

Hybrid graft vs autograft in anterior cruciate ligament reconstruction: a meta-analysis

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Lei Wang¹
Jian-gang Cao²
Jun Liu¹

¹Department of Joint Surgery, Tianjin Hospital, Tianjin, People's Republic of China; ²Department of Sport Medicine, Tianjin Hospital, Tianjin, People's Republic of China

Purpose: We conducted this meta-analysis to evaluate the efficacy of hybrid grafts in anterior cruciate ligament reconstruction (ACLR).

Methods: We performed an electronic search of the Cochrane Library, PubMed, Embase, and ScienceDirect from the inception of these databases to February 2018, based on the terms “anterior cruciate ligament or ACL reconstruction”, “autograft”, “hybrid”, and “augment”. Relevant journals and conference proceedings were searched manually. Quality assessment, data extraction, and calculation of data from the included studies were conducted independently by two reviewers using RevMan 5.1.

Results: One randomized controlled trial and eight nonrandomized controlled trials met inclusion criteria. Larger graft diameters were found in the hybrid-graft group (mean difference -1.47 , $P=0.0001$). There was no significant difference in failure rate (OR 2.13, $P=0.21$), retearing (OR 2.23, $P=0.12$), revision of ACLR (OR 1.05, $P=0.87$) or reoperation (OR 1.27, $P=0.35$). Subgroup analysis showed that hybrid-graft patients with meniscus injury suffered more revision (OR 4.10, $P=0.02$) and reoperation (OR 5.74, $P=0.001$). Both autografts and hybrid grafts performed similarly in most knee-score systems. However, autograft patients had better KT-1000 (mean difference 0.24, $P=0.05$) and quality-of-life results on the Knee Injury and Osteoarthritis Outcome Score measure (mean difference 7.23, $P=0.05$).

Conclusion: This meta-analysis of the current literature indicates similar performance of hybrid or autologous grafts in ACLR, though hybrid grafts had larger diameters than autografts. Other potential factors to influence failure, revision, or postoperative knee function, such as irradiation, age at reconstruction, meniscus injury/treatment, and hybrid-graft remodeling, should be investigated further.

Keywords: hybrid graft, autograft, anterior cruciate ligament, reconstruction

Introduction

The anterior cruciate ligament (ACL) is an important component to maintain knee-joint stability and is susceptible to injury during competitive sports.¹ More than 100,000 patients per year need ACL reconstruction (ACLR) in the US.² Autologous graft reconstruction is considered the gold-standard treatment, with better tendon–bone healing. However, evidence has shown that autografts of diameter <8 mm have no guarantee of better prognosis, especially for younger patients.³

Although allografts on their own have been reported to function similarly to autografts,⁴ the biomechanics of allografts are influenced by many factors, including irradiation and chemical processing, which is associated with the procession of tendon–bone healing and incorporation. Alvarez-Pinzon et al introduced hybrid-graft surgical techniques to permit the surgeon to customize the size of grafts.⁵ Allografts have been

Correspondence: Jun Liu
Department of Joint Surgery, Tianjin Hospital, 406 Jiefang Nan Road, Tianjin 300211, People's Republic of China
Tel +86 133 0210 9035
Email tjydrliu@126.com

used in combination with autografts in the hope of increasing inadequate diameters and achieving better outcomes.

In a randomized trial, Li et al prospectively compared autografts, allografts, and hybrid grafts. The results showed similar objective and subjective clinical outcomes for patients undergoing primary ACLR with hybrid grafts or autografts. Both groups of patients had better KT-1000 measurements compared with the γ -irradiated (2.5 Mrad) allograft group.⁶ Another retrospective comparative study, however, noticed more failure or compromised ACLRs and worse Lysholm and IKDC scores after hybrid-graft reconstruction.⁷ Jacobs et al later reported more failures in autograft patients, and attributed the better results of hybrid grafts mainly to larger diameter.⁸ Several studies have been published about hybrid grafts vs autografts, with inconsistent results. Therefore, we conducted this meta-analysis to evaluate the efficacy of hybrid grafts in ACLR.

Methods

Search strategy

The literature was searched on the Cochrane Library, PubMed, Embase, and ScienceDirect databases for articles published from 1966 to February 2018. Secondary sources were identified from studies cited in the references. No studies were excluded based on the language used. The key search terms were “autografts”, “hybrid”, “allografts”, and “anterior cruciate ligament” in combination with the Boolean operators AND or OR. Also, research on the appraisal reference list was manually reviewed for other potential trials that should be included. The process was iterated until no further articles could be determined. The meta-analysis was based on acknowledged PRISMA guidelines.

Inclusion and exclusion criteria

Studies were considered eligible for inclusion if they met criteria of: 1) population – patients with ACLR; 2) intervention – hybrid graft (autografts augmented by allografts); 3) control – autograft only; 4) outcome measures – one or more of graft-failure rate, reoperation rate, complications, postoperative knee score, operation time, and other outcomes reported; and 5) study design – randomized controlled trials (RCTs) and non-RCTs. We excluded studies without control groups, articles without available full-text versions, and those with no available outcome data.

Data extraction

Data were extracted from the included trials by two researchers independently (LW and JGC). If article data were

incomplete, the complete data were consulted from the corresponding authors of the articles. The following information: first author's name, publication year, intervening measures, outcome measures, sample size, and comparable baselines were extracted. Other relevant parameters were also extracted from individual studies.

Quality assessment

The methodological index for nonrandomized studies (MINORS) form was used to assess non-RCTs. Quality assessment for RCTs was conducted according to the *Cochrane Handbook for Systematic Reviews of Interventions*. Literature-quality evaluation was conducted by two researchers independently (LW and JGC). Consensus was reached with the senior researcher (JL).

Data analysis and statistical methods

RevMan 5.1 (Cochrane Collaboration, Oxford, UK) was used for data analysis. Mean differences (MDs) and 95% CIs were determined for continuous outcomes. Dichotomous data were calculated using ORs and 95% CIs. Heterogeneity was estimated by I^2 based on the standard χ^2 test. When $I^2 < 50\%$ and $P > 0.1$, no significant heterogeneity existed and a fixed-effect model was used for analysis, while a random-effect model was used when $I^2 > 50\%$ and $P < 0.1$. Subgroup analysis was performed to investigate sources of heterogeneity.

Results

Search results

A total of 125 studies were identified as potentially relevant literature reports based on the search strategy. After titles and abstracts had been scanned, 116 reports were excluded according to the eligibility criteria. Kraeutler et al conducted two studies – in 2016⁹ and 2018¹⁰ – that both matched eligibility criteria with overlapped data. As such, the later study was included for further data pooling and analysis, because of the larger patient sample. One additional study by Pennock et al was obtained after the reference review.¹¹ Ultimately, eight non-RCTs^{7,8,10–15} and one RCT⁶ were eligible for data extraction and meta-analysis, comprising 322 patients in the hybrid-graft group and 404 patients in the autograft group. The search process is shown in Figure 1.

Study characteristics

Demographic characteristics and details concerning literature type are summarized in Table 1. Statistically similar baseline characteristics were observed in both groups. Two studies focused on patients <18 years old.^{8,11} Most samples

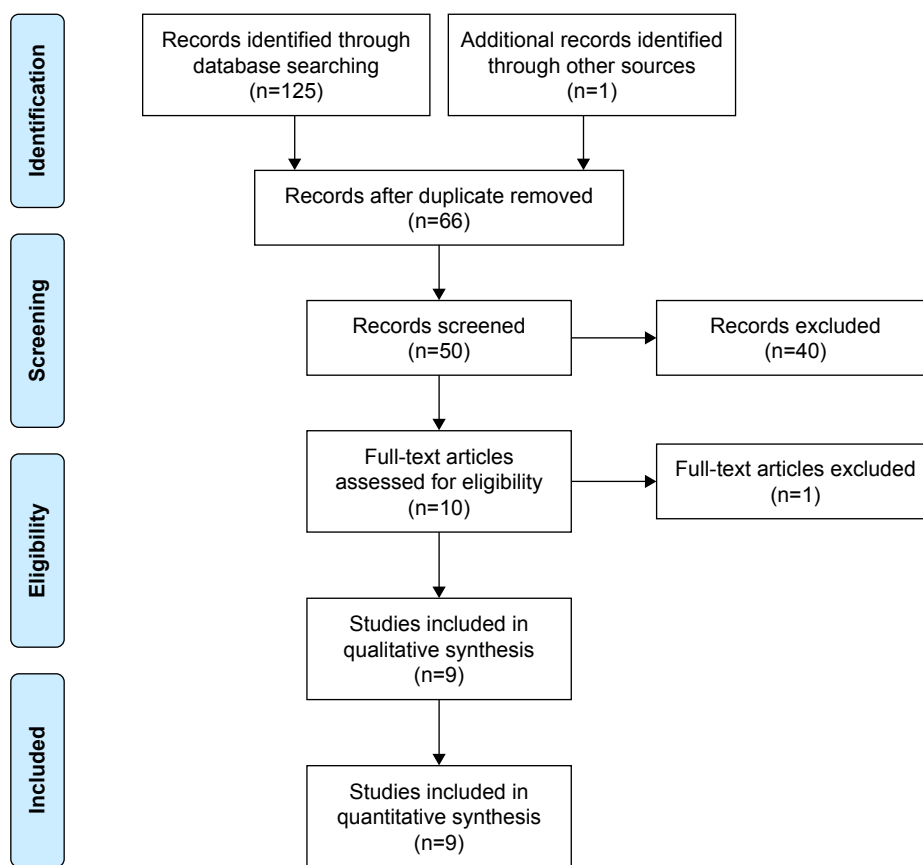


Figure 1 Flowchart of the study selection process.

were 20–71 years old, while Kraeutler et al included 84 and 119 patients in the hybrid and autograft groups, respectively. However, only 36 matched pairs were evaluated for post-operative knee function. Insufficient autograft size was the main reason for extra allograft augmentation. Cutoff sizes for autografts were <7.5 mm⁷ and <8 mm.^{6,12–14} Xu et al added an allograft if the autograft could not restore the insertion site to at least 60% of the cross-sectional area or if the augmentation was able to result in better graft occupancy.¹⁵ Graft diameter and length, patient size, growth-plate status, and desired level of sport participation were the bases of decision for another study.¹¹ Semitendinosus tendons were used solely as allografts to augment autograft hamstrings by Darnley et al¹² and Jacobs et al.⁸ Tibialis anterior tendons alone were adopted by Li et al,⁶ Leo et al,¹³ Wang et al,¹⁴ and Xu et al.¹⁵ Both semitendinosus and tibialis anterior tendons were included in Burrus et al⁷ and Pennock et al.¹¹ Posterior tibialis or peroneus longus tendons were the allografts in Kraeutler et al.¹⁰ High-dose irradiation (≥ 2.5 Mrad) was used in processing of allografts in three studies.^{6,14,15} Meniscus injury was included in four studies,^{6,7,11,12} while other studies excluded these patients.

Risk-of-bias assessment

Only one RCT had high methodological quality based on the *Cochrane Handbook for Systematic Reviews of Interventions* (Figure 2). For the eight non-RCTs, the MINORS score ranged from 18 to 24 (Table 2). Most studies were retrospective analyses, while only data were prospectively collected in Darnley et al¹² and Leo et al.¹³ Prospective calculation of sample size was also performed in these two studies. No significant publication bias was noticed, based on the funnel plot for revision (Figure 3).

Outcomes of meta-analysis

Six studies reported the diameter of grafts, and pooled data showed which was larger in the hybrid-graft group (MD -1.47 , 95% CI 0.95 – 2.00 ; $P=0.0001$; Figure 4). The definition was a little different among the studies that reported the rate of failure. Therefore, we report failure, revision, and re-tear separately in this meta-analysis. Failure rate based on six studies did not show a significant statistical difference between the two groups (OR 2.13 , 95% CI 0.66 – 6.86 ; $P=0.21$; Figure 5). However, Jacobs et al⁸ reported more than double the rate of failure in the autograft group.

Table 1 Characteristics of included studies

Study	Design	Sample size (H/A)	Mean age, years (H/A)	Female (H/A)	Follow-up (H/A)	Allograft source	Irradiation (Mrad)	Meniscus injury
Burrus et al ⁷	Retrospective	29/29	26.6/27.2	19/19	44.4/48 months	Semitendinosus or tibialis anterior tendons	1.2–1.9	Yes
Darnley et al ¹²	Prospective	27/27	20.9/20.9	10/10	2/2 years	Semitendinosus tendon	<2.5	Yes
Jacobs et al	Retrospective	42/46	15/14.6	18/26	31.2/46.7 months	Semitendinosus tendon	1.2–1.9	No
Kraeutler et al ¹⁰	Retrospective	84/119	36.6/35.8	N	3.5/4.7 years	Posterior tibialis or peroneus longus tendons	No	No
Leo et al ¹³	Retrospective	24/71	28.1/26.9	8/25	2/2 years	Tibialis tendons	No	No
Li et al ⁶	Prospective	31/32	31.6/29.8	13/15	5.9/5.8 years	Tibialis anterior tendons	2.5	Yes
Pennock et al ¹¹	Retrospective	20/20	15.4/15.9	12/13	3/3 years	Semitendinosus or tibialis anterior	0.9–1.3	Yes
Wang et al ¹⁴	Retrospective	28/29	32.6/32.8	19/19	40.6/40.6 months	Tibialis anterior tendons	2.5	No
Xu et al ¹⁵	Retrospective	37/31	33.9/32.8	10/15	2/2 years	Tibialis anterior tendons	2.5	No

Abbreviations: A, autograft; H, hybrid graft; NS, not state.

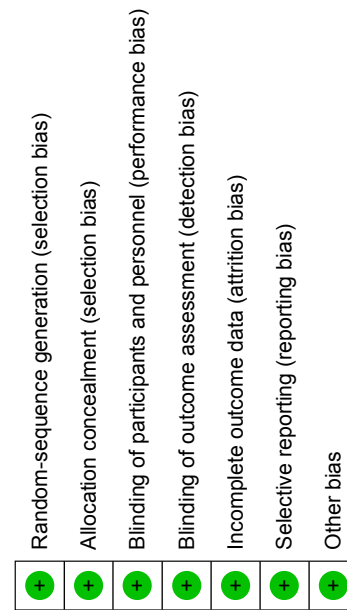


Figure 2 Risk-of-bias summary.

After exclusion of their cases, a higher failure rate was noticed in the hybrid-graft group (21 of 144) than the autograft group (six of 136), with lower heterogeneity (OR 3.93, 95% CI 1.53–10.07; $P=0.004$). There was no significantly statistical difference in postoperative graft re-tearing (OR 2.23, 95% CI 0.82–6.10; $P=0.12$) or contralateral tearing (OR 1.00, 95% CI 0.27–3.70; $P=1.00$). Two damaged hybrid grafts and seven compromised ACLRs were also reported by Xu et al¹⁵ and Burrus et al.⁷ Eight non-RCTs reported revision and reoperation. We pooled only data related to grafts. No significant difference was noticed in either revised ACLR (OR 1.05, 95% CI 0.61–1.81; $P=0.87$; Figure 6) or reoperation (OR 1.27, 95% CI 0.77–2.11; $P=0.35$). Subgroup analysis showed that hybrid-graft patients with meniscus injury suffered more revision with lower heterogeneity (OR 4.10, 95% CI 1.28–13.10; $P=0.02$) and reoperation (OR 5.74, 95% CI 2.05–16.03; $P=0.001$). When patients without meniscus injury were investigated, no significant difference existed in either autograft or hybrid-graft patients.

Postoperative knee function was investigated in different studies based on different evaluation systems. Details of meta-analysis results of knee function are illustrated in Table 3. Both autografts and hybrid grafts performed similarly in most of these scores. Also, autograft patients had better KT-1000 test scores (MD 0.24, 95% CI 0–0.47; $P=0.05$), Lysholm scores (MD –4.29, 95% CI –8.60–0.03; $P=0.05$), and quality-of-life scores (MD 7.23, 95% CI 0.07–14.38; $P=0.05$) in the Knee injury and Osteoarthritis Outcome Score (KOOS) measure. Among the five studies

Table 2 Quality assessment for nonrandomized trials

	Burrus et al ⁷	Darmley et al ¹²	Jacobs et al ⁸	Kraeutler et al ¹⁰	Leo et al ¹³	Pennock et al ¹¹	Wang et al ¹⁴	Xu et al ¹⁵
Clearly stated aim	2	2	2	2	2	2	2	2
Inclusion of consecutive patients	2	2	2	2	2	2	2	2
Prospective data collection	0	2	0	0	2	0	0	0
End points appropriate to study aims	2	2	2	2	2	2	2	2
Unbiased assessment of study end point	2	2	2	2	2	2	2	2
Follow-up period appropriate to study aims	2	2	2	2	2	2	2	2
Less than 5% loss to follow-up	0	0	2	0	2	0	2	2
Prospective calculation of sample size	0	2	0	0	2	0	0	0
An adequate control group	2	2	2	2	2	2	2	2
Contemporary groups	2	2	2	2	2	2	2	2
Baseline equivalence of groups	2	2	2	2	2	2	2	2
Adequate statistical analyses	2	2	2	2	2	2	2	2
Total score	18	22	20	18	24	18	20	20

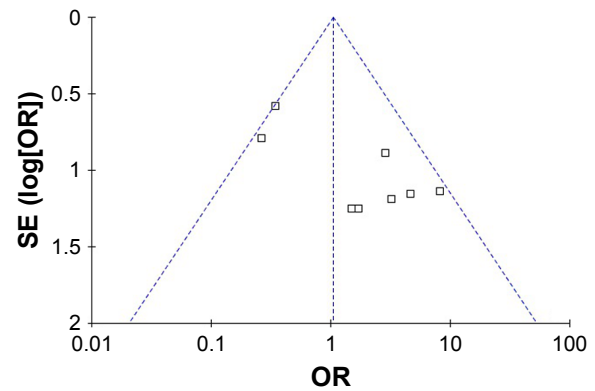


Figure 3 Funnel plot for reoperation.

reporting Lysholm scores, all patients in Pennock et al were younger than 18 years. Sensitive analysis excluding these cases surprisingly increased the heterogeneity, and again no significant difference existed ($P=0.13$). Subgroup analysis based on meniscus injury or not showed that no significant difference existed in normal-meniscus patients (MD -3.74 , $P=0.43$), while the Lysholm score was different between the two groups in meniscus-injury patients (MD -4.74 , $P=0.05$).

Discussion

Allograft tendons have been used to augment limited autograft size for ACLR in the past few years, and have achieved better results compared with the allograft solely. Based on the included studies, the current meta-analysis showed similar performance in failure, re-tearing, revision, and reoperation between hybrid-graft and autograft patients.

High heterogeneity existed in results of diameter, graft failure, revision, reoperation, IKDC score, and Lysholm score. For diameter, we did not perform further sensitivity or subgroup analysis, because it mainly depends on the surgeon's preference in our opinion. Jacobs et al reported more than double the rate of failure in the autograft group, and they attributed this to the lower diameters of autografts. In a previous in vitro biomechanical study, Boniello et al showed increasing tensile strength for increased graft diameter.¹⁶ Clinical trials also supported the view that the diameter of hamstring autografts should be ≥ 8 mm to reduce the risk of revision ACLR, especially for younger patients.³ However, grafts showed a sequence of remodeling after implantation in the knee cavity.¹⁷ The biomechanics of hybrid grafts changed at different maturity times. It is not appropriate to attribute the better results only to larger diameters. Besides, larger diameters of hybrid grafts behaved significantly differently in revision and knee function in the included studies.

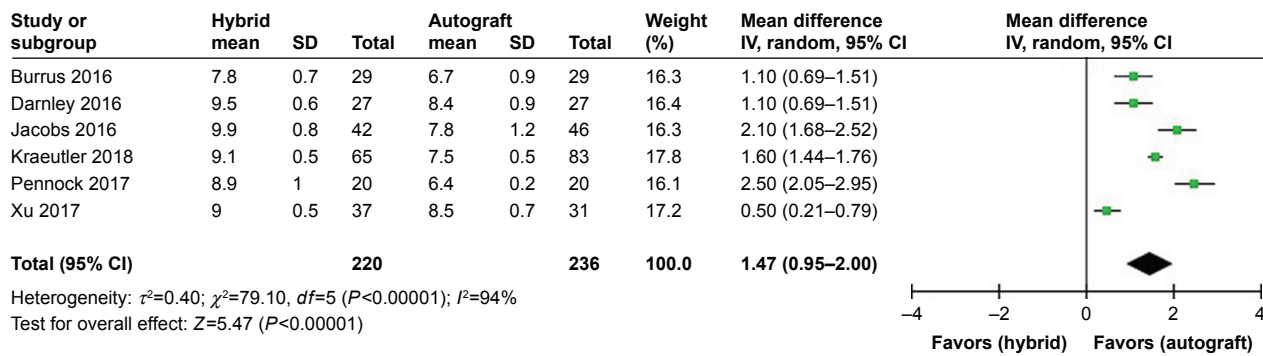


Figure 4 Forest plot showing graft diameter.

Kraeutler et al also reported much fewer revision cases in allograft patients (2.4% vs 8.4%), and they thought that nonirradiation of the allograft may be one major reason for the better results of hybrid grafts. Some previous studies showed evidence that γ -irradiation can damage the biomechanics of allografts. Using the Kaiser Permanente ACLR Registry, Maletis et al identified 14,015 cases and found a higher risk of revision in allografts with irradiation ≥ 1.8 Mrad after adjusting for age, sex, and race.¹⁸ A meta-analysis also reported a dose-dependent relationship between radiation and decreased mechanical tendon integrity. Low-dose radiation (<2.5 Mrad) showed graft weakening, with an average 4.3% decrease in load to failure.¹⁹ However, some other studies did not support this conception. A study using peroneus tendons at 1.5–2.5 Mrad γ -irradiation did not find major alterations in tendons' biomechanical properties.²⁰ In a systematic review, allograft ACL grafts appeared to be a reasonable alternative to autografts with γ -irradiation <2.2 Mrad.²¹ In our nine included studies, high-dose irradiation (2.5 Mrad) was used in three studies and subgroup analysis did not show more failure or revision in hybrid-graft patients.

Previous trials showed that younger patients were associated with more graft failure.²² Patients aged 25 years and younger had a significantly higher failure rate (16.5%) than patients >25 years (8.3%).²³ For each 10-year decrease in age, the odds of graft retearing increase 2.3 times in patients with allograft reconstruction.²⁴ The risk of revision decreased by 7% for each year increase in age.²⁵ Three studies in our study included 32 revisions in 182 patients <25 years old and 27 revisions in 481 patients >25 years old. The revision rate decreased from 17.6% to 5.6%, with average age increased from >25 years to older. However, subgroup analysis showed no significant difference between hybrid grafts and autograft patients in any age range.

Meniscus injury/procedures were reported to be significant predictors of IKDC and KOOS scores 6 years following ACLR.²⁶ Meniscus injury was included in four studies, and meniscus repair or meniscectomy was performed at the same time as ACLR. Subgroup analysis showed that hybrid-graft patients with meniscus injury suffered more revision and reoperation, with lower Lysholm scores. However, no significant difference was noticed in IKDC or Tegner activity

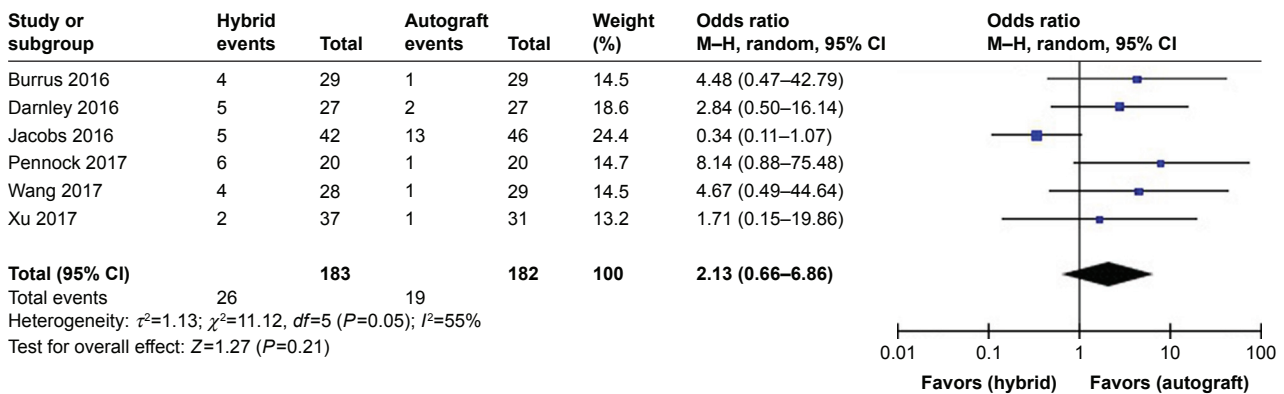


Figure 5 Forest plot showing failure.

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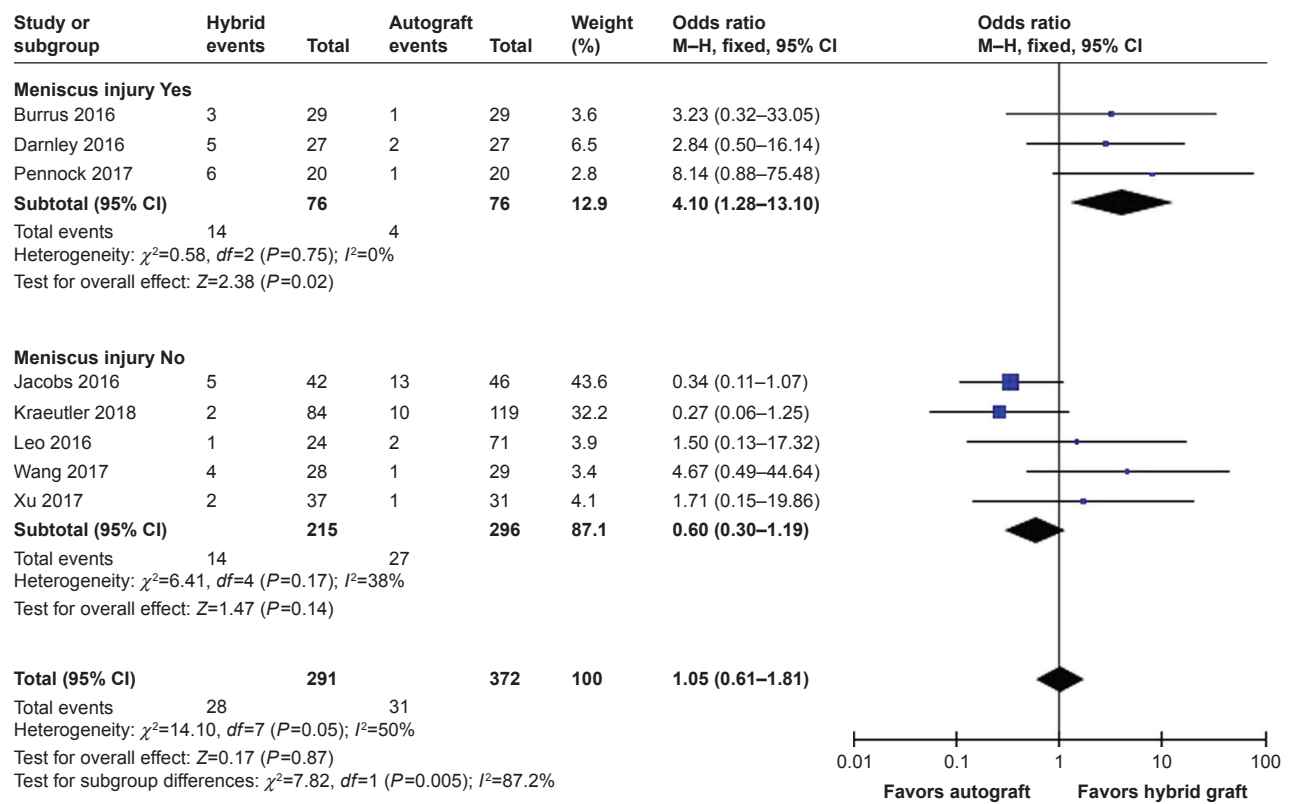


Figure 6 Forest plot showing revision.

scores. With limited detailed description on these procedures, we could not further estimate their effect on ACLR in our included studies.

Limitations

For full understanding of our research’s results, some limitations must be mentioned. First, only one RCT was included, which weakened our power to draw a definitive conclusion.

Second, samples were small in most studies, so the relatively larger samples of Jacobs et al and Kraeutler et al had an important influence on the meta-analysis results. Third, many other potential factors can affect ACLR prognosis.

Conclusion

This meta-analysis of the current literature indicates similar performance of hybrid grafts in ACLR, even though hybrid

Table 3 Meta-analysis results of knee function

Outcome	Studies	Group (hybrid/ autograft)	Overall effect			Heterogeneity	
			Effect estimate	95% CI	P-value	I ² (%)	P-value
IKDC	7	212/255	-0.22	-3.38 to 2.94	0.89	81	0.0001
Lysholm score	5	145/141	-4.29	-8.60 to 0.03	0.05	80	0.0004
Tegner score	4	116/112	0	-0.27 to 0.28	0.98	0	0.86
KT-1000 test	3	96/92	0.24	0-0.47	0.05	51	0.13
KOOS – ADL	2	63/63	0.96	-1.78 to 3.70	0.49	42	0.19
KOOS – QOL	2	63/63	7.23	0.07-14.38	0.05	0	0.46
KOOS – sport	2	63/63	4.65	-2.14 to 11.44	0.18	36	0.21
KOOS – symptoms	2	63/63	3.24	-1.47 to 7.94	0.18	36	0.21
VAS pain score	2	44/91	0.14	-0.64 to 0.93	0.72	21	0.26

Abbreviations: ADL, activities of daily living; IKDC, International Knee Documentation Committee; KOOS, Knee Injury and Osteoarthritis Outcome Score; KT, knee test; QOL, quality of life.

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grafts had larger diameters than autograft reconstructions. Irradiation, age at reconstruction, meniscus injury/treatment, hybrid-graft remodeling, and other potential factors that influenced failure, revision, or postoperative knee function should be investigated further. Also, more RCTs with more patients and homogeneous design are needed to investigate predictive factors further.

Author contributions

LW and JGC conducted the literature search and determined studies for exclusion and inclusion. LW, JL, and JGC extracted data from the studies included, performed the meta-analysis, and drafted the manuscript. LW, JL, and JGC conceived the idea of the study, designed the study, and critically revised the manuscript for important intellectual content. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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