and thorough risk of bias assessment. Such a study may provide information about prognostic factors that can be targeted with early treatment, and can thereby help to improve outcomes for patients with ACL injury.

Current evidence suggests similar clinical courses following rehabilitation alone and ACLR (3, 22-26), but we do not know if prognostic factors differ in the two treatment groups. There is great clinical interest to identify early prognostic factors associated with better

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outcome after both ACLR and rehabilitation alone. This knowledge can help inform treatment choices. No systematic review has previously addressed this topic.

Therefore, the aims of our systematic review were (1) to assess prognostic factors for PROMs and physical activity two to ten years after ACL injury or ACLR, and (2) to assess differences in prognostic factors between patients treated with ACLR and with rehabilitation alone.

METHODS

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (27). Our study protocol was published in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42018095602) on June 7th 2018.

Eligibility criteria

Studies were included using the following criteria: (1) Prospective cohort studies and randomised clinical trials (RCT), that (2) reported prognostic factors for PROMs or level of physical activity, at (3) a mean of ≥ two and <ten years, in (4) adults and adolescents (mean age > 13 years), (5) undergoing either ACLR or rehabilitation alone after complete ACL rupture. (6) Studies had to assess the association between exposure and outcome with regression analyses. Studies *only* on revision ACLR, knee dislocations, partial tears or bilateral injury were excluded. We included studies where a subset of patients had these conditions. Prognostic factors were defined as either patient characteristics (all factors that describes a patient (e.g. age, sex, psychological factors), factors related to the injury (e.g. concomitant injury) or knee symptoms and function (e.g. functional performance, patient reported outcome measures) that were assessed within one year after injury or ACLR.

The following PROMs were selected; Knee injury and Osteoarthritis Outcome Score (KOOS), International Knee Documentation Committee Subjective Knee Form (IKDC-SKF) and Knee Outcome Survey Activities of Daily Living Scale (KOS-ADLS). These PROMs were chosen based on their frequent use as stand-alone PROMs for long-term outcomes during the last decade and because they have good measurement properties (28-34). The KOOS consists of five subscales: pain, other symptoms, function in daily living (ADL), function in sport and recreation (S/R), and knee-related quality of life (QoL) (32). KOOS can be reported as individual subscales or as $KOOS_4$ which is an average score of four subscales (ADL excluded). The IKDC-SKF measures symptoms, function and sports activity in patients with different types of knee problems (34). The KOS-ADLS assesses the impact of symptoms on patients' ability to perform daily activities (28). All three questionnaires are scored from 0 (worst) to 100 (best).

We included *all* outcomes that reflect type and level of physical activity, including the three components defining physical activity: frequency, intensity and duration (35) (eg objective measures such as accelerometers, patient-reported physical activity questionnaires and return to sports). An example of a patient-reported outcome measure of physical activity for ACL injured individuals is the Marx Activity Rating Scale (Marx). Marx is a brief survey on the

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frequency of participation in sports involving running, pivoting, cutting, and deceleration (36).

Data sources and searches

We systematically searched PubMed, Web of Science and SPORTDiscus for articles published from database inception to 20th September 2018. See search strategy for PubMed in TABLE 1. Filters on “Humans” and “English language” were used and all free text words/terms were searched on "Title/abstract". Relevant systematic reviews were identified with the same search terms in PubMed. Reference lists from systematic reviews and included studies were hand searched for relevant material to supplement electronic database searches. To identify additional literature, the following simplified search was performed in Google Scholar: "Anterior cruciate ligament"|ACL Prognosis|"Prognostic factors"|Predict|Associations "Return to sports"|Participation|"Activity level"|"Physical activity"|Tegner|Marx|KOOS |IKDC|KOS "Prospective study"|"Observational study"|"Cohort study"|RCT”. The 100 first (and most relevant) results from Google Scholar were screened. The searches were performed with assistance from and reviewed by librarians at the Norwegian School of Sport Sciences and the University of Oslo.

Study selection and data extraction

Two independent researchers (MP and JLJ) screened for eligibility and extracted data with customized data extraction forms. Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia, available at www.covidence.org) was used to assist this process. Calibration exercises were performed to ensure consistency between reviewers, but without testing agreement. Discrepancies were resolved by discussion or a third reviewer (HG or MAR). We contacted study authors to resolve uncertainties when necessary. Titles and abstracts were screened to identify potentially relevant studies for full text eligibility assessment. The reasons for exclusion were recorded. When several exclusion criteria were fulfilled, the first reason on a predefined list was chosen.

Risk of bias assessment

Risk of bias was assessed with the Quality in Prognosis Study (QUIPS) risk of bias tool (37). We chose this tool because it was developed specifically for the methodological assessment of prognostic studies. QUIPS is a reliable tool for systematically assessing risk of bias in the following six domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding and statistical analysis and reporting (37). Three independent reviewers (MP, JLJ and KM) performed the scoring of the different domains. Our operationalization of the QUIPS items is described in APPENDIX 1. For studies where the objective was prediction and not etiology, the confounding domain was classified as irrelevant (because the goal of a prediction model is to predict the total individual risk given *all* information, for example independent of the covariates’ influence on each other) (11, 12).

The overall risk of bias for each study was classified: (1) low, if there was low risk of bias in all domains, (2) moderate, if there was moderate risk of bias for ≥one domain and (3) high, if there was high risk of bias for ≥one domain (38). For all domains, high risk of bias was

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defined as a level where the results of the study should not be trusted, and/or it was impossible to interpret due to research methodology and/or inadequate description of methodology. This was an overall assessment and decision, and hence, no study was classified as high risk of bias in any domain based on only one question.

Data synthesis and analysis

Results from all included studies (n=20) are presented in APPENDIX 2 and 3. We included only studies with low or moderate risk of bias in the data synthesis. The purpose was to ensure that conclusions and recommendations to clinicians and patients were robust, and to make the results easier to interpret and easier to translate into practice. When data from the same patients were used in publications on the same prognostic factors and outcomes at different time points, we included the most recent publication. Results were presented separately for the outcomes PROMs and level of physical activity and for patients undergoing ACLR and rehabilitation alone. When possible, results from studies on each treatment group were extracted separately. Results from adjusted analyses were preferred. It was not possible to perform a meta-analysis due to methodological diversity in outcome measures and follow-up time.

Quality of evidence for each prognostic factor was judged as high, moderate, low or very low according to the “Grading of Recommendations Assessment, Development and Evaluation” (GRADE) approach (39, 40). We used GRADEpro (41) to help generate evidence summaries.

RESULTS

Search results

Database searches identified 974 references, and 23 additional references were identified through bibliographies (n=2), Google Scholar (n=3) and reference lists (n=18). After removing duplicates, 561 references remained. All were screened for eligibility and 431 were ineligible due to objectives, outcome or follow-up time. The remaining 130 articles were read in full text and 20 met all eligibility criteria (FIGURE 1). Seventeen of the included studies were identified through the systematic search, while three were identified through other sources. Due to more recent publications on the same prognostic factors and outcomes, we excluded the results on concomitant cartilage lesions, but not meniscus lesions from Røtterud et al. (42) and all results from Magnussen et al. (43) from 2016. Seven studies with low or moderate risk of bias remained for data synthesis (42, 44-49).

Study characteristics

Characteristics of the included studies (n=20) are presented in TABLE 2. Most of the cohort studies were based on data from the Multicenter Orthopedic Outcomes Network (MOON) cohort (n= 8) (43, 47, 48, 50-54) and the Swedish and/or Norwegian Knee Ligament Registries (SKLR/NKLR) (n= 5) (42, 44, 46, 49, 55). In the included RCTs, both treatment groups were treated as one cohort for the assessment of prognostic factors (45, 56-58). Three of the RCT publications were based on the Knee Anterior Cruciate Ligament, Nonsurgical versus Surgical Treatment (KANON) trial (45, 57, 58). The studies included median (Q1-

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Q3) 495 (121-2333) patients. Due to several publications on the same patients in the large registry studies, it was challenging to estimate the total number of unique patients included in this systematic review. Most studies included patients undergoing primary ACLR only, and no study included only patients treated with rehabilitation alone. Patients with substantial concomitant injuries (43, 45-47, 51, 53, 55-61) and/or contralateral ACL injury (42, 46, 48, 49, 51-54, 56) were frequently excluded from the included studies. The median age at inclusion was 26 years (range 18-27). The median percentage of females was 44% (range 26-77%). Preinjury activity level was reported in seven studies, where four (52, 59-61) included patients active in pivoting sports preinjury and three (45, 57, 58) included patients with Tegner Activity Scale between 6 and 9 (6=recreational pivoting sports, 9=competitive sports).

Sixteen studies were etiological (42-47, 49-53, 56-59, 61) and four were predictive (48, 54, 55, 60). Among the studies included in our data synthesis, only Spindler et al. (48) was a predictive study.

Risk of bias

Risk of bias for the six QUIPS-domains and an overall rating is shown in TABLE 3. Studies generally performed poorly on the domains “Study confounding” and “Analysis and reporting” because they did not explicitly state what covariates were adjusted for and why, did not separate between confounders, mediators and colliders (and subsequently did not treat these covariates in accordance with existing rules for adjustment), or had mixed predictive and etiological statistical approaches, which led to uninterpretable results (10, 12, 62).

Data synthesis of studies with low or moderate risk of bias (n=7)

Prognostic factors for PROMs in patients treated with ACLR—Prognostic factors for PROMs in patients treated with ACLR were assessed in seven studies from four cohorts. The IKDC-SKF was an outcome in two studies (47, 48) and the KOOS was an outcome in seven studies (42, 44-49). The following 13 factors were assessed by ≥1 study with low or moderate risk of bias: sex, age, body mass index (BMI), smoking, ethnicity, type of sport, concomitant injury on medial or lateral concomitant ligaments (MCL/LCL), meniscus or cartilage, hearing a pop at injury, knee laxity, extension range of motion deficit and baseline PROMs. These factors were measured at baseline, preoperatively or during ACLR.

Patient characteristics: One predictive study reported higher baseline BMI as a prognostic factor for worse six-year IKDC-SKF and KOOS S/R outcomes and smoking for worse IKDC-SKF (48). The same study found no association between higher BMI and KOOS QoL, or between smoking and KOOS QoL and KOOS S/R.

There were no statistically significant association between the factors sex, age, ethnicity and type of sport and the outcomes two- and six-year IKDC-SKF and KOOS (44, 48).

Factors related to the injury: Concomitant meniscus injury was reported as a prognostic factor in some studies, but not in others. Three studies (two etiological and one predictive) of

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three different cohorts, found a statistically significant negative association between concomitant meniscus injury and two-year patient-reported success ($KOOS_4 \geq 80^{th}$ percentile) (46) and five- and six-year KOOS S/R and QoL outcomes (45, 48). The mean difference between those with and without concomitant meniscus injury was 10-14.4 points for KOOS S/R (45, 48) and 8.9 points for KOOS QoL (48). The same studies found, however, no statistically significant associations between meniscus injury and the other KOOS subscales and IKDC-SKF (45, 48). In one etiological study, concomitant meniscus injury was not a prognostic factor for any two-year KOOS subscale (42).

Concomitant cartilage injury was assessed in four studies from four different cohorts (45, 46, 48, 49). In two etiological studies, there was a statistically significant association between concomitant cartilage lesions and five-year KOOS (all subscales), particularly for the full-thickness lesions (45, 49). The mean difference between those with and without concomitant cartilage injury was 8.1 points for KOOS S/R (49) and 8-2.3 points for KOOS QoL (45, 49). The results of Filbay et al. (45) applied only for the five-year KOOS QoL in patients with early (not delayed) ACLR. In a third etiological study, the absence of concomitant cartilage injury predicted two-year patient-reported success (as previously defined) while having a concomitant cartilage injury predicted failure ($KOOS_4 \leq 20^{th}$ percentile) (46). One predictive study found no association between concomitant cartilage injury and six-year KOOS S/R and QoL and IKDC-SKF (48).

There were no statistically significant associations between concomitant MCL/LCL injury or hearing a pop at injury and the outcomes two-year patient-reported success or failure (46) and six-year IKDC-SKF, KOOS QoL and KOOS S/R (48).

Knee symptoms/function: In one etiological study, baseline $KOOS_4$ predicted five-year KOOS Symptoms, KOOS S/R and KOOS QoL, but not KOOS pain, in patients with early ACLR (45). In those with delayed ACLR, $KOOS_4$ did not predict any of the five-year KOOS subscales (45). A predictive study found conflicting results for the association between baseline and five-year KOOS scores (48).

Preoperative knee laxity, defined as severely abnormal either Lachman, anterior drawer or pivot-shift test, was assessed in one etiological study (47). There was a small statistically significant association between preoperative knee laxity and six-year IKDC-SKF and KOOS QoL (mean difference between those with and without preoperative laxity of 2.3 and 2.7 points, respectively) that was not considered as clinically relevant (47).

There were no statistically significant associations between baseline Short-Form 36 and knee extension deficit >10 degrees and five-year KOOS outcomes (45).

GRADE evaluation for prognostic factors for PROMs in patients treated with ACLR: The evidence for concomitant meniscus and cartilage injuries was moderate, while for the other factors it was low or very low (TABLE 4). Our conclusions did not differ when all 20 eligible studies were included in a GRADE evaluation (APPENDIX 4).

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Prognostic factors for Physical Activity in patients treated with ACLR— Prognostic factors for level of physical activity in patients treated with ACLR was assessed in two studies from the same cohort, both using the Marx questionnaire as the outcome (47, 48). The following 13 factors were assessed by ≥1 study with moderate risk of bias: sex, age, BMI, smoking, marital status, ethnicity, type of preinjury sport, baseline PROMs, concomitant injury to the LCL/ MCL, meniscus or cartilage, knee laxity and hearing a pop at injury (TABLE 2).

Patient characteristics: One predictive study assessed several demographic factors as possible prognostic factors for six-year Marx (48). Female sex and worse baseline Marx were prognostic factors for worse six-year Marx, while age, BMI, smoking, marital status, ethnicity and type of preinjury sport were not (48).

Factors related to the injury: None of the following factors were prognostic factors for six-year Marx score: concomitant MCL/LCL, meniscus or cartilage injuries and hearing a pop at injury (48). One etiological study found a statistically significant association between preoperative laxity (as previously defined) and six-year Marx (47). The mean difference between those with and without preoperative laxity was small (0.5 points) and not clinically relevant (47).

GRADE evaluation for prognostic factors for level of physical activity in patients treated with ACLR: Quality of evidence was judged as very low for all the prognostic factors for level of physical activity in patients treated with ACLR. Serious limitations in several GRADE domains occurred because evidence for all factors was based on only one study with moderate risk of bias.

Prognostic factors for PROMs and physical activity in patients treated with rehabilitation alone—One etiological study assessed prognostic factors for five-year $KOOS_4$ for a group of patients treated with rehabilitation alone separately (45). None of the following factors were prognostic factors: baseline cartilage defect, meniscus damage, osteochondral lesion, extension deficit, SF-36 and $KOOS_4$ (45). Quality of evidence was judged as very low due to few studies. No study assessed prognostic factors for physical activity in this patient group.

Differences in prognostic factors between treatment groups—One etiological study with low risk of bias assessed differences in prognostic factors between those treated with rehabilitation alone and with ACLR (45). Based on differences in prognostic factors for five-year $KOOS_4$ between the treatment groups, the authors suggested that patients with concomitant meniscus injury and those with worse KOOS symptoms, S/R and QoL in the early phase may benefit most from exercise therapy before choosing treatment (45).

DISCUSSION

Concomitant meniscus and cartilage injuries were, with moderate certainty, prognostic factors for worse PROMs two to ten years after ACLR. Smoking, BMI and baseline PROMs were prognostic factors for two to ten-year PROMs with very low certainty. For level of

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physical activity two to ten years after ACLR, we concluded with very low certainty that female sex and worse baseline Marx were prognostic factors for worse long-term Marx. The other factors assessed in this systematic review were not associated with the outcomes. No studies included only patients treated with rehabilitation alone. One study assessed differences in prognostic factors between patients treated with rehabilitation alone and with ACLR (45). Patients with concomitant meniscal and cartilage injuries and lower KOOS scores in the acute phase may benefit most from an initial non-surgical treatment choice, but further research on the topic is needed to draw conclusions. Hence, we could not answer the second aim of this systematic review.

For the prognostic factors BMI, smoking, baseline PROMs, sex and baseline Marx, the impact on outcomes was small (see appendix 2 and 3) and probably not clinically relevant. The impact of concomitant meniscus injury as a prognostic factor was larger, as the mean difference between those with and without meniscus injury was 10-14.4 points for KOOS S/R (45, 48) and 8.9 points for KOOS QoL (48). For KOOS S/R, but not KOOS QoL, the impact of having a concomitant meniscus injury was clinically relevant as the minimal important change (MIC) (95% CI) are 12.1 (9.3 to 14.8) points for KOOS S/R and 18.3 (16.0 to 20.6) points for KOOS QoL (63). The impact of having a concomitant cartilage injury on KOOS S/R (8.1 points) and QoL (8-12.3 points) outcomes also seemed important, but the mean difference between those with and without concomitant cartilage was below the MIC for the instruments (45, 49).

Comparison with other studies

The high methodological quality of this systematic review makes an important contribution to this field. Our high-quality search strategy, rigorous risk of bias assessment and data synthesis ensured robust conclusions and recommendations for clinicians and patients. Due to these methodological factors, we could not replicate the findings of previous systematic reviews, such as that male sex, younger age and psychological factors are positive prognostic factors and that quadriceps weakness and range of motion deficits are negative factors (19, 64).

To our knowledge, ours is the first systematic review to assess prognostic factors for PROMs and level of physical activity after ACL injury both in patients treated with ACLR and with rehabilitation alone. Although the paucity of studies on patients treated with rehabilitation alone made it impossible to answer our review questions regarding prognostic factors for PROMs and level of physical activity for this treatment group, or to assess differences in prognostic factors between treatment groups.

Our results highlighted the importance of risk of bias assessments in systematic reviews as 12 of 20 included studies (60%) were rated as having high risk of bias. Bias was suspected especially in the domains “Study confounding” and “Statistical analysis and reporting”. Lack of clarity in aims and methods about whether studies were predictive or etiological was a recurring limitation. Effect estimates calculated from one model, often a prediction model, which is presented in one table may mislead because the underlying associations between covariates are not accounted for (10). In many papers with etiological aims, but statistically driven rather than theoretically driven approaches, it was unclear if the estimates were

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adjusted for all relevant confounders, and whether they should have been interpreted as total or direct effects (11). Epidemiological research methodology has developed over time, and the distinction between explanatory and predictive aims was less clear at the time when the included studies were performed.

Limitations

An important limitation in the literature in this field was the likely between-study overlap of patients within the different publications from the MOON cohort and the SKLR/NKLR. This overlap may have led to a correlation between study results that we could not account for. To minimize this problem, we only included the most recent publication of data from the same patients and on the same prognostic factors. Further, our strict inclusion criteria might have led us to miss high quality research where other PROMs than IKDC-SKF, KOOS and KOS-ADLS were used, such as Lysholm, ACL Return to Sport after Injury scale (ACL-RSI) and Short Form-36 (SF-36). The included studies did not differentiate between types of meniscus injuries, and we therefore lack knowledge on the prognosis after different injury types (eg. dislocated bucket-handle tears versus stable, horizontal tears).

Our results apply to individuals with first time complete unilateral ACL-injury, not including knee dislocations. The prognostic factors are also only applicable to the outcomes PROMs and level of physical activity ≥ two and <ten years after ACLR. We did not consider psychological, overall health or quality of life outcomes.

Implications for clinical practice

When planning future physical activities and discussing patient expectations, it is useful for patients, physical therapists, orthopaedic surgeons and athletic trainers to be aware that concomitant meniscus or cartilage injuries may lead to worse knee function two to ten years after ACLR. As concomitant meniscus injuries are also the most frequently reported prognostic factor for knee OA after ACL injury (5, 13), patients should be informed about preventive interventions for knee OA such as knee extensor muscle strength training and maintaining a healthy body weight (65-71). Although with very low certainty, higher BMI was a prognostic factor for worse PROMs after ACLR. Due to the relation to both knee function and development of knee OA, BMI as a prognostic factor is important and needs to be incorporated in the early patient education. We also found that smoking is a negative prognostic factor for PROMs. As this factor is modifiable, patients should be informed that avoiding smoking might contribute to better long-term outcomes.

Implications for future research on prognostic factors after ACL injury and ACLR

Future studies should be clear whether their aims and methods are aimed at prediction or etiology. If the aim is etiological, authors should carefully state their hypothesis with background and run an informed causal effect analysis, ensuring that rules for adjustment for different types of covariates (confounders, mediators and colliders) are followed (11, 72). If the aim is predictive, studies should systematically build a prediction model based on all available predictors and study the model's discriminative ability and calibration and subsequently internally and externally validate findings (73, 74). Pre-registration of study

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protocols for observational studies on prognostic factors might enable researchers to assess if selective reporting and publication bias occur within this field.

Future high-quality prognosis studies should include patients treated with rehabilitation alone. This patient group is important as it represents between 26% and 77% of the ACL-injured population (75-77). New studies should also compare prognostic factors between patients treated with rehabilitation alone and with ACLR in order to help clinicians identify who might have the best prognosis with ACLR and who might succeed with rehabilitation alone. Future studies should also assess modifiable prognostic factors which can be targeted in early rehabilitation, such as muscle strength, range of motion and hop performance.

Our systematic review also uncovered a lack of studies on level of physical activity long-term after ACL injury. Most studies were at high risk of bias and the study outcomes were only activity rating scale (Marx) and the prevalence of return to sport, neither of which align with the most common definition of level of physical activity (35) as they only measure participation in specific types of sports. Future studies should therefore include more general level of physical activity as outcomes (eg accelerometery, International Physical Activity Questionnaire).

CONCLUSION

Concomitant meniscus and cartilage injuries were prognostic factors for worse PROMs two to ten years after ACLR. There was very low certainty evidence that BMI, smoking and worse baseline PROMs were prognostic factors for worse PROMs, and that female sex and worse baseline Marx score were prognostic factors for worse Marx score two to ten years after ACLR.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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KEY POINTS

FINDINGS: We have moderate confidence that concomitant meniscus and cartilage injuries are prognostic factors for worse long-term PROMs after ACLR. The certainty is low/very low for other prognostic factors.

IMPLICATIONS: When planning future activities and discussing patient expectations, it is useful for patients, physical therapists, orthopaedic surgeons and athletic trainers to consider that concomitant meniscus or cartilage injuries may lead to worse knee function two to ten years after ACLR.

CAUTION: A large proportion (60%) of included studies in this systematic review were at high risk of bias, and there is a lack of studies on prognostic factors in patients treated with rehabilitation alone.

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STUDY DETAILS

Data sharing: All data relevant to the study are included in the article or are available as supplementary files.

Patient and public involvement: There was no patient or public involvement in this research.

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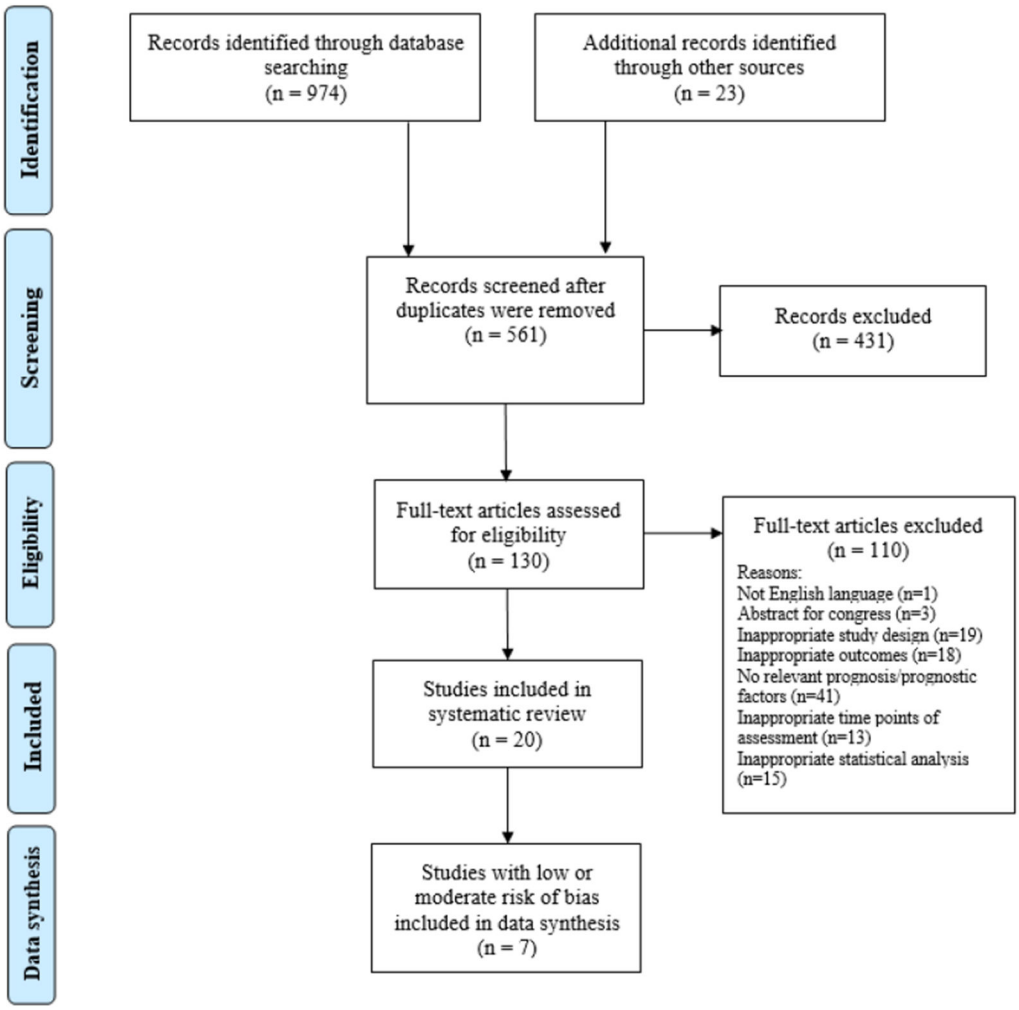

FIGURE 1.
Flow chart

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Table 1.

PubMed search

1)	Anterior cruciate ligament[mesh terms] OR Anterior cruciate ligament injury[mesh terms] OR Anterior cruciate ligament reconstruction[mesh terms]
2)	Anterior cruciate ligament Or ACL
3)	Prognosis[mesh terms]
4)	Prognosis OR Prognostic factors OR Prognostic factor OR Predictor OR Predictors OR Predict OR Prediction OR Predictive OR Effect modifiers OR Effect modifier OR Risk factors OR Risk factor OR Factor OR Factors OR Associated OR Association OR Associations
5)	Return to sport[mesh terms]
6)	Return to sport OR Return to sports OR Participation OR Activity level OR Physical activity OR "Tegner activity scale" OR "Marx activity rating scale" OR Return to play OR KOOS OR "Knee injury and Osteoarthritis Outcome score" OR "International Knee Documentation Committee subjective knee form" OR "IKDC-SKF 2000" OR IKDC-SKF2000 OR "International Knee Documentation Committee Subjective Knee Evaluation Form" OR "IKDC-SKF" OR "Knee Outcome Survey" OR KOS
7)	Prospective studies[mesh terms]
8)	Prospective studies OR Prospective study OR Observational study OR Cohort study OR Randomized controlled trial OR Randomized clinical trial OR Randomised controlled trial OR Randomised clinical trial OR RCT OR Randomised trial OR Randomized trial
9)	1 OR 2
10)	3 OR 4
11)	5 OR 6
12)	7 OR 8
13)	9 AND 10 AND 11 AND 12

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Table 2.

Characteristics of included studies (n=20)

Study characteristics								Patients' characteristics	
	Study	**n**	**Treatment**	**FU Years**	**Prognostic factors assessed**	**Outcome**	**Included in data synthesis**	**Sex % female**	**Median/ mean age Years**
Ageberg et al. (2010) [44]	SKLR	10164	Primary ACLR	2	Age	KOOS	✓	42%	27
Barenius et al. (2013) [55]	SKLR	8584	Primary ACLR	2	Sex, age, baseline PROMs, concomitant meniscus/ cartilage, knee laxity, previous knee surgery	KOOS		49%	NR
Brophy et al. (2016) [50]	MOON	2198	Primary or revision ACLR	2	Diabetes	IKDC-SKF KOOS Level of PA		44%	24
Cox et al. (2014) [51]	MOON	1512	Primary or revision ACLR	6	Sex, age, BMI, smoking, education, ethnicity, type of sport, competition level, baseline PROM, concomitant meniscus/cartilage	IKDC-SKF KOOS Level of PA		44%	23
Dunn et al. (2010) [52]	MOON	446	Primary or revision ACLR	2	Sex, age, BMI, smoking, education, marital status, ethnicity, type of sport, competition level, baseline PROM, concomitant meniscus/ cartilage, hearing a pop at injury	Level of PA		44%	23
Ericsson et al. (2013) [57]	KANON	121	ACLR or non-surgical	2 + 5	Early physical performance	KOOS		26%	26
Filbay et al. (2017) [45]	KANON	121	ACLR or non-surgical	5	Baseline PROM, concomitant meniscus/cartilage, knee extension deficit	KOOS	✓	26%	26
Hamrin Senorski et al. (2018) [46]	SKLR	15204	Primary ACLR	2	Concomitant MCL/LCL/ meniscus/ cartilage	KOOS	✓	50%	NR
Ithurburn et al. (2017) [59]	Cohort	48	Primary ACLR	2	Early physical performance	KOOS		77%	18
Magnussen et al. (2016) [43]	MOON	2333	Primary ACLR	2	Knee laxity	IKDC-SKF KOOS		44%	27
Magnussen et al. (2018) [47]	MOON	2333	Primary ACLR	6	Knee laxity	IKDC-SKF KOOS Level of PA	✓	44%	27
Nawasreh et al. (2018) [60]	Cohort	107	Primary ACLR	2	Sex, age, baseline PROM, early physical performance	Level of PA		34%	27
Roessler et al. (2015) [58]	KANON	121	ACLR or non-surgical	2	Psychological factors	KOOS		26%	26

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Study characteristics								Patients' characteristics	
	Study	n	Treatment	FU Years	Prognostic factors assessed	Outcome	Included in data synthesis	Sex % female	Median/ mean age Years
Rotterud et al. (2013) [42]	S/N KLR	15783	Primary ACLR	2	Concomitant meniscus/ cartilage	KOOS	✓	42%	26
Sasaki et al. (2016) [56]	RCT	150	Primary ACLR	2	Sex, age, BMI, baseline PROM, concomitant meniscus	KOOS		58%	26
Sonnery-Cottet et al. (2017) [61]	Cohort	541	Primary ACLR	3	Sex, age, type of sport, concomitant meniscus	Level of PA		27%	22
Spindler et al. (2005) [53]	MOON	314	Primary ACLR	5	Sex, age, type of sport, concomitant meniscus/cartilage, hearing a pop at injury, onset of swelling after injury	IKDC-SKF KOOS		45%	27
Spindler et al. (2011) [48]	MOON	448	Primary or revision ACLR	6	Sex, age, BMI, smoking, ethnicity, marital status, type of sport, baseline PROM, concomitant MCL/LCL/ meniscus/ cartilage, hearing a pop at injury	IKDC-SKF KOOS Level of PA	✓	43%	23
Ulstein et al. (2018) [49]	S/N KLR	15783	Primary ACLR	5	Concomitant cartilage	KOOS	✓	42%	27
Wasserstein (2015) [54]	MOON	1761	Primary ACLR	2 + 6	Sex, age, BMI, smoking, education, baseline PROM, concomitant meniscus/ cartilage, previous knee pathology	KOOS		44%	23

FU, follow-up; NR, not reported; SKLR/NKLR, Swedish/Norwegian Knee Ligament Registry; MOON, Multicenter Orthopedic Outcomes Network; KANON, Knee Anterior Cruciate Ligament, Nonsurgical versus Surgical Treatment

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Table 3:

Risk of bias assessment (n=20)

	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Study Confounding	Analysis and reporting	OVERALL
Ageberg (2010)	☺	😐	☺	☺	😐	☺	😐
Barenius (2013)	☺	😐	☺	😐	Irrelevant	☹	☹
Brophy (2016)	☺	☺	☺	☺	☹	☹	☹
Cox (2014)	☺	☺	☺	☺	☹	☹	☹
Dunn (2010)	☺	☺	☺	☺	☹	☹	☹
Ericsson (2013)	☺	😐	😐	☺	☹	☹	☹
Filbay (2017)	☺	☺	☺	☺	☺	☺	☺
Hamrin Senorski (2018)	☺	😐	😐	☺	☺	☺	😐
Itherburn (2017)	😐	☹	☺	☺	☹	☹	☹
Magnussen (2016)	☺	☺	☺	☺	😐	😐	😐
Magnussen (2018)	☺	☺	☺	☺	😐	😐	😐
Nawasreh (2018)	☺	☹	☺	☺	Irrelevant	☺	☹
Roessler (2015)	☺	☺	☺	☺	☹	😐	☹
Røtterud (2013)	☺	😐	☺	☺	☺	☺	😐
Sasaki (2016)	☺	☺	☺	☺	☹	☹	☹
Sonnery-Cottet (2017)	☺	☺	☺	☺	☹	☹	☹
Spindler (2005)	☺	☹	☺	☺	☹	☹	☹
Spindler (2011)	☺	☺	☺	☺	Irrelevant	😐	😐
Ulstein (2018)	☺	😐	☺	☺	😐	☺	😐
Wasserstein (2015)	☺	☺	☺	☺	Irrelevant	☹	☹

Low risk of bias= white □
Moderate risk of bias= pale grey □
High risk of bias= dark grey □

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Table 4

GRADE[a] evidence profile: potential prognostic factors for 2- to 10-year PROMs in ACL [b] reconstructed patients. Studies with low- and moderate risk of bias (n=7).

		GRADE factors							Summary of findings						
Potential prognostic factors (№ of studies)	№ of patients	Study limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Moderate/ large effect size	Dose effect	Univariable analysis			Multivariable Analysis[g]			Cer
									+	0	−	+	0	−	
Sex (1)	448	×[c]	✓	✓	×	×[h]	×	×					1		⊕◯◯◯ VERY LOW
Age (2)	10612	×[d]	✓	✓	×	×[h]	×	×		1			1		⊕⊕◯◯L
Higher BMI (1)	448	×[c]	✓	✓	×[c]	×[h]	×	×						1	⊕◯◯◯ VERY LOW
Smoking (1)	448	×[c]	×[e]	✓	×	×[h]	×	×						1	⊕◯◯◯ VERY LOW
Ethnicity (1)	448	×[c]	✓	✓	×	×[h]	×	×					1		⊕◯◯◯ VERY LOW
Type of sport (1)	448	×[c]	✓	✓	×	×[h]	×	×					1		⊕◯◯◯ VERY LOW
Concomitant MCL or LCL injuries (2)	15652	×[d]	✓	✓	×	×[h]	×	×					2		⊕⊕◯◯L
Concomitant meniscus injuries (4)	31556	✓	×[e]	✓	✓	×[h]	✓	×					1	3	⊕⊕⊕◯M
Concomitant cartilage injuries (4)	31556	✓	×[e]	✓	✓	×[h]	✓	✓					1	4	⊕⊕⊕◯M
Hearing pop at injury (1)	448	×[c]	✓	✓	×	×[h]	×	×					1		⊕◯◯◯ VERY LOW
Preoperative knee laxity (1)	2333	×[c]	✓	✓	×	×[h]	×	×					1		⊕◯◯◯ VERY LOW
Preoperative extension deficit (1)	121	×[f]	✓	✓	×	×[h]	×	×					1		⊕◯◯◯ VERY LOW
Higher baseline PROMs (2)	569	×[d]	×[e]	✓	×	×[h]	×	×				2			⊕◯◯◯ VERY LOW

For uni− and multivariable analyses: +, number of significant effects with a positive value; 0, number of non-significant effects; −, number of significant effects with a negative value.

For GRADE factors: ✓, no serious limitations; ×, serious limitations (or not present for moderate/large effect size, dose effect)

a) Grading of Recommendations Assessment, Development and Evaluation

b) Anterior Cruciate Ligament

c) Evidence is based on only one study with moderate risk of bias

[d] Evidence is based on only two studies with moderate risk of bias

[e] Inconsistency within/between study/studies

[f] Evidence is based on only one study with low risk of bias

[g] Summary of authors conclusions when several outcomes for each factor were assessed

[h] Due to a small number of included studies, we could not assess small study biases with a funnel plot. We therefore cannot rule out publication bias

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