INPLASY PROTOCOL

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Review Stage at time of this submission: **The review has not yet started.**

Conflicts of interest:

Assessment of Graft Maturation After Anterior Cruciate Ligament Reconstruction with Remnant Preservation versus Standard Anterior Cruciate Ligament Reconstruction: A Systematic Review and Meta-analysis of Magnetic Resonance Imaging studies

Li, MX[1]; Li, H[2]; Xue, XA[3]; Hua, YH[4].

Review question / Objective: **We undertake a systematic review and meta-analysis of studies evaluating the effect of remnant preservation versus standard ACLR on graft maturation, using SI and/or SNQ as the primary outcome. We aim to asked 2 primary questions: (1) Can remnant preservation facilitate graft maturation? (2) Can remnant preservation improve clinical outcomes and promotes safe return-to-sport through acceleration of graft ligamentization? Population: The population included in the review entails adult patients with a primary ACL rupture regardless of sex or race. Intervention/comparators: The intervention is primary arthroscopic ACL reconstruction surgery with remnant preservation. The comparator is standard ACLR. Outcomes: Outcomes are MRI evaluation of the graft ligamentization at any time after ACLR, including signal intensity of the surgically implanted ACL graft. Signal intensity is reported as the signal/noise quotient (SNQ) and/or scoring scale, normalized to surrounding tissue or background noise. Study designs: Any comparative study design, including randomized controlled studies, prospective cohort studies, case-control studies, and retrospective comparative studies.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 30 August 2021 and was last updated on 30 August 2021 (registration number INPLASY202180116).

INTRODUCTION

Review question / Objective: **We undertake a systematic review and meta-analysis of studies evaluating the effect of remnant preservation versus standard ACLR on graft maturation, using SI and/or SNQ as the primary outcome. We aim to asked 2 primary questions: (1) Can remnant preservation facilitate graft maturation? (2)**

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Condition being studied: Anterior cruciate ligament (ACL) ruptures are a common knee injury, and ACL reconstruction (ACLR) remains the gold standard surgical option for patients with ACL ruptures. (Hughes et al., 2020) However, despite advances in surgical techniques, with increased focus on anatomic and patient-specific factors, 5-year graft failure rates of 4% to 7% are commonly reported following ACLR (Wright et al., 2011 , Shelbourne et al., 2009 , Maletis et al., 2015 , Ahldén et al., 2012). Problematic graft maturation is one of the contributing factors (Ekdahl et al., 2008), which involves intra-articular graft ligamentization and bone-tunnel integration. The intra-articular graft ligamentization could be evaluated with using the magnetic resonance imaging (MRI) parameter signal intensity (SI) and/or signal/noise quotient (SNQ). (Ahn et al., 2016). Remnant preservation is hypothesized to facilitate graft ligamentization because it contains blood vessels and stem cells. (Chen et al., 2018) Nevertheless, the effect of remnant preservation on graft maturation and clinical outcomes following ACLR remains controversial. (Zhang et al., 2016 , Takahashi et al., 2016 , Sun et al., 2013 , Wang et al., 2018 , Tie et al., 2016 , Tanabe et al., 2016 , Hu et al., 2014).

METHODS

Participant or population: The population included in the review entailed adult patients with a primary ACL rupture regardless of sex or race.

Intervention: The intervention was primary arthroscopic ACL reconstruction surgery with remnant preservation.

Comparator: The comparator was standard ACL reconstruction surgery.

Study designs to be included: Any comparative study design was eligible, including randomized controlled studies, prospective cohort studies, case-control studies, and retrospective comparative studies. Randomized controlled trial, cohort study and retrospective comparative study

Eligibility criteria: Population: The population included in the review entailed adult patients with a primary ACL rupture regardless of sex or race.Intervention/ comparators: The intervention was primary arthroscopic ACL reconstruction surgery with remnant preservation. The comparator was standard ACLR. Studies lack of comparisons of MRI and/or clinical outcomes between remnant-preserving and standard ACLR are excluded.Outcomes: Outcomes were MRI signal intensity of the intra-articular portion of the surgically implanted ACL graft, evaluated at any time after ACLR. Signal intensity is reported as the signal/noise quotient (SNQ) and/or scoring scale, normalized to surrounding tissue or background noise. Studies that failed to quantify or score the intra-articular graft signal on MRI following ACLR are excluded. Study designs: Any comparative study design was eligible, including randomized controlled studies, prospective cohort studies, case-control studies, and retrospective comparative studies. Excluded study designs included case reports, reviews, editorials, commentaries,

personal opinions, surveys, and case series.primary ACL rupture regardless of sex or race.• Intervention/comparators: The intervention was primary arthroscopic ACL reconstruction surgery with remnant preservation. The comparator was standard ACLR. Studies lack of comparisons of MRI and/or clinical outcomes between remnant-preserving and standard ACLR are excluded.• Outcomes: Outcomes were MRI signal intensity of the intra-articular portion of the surgically implanted ACL graft, evaluated at any time after ACLR. Signal intensity is reported as the signal/noise quotient (SNQ) and/or scoring scale, normalized to surrounding tissue or background noise. Studies that failed to quantify or score the intra-articular graft signal on MRI following ACLR are excluded. • Study designs: Any comparative study design was eligible, including randomized controlled studies, prospective cohort studies, case-control studies, and retrospective comparative studies. Excluded study designs included case reports, reviews, editorials, commentaries, personal opinions, surveys, and case series.

Information sources: The strategy for the systematic literature search comprised searching of electronic bibliographic databases and examination of references of included studies and any identified systematic reviews. Searches will be performed using PubMed, EMBASE, the Cochrane CENTRAL, CINAHL, Web of Science and Scopus, with no language or publication year limit. In case of missing data, the authors of the study in question will be contacted via email. If no response is received after 2 attempts spaced 1 month apart, data will be left as missing.

Main outcome(s): Imaging outcomes: details regarding the evaluation of graft ligamentization using normalized signal intensity of the ACL graft, including region of interests, calculation and/or scoring scale, imaging follow-up and imaging findings.

Additional outcome(s): Clinical outcomes: clinical outcomes and/or evaluations, clinical follow-up, clinical findings and statistical measures describing the correlation between image and clinical outcomes.

Quality assessment / Risk of bias analysis: The methodological quality of each study will be assessed by the 2 reviewers (Li. MX, Xue. XA) independently. Discrepancies will be refereed by a senior experienced author (Li. H) when necessary. For randomized controlled trials (RCTs), the Cochrane Risk of Bias Tool is applied. (Higgins et al., 2011) For observational comparative (cohort) studies, the Newcastle-Ottawa Scale is used. For retrospective comparative studies, the revised and validated version of the Methodological Index for Non-randomized Studies (MINORS criteria) is applied. (Slim et al., 2003) The overall quality of the evidence in this study is assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.(Guyatt et al., 2008)

Strategy of data synthesis: To explore whether remnant preservation accelerates graft maturation, we will conduct the meta-analysis for normalized signal intensity in different regions of the ACL graft at different time points after ACLR. Because studies used different equations to measure normalized signal intensity, calculation of effect size for each study will be performed through standardized mean difference (SMD). SMD is calculated using Hedges g (Hedges and Olkin, 2014). A random-effects model using the Sidik and Jonkman method is chosen because of the inherent heterogeneity expected in clinical studies. Outcomes are reported as the SMD and 95% CI. Heterogeneity was assessed using τ^2, I^2, Q, and P values.

Subgroup analysis: Subgroup analysis of study design will be conducted if there is statistical heterogeneity among studies.

Sensitivity analysis: The sensitivity analysis, based on a leave-one-out design, will be undertaken to identify if a single influential study significantly altered the heterogeneity. If such an influencer is

found, this study will be removed, and the meta-analysis will be rerun.

Country(ies) involved: China.

Keywords: anterior cruciate ligament; ACL reconstruction; remnant tissue; MRI; ligamentization.

Contributions of each author:
Author 1 - Moxin Li.
Author 2 - Hong Li.
Author 3 - Xiaoao Xue.
Author 4 - Yinghui Hua.