

# Comparative Efficacy of Graft Options in Anterior Cruciate Ligament Reconstruction: A Systematic Review and Network Meta-Analysis



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**Purpose:** To evaluate the effectiveness of various graft options for anterior cruciate ligament reconstruction using network meta-analysis. **Methods:** A medical literature search was conducted of PubMed, the Cochrane Library, Embase, SCOPUS, and Web of Science from their inception through March 1, 2019. The outcomes, including International Knee Documentation Committee (IKDC) form, Lachman test, Lysholm score, Pivot shift test, and Tegner score, were evaluated among graft options. Data extraction was carried out according to inclusion and exclusion criteria, and a network meta-analysis was performed using STATA 14.0. **Results:** A total of 45 trials with 3992 patients were included. The forest plots revealed no significant differences in IKDC, Lysholm, or Tegner score among the grafts. In Lachman score, a significant difference was found in the comparisons of hamstring tendon allograft (HT-AL) versus patellar tendon autograft (PT-AU) and HT-AL versus hamstring tendon autograft (HT-AU). In pivot shift test, PT-AU was superior to all the other grafts, and quadriceps tendon autograft (QT-AU) was superior to HT-AL and artificial ligament (Art-L) in the number of cases with negative results. According to surface under the cumulative ranking area (SUCRA), PT-AU had the highest probability to be the best intervention in Lachman test and Tegner score; tibialis anterior tendon allograft (TA-AL) in IKDC and Lysholm score; and QT-AU in pivot shift test. Based on the cluster analysis of SUCRA, PT-AU was considered the most appropriate intervention by IKDC and Lachman test. **Conclusion:** This study suggests that PT-AU may be the most appropriate graft for ACL reconstruction according to IKDC and Lachman test results. **Level of Evidence:** Level I, network meta-analysis of randomized controlled trials.

## Introduction

As a critical component of anterior–posterior and rotational stabilizers, the anterior cruciate ligament (ACL) plays an important role in maintaining the stability of the knee joint.<sup>1</sup> With the prevalence of sport and the improvement of competitive sport level, the incidence rate of ACL injury has been rising rapidly.<sup>2,3</sup> Damage to the ACL is one of the most common knee injuries, and in the United States it occurs in >250,000

people per year.<sup>4</sup> Furthermore, patients with ruptured ACL have unstable knee, cartilage injury, and meniscal damage that may lead to the occurrence of osteoarthritis (OA) and adversely affect the quality of life.<sup>5,6</sup>

The standard procedure for ACL tear is surgical reconstruction, as conservative treatment is ineffective and direct repair is difficult.<sup>7,8</sup> Approximately 100,000 cases of ACL reconstruction are performed in the United States annually, with the goal of returning individuals to stability and function.<sup>9</sup> The efficacy of ACL reconstruction is mainly attributed to the type of graft.<sup>10,11</sup> There are several conditions for ideal grafts, including easy accessibility, little donor site morbidity, immediate rigid fixation, and rapid wound healing, which may maximally reproduce those of native ACL.<sup>12-15</sup> In clinical management, patellar tendon (PT) and hamstring tendon (HT) autografts are the most common and traditional choices.<sup>16,17</sup> Nevertheless, they have some disadvantages, such as postoperative anterior knee pain, donor site morbidity, and quadriceps weakness in PT autograft and decreased hamstring tendon strength, delayed graft incorporation, and increased joint laxity in HT autograft.<sup>18-21</sup> In recent decades, surgeons and researchers have tried to find

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The authors report that they have no conflicts of interest in the authorship and publication of this article. Full ICMJE author disclosure forms are available for this article online, as [supplementary material](#).

Received August 23, 2019; accepted May 13, 2020.

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2666-061X/191005

<https://doi.org/10.1016/j.asmr.2020.05.007>

more graft sources for ACL reconstruction, and now many kinds of grafts such as quadriceps tendon (QT) autograft, anterior or posterior tibialis tendon (TA/TP) allograft, peroneus longus tendon (PLT), and artificial ligament (ArtL) are also used in clinical practice.<sup>13,22-24</sup>

But which is the best graft for ACL reconstruction? Some systematic reviews and direct meta-analyses have been published to evaluate the effectiveness of graft options. In 1 direct meta-analysis, Xie et al.<sup>11</sup> found no significant differences in IKDC score, Lachman test, or pivot shift test between PT and HT autograft, but PT autograft resulted in a higher incidence of anterior knee pain, kneeling pain, and osteoarthritis. In another direct meta-analysis, Riaz et al.<sup>25</sup> found no significant differences in graft failure, stability, or percentage of patients with a positive result of pivot shift test, but found significant differences in graft site pain and kneeling pain between QT and PT. Given the limitations of systematic review and direct meta-analysis, it is difficult to determine which kind of graft is the most appropriate for ACL reconstruction.

In recent years, network meta-analysis has been developed rapidly. Network meta-analysis is a new methodology to evaluate >3 interventions. Using frequency or Bayesian models, network meta-analysis can provide estimates of relative efficacy between all interventions, even though some have never been compared head to head. Compared with direct meta-analysis, it has many advantages, including comparisons of multiple interventions, calculation of indirect evidence, and rank of included treatments.<sup>26,27</sup> We hypothesize that network meta-analysis will show no difference in clinical outcomes among ACL graft options, and we performed this network meta-analysis to evaluate the effectiveness of various graft options for ACL reconstruction.

## Methods

### Data Sources

A medical literature search was conducted in the following databases from their inception through March 1, 2019: PubMed, the Cochrane Library, Embase, SCOPUS and Web of Science. The search strategy consisted of medical subject headings (MeSH) and key words, including “anterior cruciate ligament reconstruction,” “patellar tendon,” “hamstring tendon,” “semitendinosus and gracilis tendons,” “semitendinosus tendon,” “gracilis tendon,” “Leeds-Keio synthetic graft,” “artificial ligament,” “Achilles tendon,” “posterior tibialis tendon,” “anterior tibialis tendon,” “quadriceps tendon,” “peroneal longus tendon,” “iliotibial band,” and “randomized controlled trial.” The language of the included studies was restricted to English. Two investigators performed the search independently to

confirm its consistency. After deleting duplicates, 2 investigators independently read the titles and abstracts of the articles and selected the potential ones. The full texts of the selected articles were reviewed based on inclusion and exclusion criteria, in which a third investigator checked the controversial articles.

### Inclusion Criteria

Studies were included according to following criteria: (1) randomized controlled trials (RCTs); (2) patients who underwent ACL reconstruction; (3) studies comparing the effectiveness of graft options in ACL reconstruction; (4) follow-up  $\geq 1$  year; and (5) studies with complete data.

### Exclusion Criteria

The following studies were excluded: (1) literature reviews; (2) duplicate studies; (3) formats other than randomized controlled trials; (4) studies comparing different fixations in which the same graft was used; (5) studies in which patients had surgical history or multiligament injuries in the knee joint.

### Data Extraction

Two investigators worked on the data extraction independently and gathered the following information: (1) basic characteristics, including study identification, intervention, age and sex of patients, fixation, graft, and follow-up duration; (2) outcome measurements, including International Knee Documentation Committee (IKDC) form, Lachman test, Lysholm score, Pivot shift test, and Tegner score. For IKDC, the evaluation of overall IKDC was used, and the number of the patients with grade A or B was collected. For Lachman and Pivot shift tests, the number of patients with negative results was collected.

### Quality Assessment

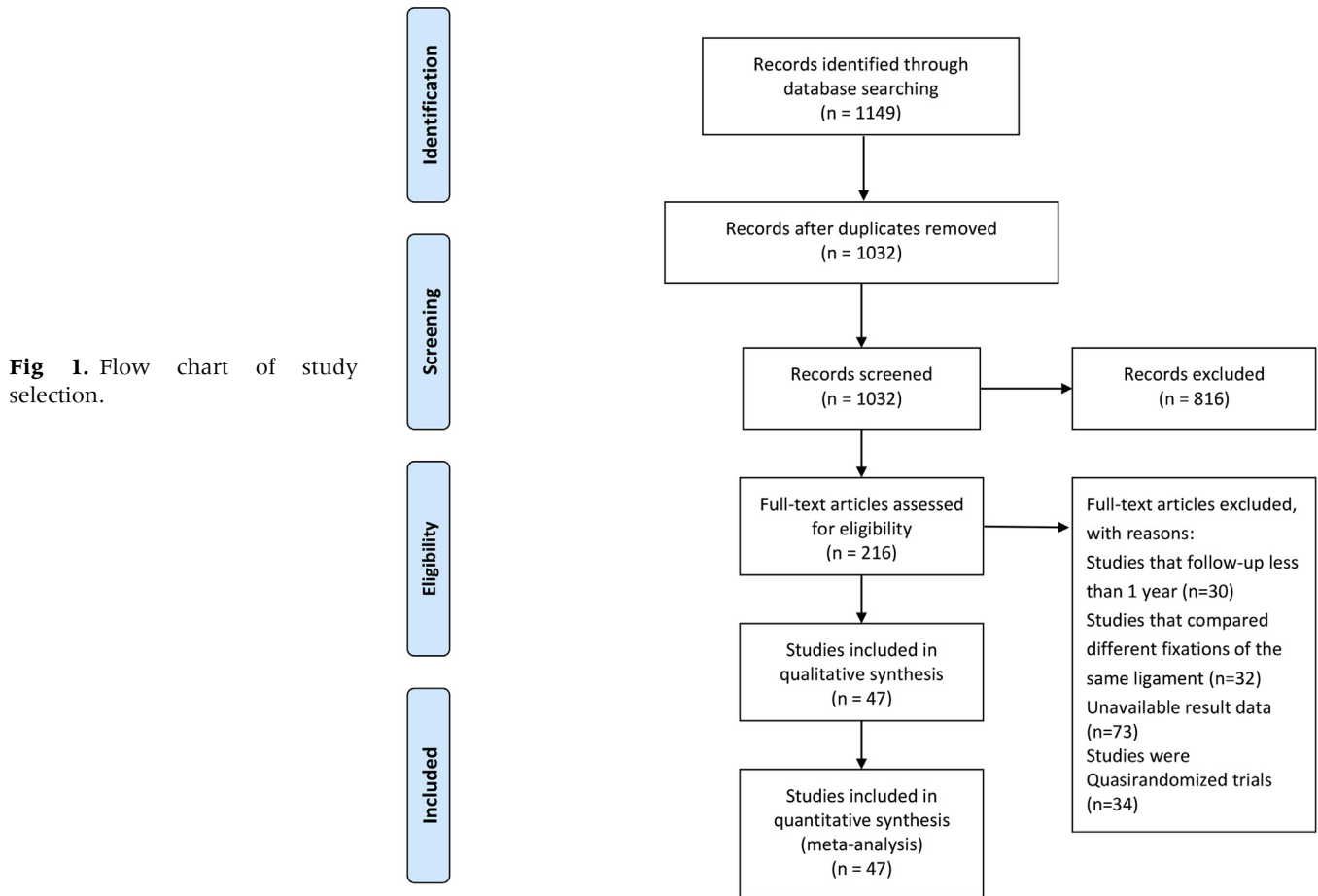
Risk of bias was evaluated using the Cochrane Risk of Bias Tool, which includes 6 domains: randomization sequence generation, allocation concealment, blinding of participants and outcome assessors, attrition bias, reporting bias, and other bias. Each term was judged as high risk, low risk, or unclear risk. The certainty of evidence was evaluated based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE), which consists of 6 aspects: within-study bias, across-studies bias, indirectness, imprecision, heterogeneity, and incoherence, and the procedure was performed using the CINeMA website (<http://cinema.ispm.ch>). Quality assessment was independently performed by 2 investigators, and disagreements were checked by a third investigator.

### Statistical Analysis

A network meta-analysis was performed using STATA version 14.0. Continuous variables (Lysholm



## PRISMA 2009 Flow Diagram



score and Tegner score) were analyzed using mean difference (MD) and its 95% credible interval (CrI), whereas the dichotomous variables (IKDC, Lachman test, and pivot shift test) used odds ratios (ORs). At the beginning of the network meta-analysis, pairwise meta-analyses were carried out for studies within DerSimonian-Laird random effects, then direct and indirect comparisons were performed, and interventions were ranked in order. A network plot was used to demonstrate different arms and integrations in each outcome, and a forest plot was used to show the results of network meta-analysis, the bold part indicating a significant difference. Rank was demonstrated according to the surface under the cumulative ranking area (SUCRA). Global inconsistency, loop specific inconsistency analysis, and node-splitting method were performed to estimate the inconsistency, and the result indicated no statistical inconsistency when  $p > .05$ . Furthermore, a subgroup analysis of IKDC and Lachman test was carried out based on the variables

including follow-up, allocation concealment, and sample size, in which the result of B represented a significant difference.<sup>28</sup> In addition, a meta-analysis of direct comparisons was performed for adverse events using Review Manager 5.3.

## Results

### Identification of Relevant Studies

1149 studies were identified according to our search strategy; 117 were excluded for duplication. The remaining 1032 studies were checked by reading titles and abstracts, of which 356 were excluded for systematic reviews and 460 for irrelevant topics. The full texts of 216 studies were assessed for eligibility, of which 32 were excluded for <1 year follow-up, 32 for comparing different fixations using the same graft, 34 for quasirandomized controlled trials, and 73 for no related data provided. Finally, 45 studies<sup>7,29-72</sup> were included

for our analysis. Fig 1 shows the selection process for relevant studies.

### Characteristics of the Included Studies

The characteristics of included studies are summarized in the Appendix. All 45 studies were published in English, 3992 patients were involved, and the sample size ranged from 38 to 282 cases. In the included trials, Aune 2001<sup>30</sup> and Holm 2010<sup>43</sup>; Barenius 2010<sup>31</sup> and Eriksson 2001<sup>38</sup>; and Feller 2003<sup>39</sup> and Webster 2015<sup>70</sup>; belonged to the same trials with different follow-up durations.

In the included studies, the mean age of patients ranged from 20.1 to 42 years, and the percentage of female patients ranged from 13% to 100%. In terms of the grafts used, 17 studies<sup>29,30,32,33,36,39,43,47,51,54,55,58,66,69-72</sup> compared patellar tendon autograft (PT-AU) with hamstring tendon autograft (HT-AU), 5 studies<sup>31,37,38,48,52</sup> compared PT-AU with semitendinosus tendon autograft (ST-AU), 4 studies<sup>63,64,67,68</sup> compared HT-AU with hamstring tendon allograft (HT-AL), 3 studies<sup>7,40,42</sup> compared PT-AU with Art-L, 2 studies<sup>41,46</sup> compared HT-AU with ST-AU, 2 studies<sup>49,65</sup> compared HT-AU with tibialis anterior tendon allograft (TA-AL), 2 studies<sup>61,62</sup> compared PT-AU with patellar tendon allograft (PT-AL), 2 studies<sup>35,56</sup> compared PT-AL with HT-AL, and 1 study<sup>50</sup> performed a comparison among PT-AU, HT-AU, and ST-AU. In addition, 1 study compared HT-AU with tibialis posterior allograft (TP-AL),<sup>34</sup> 1 compared HT-AU with PT-AL,<sup>44</sup> 1 compared PT-AL with tibialis anterior allograft (TA-AL),<sup>45</sup> 1 compared PT-AU with QT-AU,<sup>53</sup> 1 compared HT-AU with Achilles tendon allograft (Ac-AL),<sup>57</sup> 1 compared HT-AU with peroneus longus tendon autograft (PLT-AU),<sup>59</sup> and 1 compared PT-AU with iliotibial band autograft (ITB-AU).<sup>60</sup>

### Quality Assessment and GRADE

Based on the Cochrane Risk of Bias tool, the risk of bias varied in the studies (Appendix). All the studies had low risk of bias in randomized sequence generation, attrition bias, and reporting bias; 15 studies<sup>7,31,34,36-38,40,44,47,48,50,52,53,65,66</sup> had low risk of bias in allocation concealment, 4 studies<sup>40,41,46,55</sup> had low risk of bias in blinding participants, and 26 trials<sup>30,35-37,39,41,43,44,46,50-53,55,60-68,70-72</sup> had low risk of bias in blinding outcome assessors (Appendix). In terms of GRADE evaluation, 110 comparisons were judged as moderate evidence, 21 as low evidence, and 5 as very low evidence (Appendix).

### Results of Pairwise Meta-Analysis

A total of 24 direct comparisons from 5 outcomes were analyzed. The results (Appendix) indicated that 16 comparisons were low heterogeneity ( $I^2 < 25\%$ ), 2

comparisons were moderate heterogeneity ( $25\% \leq I^2 \leq 50\%$ ), and 6 comparisons were high heterogeneity ( $I^2 > 50\%$ ).

### Results of Network Meta-Analysis

As illustrated in Fig 2, IKDC outcome was reported in 21 studies<sup>29,32,33,37-41,49-52,57,58,61-66,69</sup> involving 8 interventions. The forest plot showed no significant difference in this outcome among the comparisons. The results of SUCRA indicated that TA-AL had the highest probability to be the best intervention, followed by PT-AU, HT-AU, ST-AU, PT-AL, HT-AL, ArtL, and Ac-AL (Appendix).

The outcome of Lachman test was reported in 20 studies<sup>33,35,37,38,40,42,44,45,48,52,57-59,61-64,67,68,72</sup> involving 9 interventions (Fig 3). Two comparisons, HT-AL versus PT-AU and HT-AL versus HT-AU, demonstrated a significant difference in this outcome. SUCRA indicated that PT-AU had the highest probability to be the best intervention, followed by ST-AU, TA-AL, PT-AL, ArtL, HT-AU, PLT-AU, Ac-AL, and HT-AL (Appendix).

In terms of Lysholm score, 16 studies<sup>32,35,36,43,45-47,56,60-65,67,68</sup> were analyzed (Appendix). Similar to the results of IKDC, no significant difference was found in this outcome among the comparisons. The cumulative probability of PT-AU, HT-AU, ST-AU, PT-AL, HT-AL, TA-AL, and ITB-AU to be the best intervention was 27.7%, 51%, 74.3%, 61%, 26.4%, 84%, and 25.7%, respectively (Appendix).

Concerning pivot shift test, the results showed that PT-AU was superior to other interventions in improving knee function (Appendix). Compared with QT-AU, HT-AL and Art-L showed fewer cases with negative results. The results of SUCRA showed that QT-AU had the highest probability to be the best intervention, followed by PT-AU, TA-AL, ST-AU, HT-AU, Ac-AL, PT-AL, HT-AL, and ArtL (Appendix).

The outcome of Tegner score was reported in 11 studies<sup>32,34,43,55,61-64,67,68,72</sup> involving 5 kinds of grafts (Appendix). The forest plot indicated no significant difference in this score among the comparisons. The cumulative probability of PT-AU, HT-AU, PT-AL, HT-AL, and TP-AL to be the best intervention was 69.2%, 65.1%, 34.9%, 23.6%, and 57.1%, respectively (Appendix).

### Cluster Analysis

According to the different probability of intervention in different outcomes, we perform a cluster analysis based on IKDC and Lachman test outcomes. As illustrated in Fig 4, PT-AU both got the higher probability in 2 outcomes among the included grafts.

### Consistency Analysis, Contribution Plot, and Funnel Plot

As shown in the Appendix, no significant inconsistency was found in global inconsistency, loop-specific inconsistency, and node-splitting analysis. In

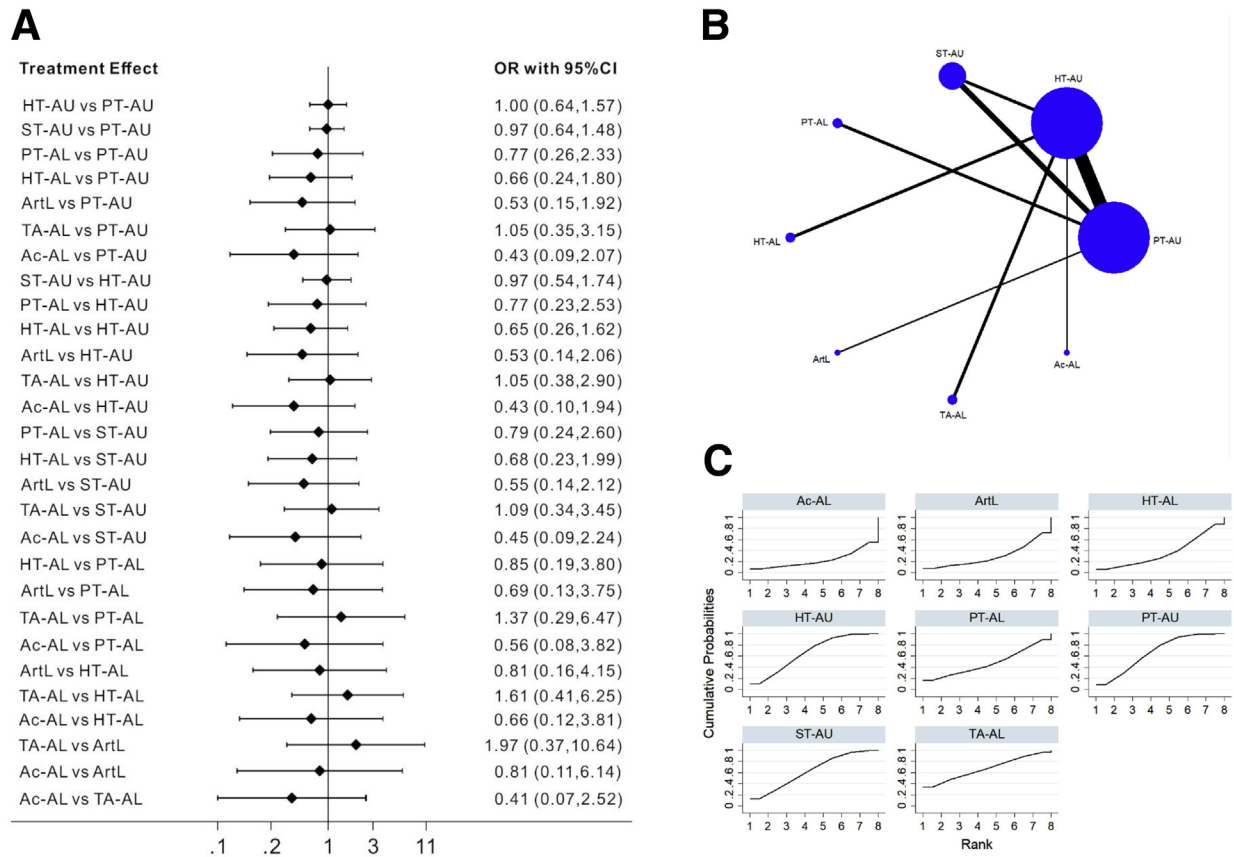


Fig 2. Results of IKDC score, including forest plot (A), network plot (B), and SUCRA plot (C).

addition, the subgroup analysis showed no significant differences in IKDC and Lachman test based on follow-up, allocation concealment, and sample size (Appendix). The results of contribution plots and funnel plots are presented in the Appendix.

**Complications**

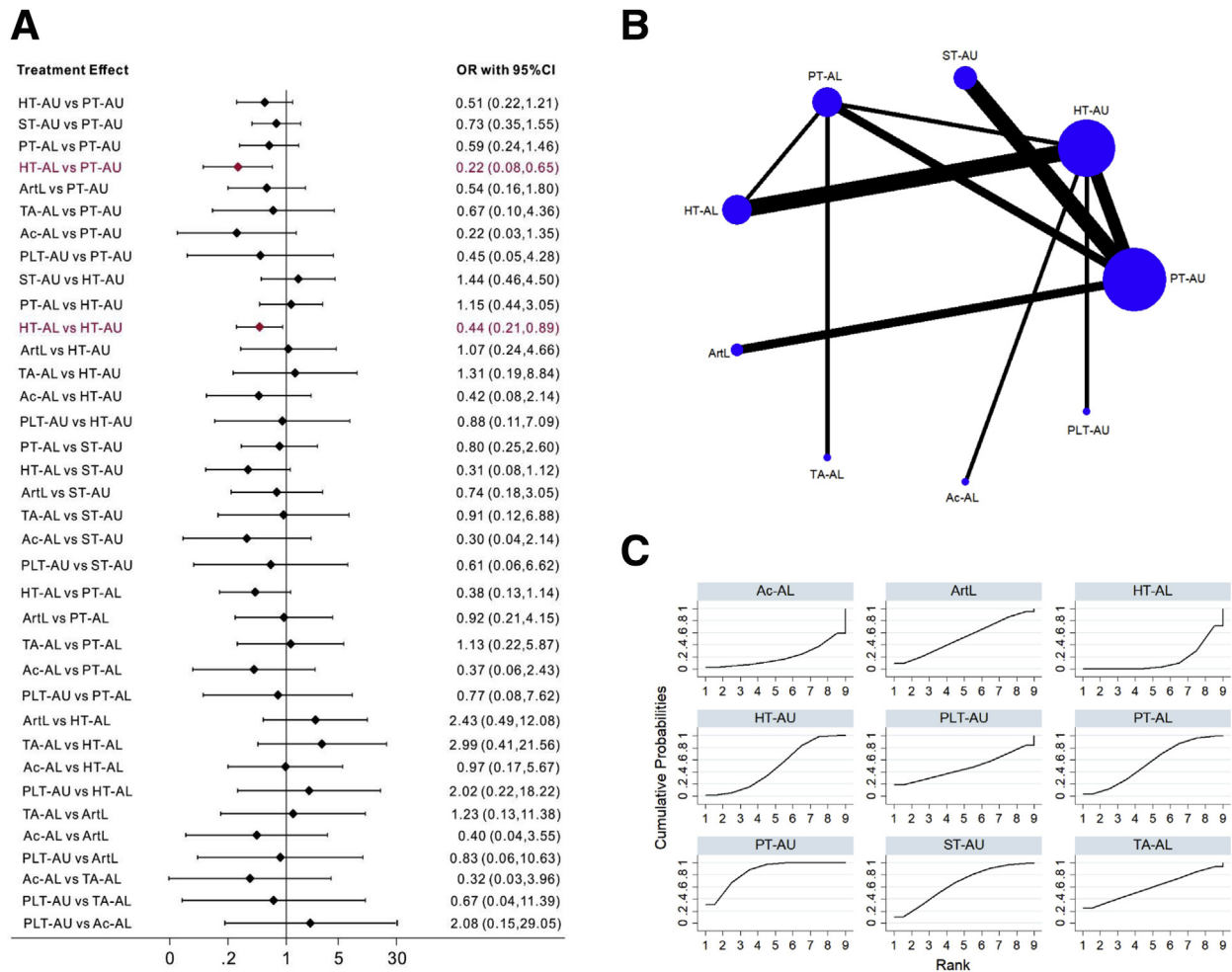
Thirty-seven studies mentioned complications, of which 4 studies<sup>35,45,71,72</sup> reported no complications and 33 studies<sup>7,29-31,34,37-43,47-50,52-54,56-68,70</sup> mentioned various complications. All the complications are listed in the Appendix. The complications with relatively higher incidence in ACL reconstruction, including graft rupture, graft failure, superficial infection, deep infection, and nerve injury, were analyzed. Based on the results of Fig 5, no significant difference was found in graft rupture, superficial infection, or deep infection among studies, whereas HT-AU showed a lower incidence than TP-AL (MD 0.25, 95% CrI 0.08 to 0.84), and PT-AL showed a lower incidence than HT-AL (MD 0.19, 95% CrI 0.04 to 0.95) in graft failure, and HT-AU showed a higher incidence than HT-AL in nerve injury (MD 28.50, 95% CrI 1.68 to 482.30).

**Discussion**

**Main Findings**

In this study, according to cluster analysis, PT-AU demonstrated superiority to other grafts in IKDC and Lachman test, which may be because the patellar tendon is 3 to 4 times stiffer than anterior cruciate ligaments.<sup>73</sup> In previously published direct meta-analysis, PT-AU was reported to have better stability<sup>74,75</sup>; in this network meta-analysis, the same conclusion was confirmed. Regarding the outcome of pivot shift test, QT-AU had the highest probability to be the best intervention. Meanwhile, the QT-AU showed the highest effect and widest CrI in the forest plot. However, only 1 study involving QT-AU was included and the superiority of QT-AU in the results should be taken cautiously.

Although no significant consistency was found in our research, the data that only compared the type of graft may have some problems. In the clinic, the graft options in ACL reconstruction involve different surgical technique, fixation systems, and number of grafts. The surgical method involving the type of graft, fixation, and other characteristics should be treated as a unique

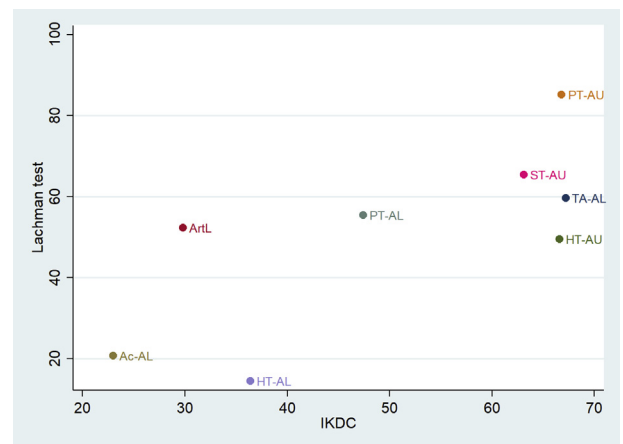


**Fig 3.** Results of Lachman test, including forest plot (A), network plot (B), and SUCRA plot (C). The red parts of forest plots represent significant differences.

intervention in the comparison of network meta-analysis. Nevertheless, up to now, few trials have concentrated on comparing different surgical methods in ACL reconstruction. Meanwhile, the type of graft has an important effect on ACL reconstruction. Our research tried to find out the appropriate graft based on the existing trials, and we look forward to performing a comprehensive network meta-analysis that involves the detailed interventions.

Moreover, in the outcomes of SUCRA for IKDC and Lysholm score, TA-AL was the best intervention, which may be attributed to the higher effect of the studies involving TA-AL according to contribution plot and the small sample size of these studies in network plot. Meanwhile, the reoperation rate of allograft was higher than that of autograft,<sup>76</sup> and consequently, the second choice, PT-AU, may be more appropriate than TA-AL in IKDC. In addition, a previous study<sup>77</sup> suggested that a validated minimal clinically important difference has not been established for Lysholm score, and an 8-point difference

likely trends toward a clinically important difference. However, our results of TA-AL in Lysholm score did not reach the suggested value.



**Fig 4.** Cluster analysis based on the SUCRA values of IKDC and Lachman test.

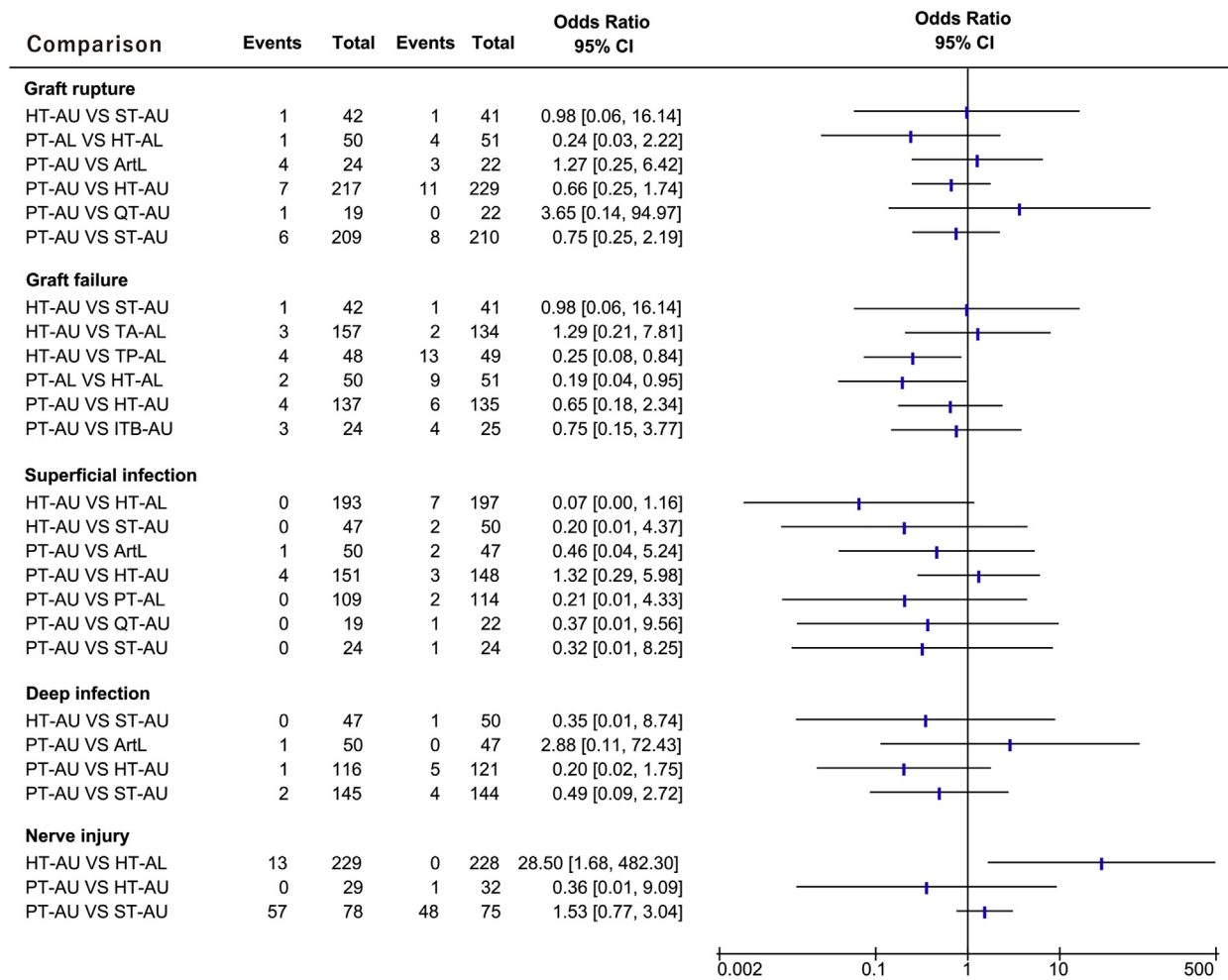


Fig 5. Forest plot of comparisons for complications.

Based on the cluster analysis in Fig 4, PT-AU may be the best graft for ACL reconstruction. However, the forest plots indicated no significant differences in IKDC, Lysholm, and Tegner score among the grafts, except that PT-AU and HT-AU were superior to HT-AL in postoperative negative rates of Lachman test, and PT-AU and QT-AU showed a favorable effect compared with HT-AL and Art-L in postoperative negative rate of pivot-shift test. The results of forest plots were not consistent with those of SUCRA, which may be attributed to the small quantities of the included trials. There are some methodological strengths in our review: (1) most of the included studies were high-quality RCTs based on the Cochrane Risk of Bias Tool; (2) no significant inconsistency existed in the included studies according to inconsistency analysis; and (3) no conspicuous publication bias was observed in our results.

**Limitations**

Our network meta-analysis has some limitations. First, in the included trials, different fixation systems were used for ACL reconstruction, which may affect the

final outcomes, but we did not take it into consideration because of the diversity of the fixation systems used in the trials. Second, the complications were various, and each complication involved  $\leq 3$  grafts, so we did not make a network meta-analysis for it. Third, the small sample size of some interventions was an intrinsic weakness. On the one hand, most of the highly inconsistent results in pairwise meta-analysis involved fewer comparisons. On the other hand, some interventions that involved small sample sizes but reached a large difference make our results unsteady. Furthermore, most of the comparisons in GRADE in our research were moderate evidence.

**Conclusions**

This study suggests that PT-AU may be the most appropriate graft for ACL reconstruction according to IKDC and Lachman test results.

**Acknowledgments**

Z. Mo and D. Li contributed equally to this article.

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