Meta-analysis

Autograft or Allograft? Irradiated or Not? A Contrast Between Autograft and Allograft in Anterior Cruciate Ligament Reconstruction: A Meta-analysis

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Purpose: To compare the clinical outcomes and adverse events associated with irradiated and nonirradiated allografts in anterior cruciate ligament (ACL) reconstruction. **Methods:** PubMed, Web of Science, and EMBASE were searched for randomized controlled trials from January 1990 to March 2018 to compare autograft with allograft in ACL reconstruction. Both objective and subjective outcomes of the function and adverse events were meta-analyzed. Two comparisons were summarized: (1) autograft and nonirradiated allograft and (2) autograft and irradiated allograft. The bias risk was based on the *Cochrane Handbook for Systematic Reviews of Interventions*. The overall risk ratio or weighted mean difference was calculated using a fixed- or random-effects model. Heterogeneity between studies was evaluated by the Q and the I^2 statistics. **Results:** Eleven trials were included in this review for meta-analysis. A total of 1,172 patients were involved (465 autograft and 461 nonirradiated allograft; 141 autograft and 138 irradiated allograft patients). The average follow-up varied from 2 to >10 years. The mean patient age varied from 22 to 32.8 years. The total failure rate was 2.5%. Our analyses demonstrated better clinical outcomes in autograft than irradiated allograft, which could be observed clearly through the International Knee Documentation Committee score (3.84; 95% confidence interval [CI], 1.93-5.76; $P < .0001$; $I^2 = 0\%$), Lysholm score (2.94; 95% CI, 0.66-5.22; $P = .01$; $I^2 = 0\%$), and Tegner score (0.14; 95% CI, −0.08 to 0.36; $P = .22$; $I^2 = 0\%$) with fewer adverse events 0.20 (95% CI, 0.11-0.39; $P < .00001$; $I^2 = 0\%$). There were no significant differences in autograft and nonirradiated allograft groups ($P = .47$, $P = .27$, $P = .24$, and $P = .24$, respectively). **Conclusions:** Autograft offered greater advantages in functional outcomes and adverse events than irradiated allograft in ACL reconstruction; however, there were no significant differences between autograft and nonirradiated allograft in ACL reconstruction. **Level of Evidence:** Level II, meta-analysis of Level I and Level II studies.

Currently, anterior cruciate ligament (ACL) reconstruction has been regarded as the standard treatment procedure for ACL injury by aiming to restore knee stability and improve functional outcomes; however, autograft or allograft in ACL reconstruction remains controversial. The most common choice for autograft is the hamstring tendon because of its lower harvest site morbidity, anterior knee pain, and immune response, as well as greater patient satisfaction.[1-3] In addition, using an allograft can achieve shorter surgical time with no harvest site morbidity and more controllable graft size.[4,5] Allograft, however, has a relatively high rerupture rate, decreased mechanical properties, possible inflammation risk, and potential spread of infectious diseases.[1,2,5-7] The sterilization processes used in allograft may help eliminate or decrease the chance of disease transmission, but there are few satisfactory sterilization methods that do not alter an allograft's biomechanical properties.[8]

Choosing between autograft and allograft in ACL reconstruction remains controversial. Both options offer different advantages and disadvantages. Irradiation as a sterilization method has a certain effect on pathophoresis; however, whether it affects the clinical outcomes after the ACL reconstruction is uncertain. Previous systematic reviews and meta-analyses have compared the outcomes of autograft and allograft in ACL reconstruction[9,10]; however, there are concerns

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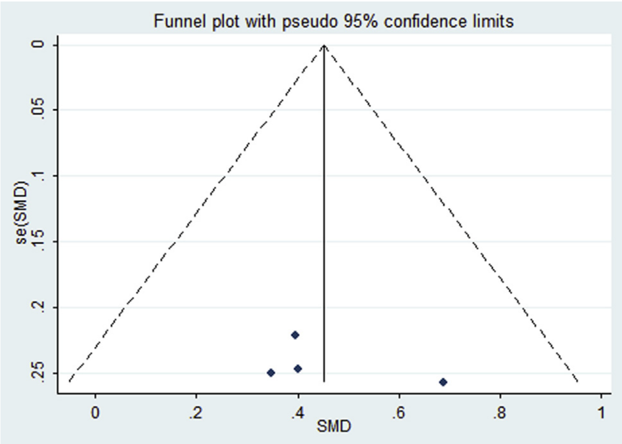

Fig 1. Funnel plot of International Knee Documentation Committee score results. (SE, standard error; SMD, standardized mean difference.)

that the included trials were not all randomized clinical trials or well-organized ones, that there was less focus on complications other than failure and infection rates, and that that there was less attention on different sterilization methods, which have been reported to influence the properties of allografts.[6,11] The purpose of this meta-analysis was to compare the clinical outcomes and adverse events associated with irradiated and nonirradiated allografts in ACL reconstruction. We hypothesized that irradiated allograft possibly resulted in poorer clinical outcomes and more adverse events compared with autograft and nonirradiated allograft.

Methods

A search of the literature was conducted from January 2000 to March 2018 by using the electronic databases Web of Science, PubMed, and EMBASE with the following inputs: “allograft” or “autograft” combined with keywords “anterior cruciate ligament” or “ACL” or “knee.”

The retrieved articles were initially screened for their relevance through title and abstract. The eligibility criteria were (1) Level I and II evidence studies comparing autograft with allograft in ACL reconstruction, (2) a unilateral ACL injury requiring primary ACL reconstruction, (3) adequate statistical power to defect differences with 95% confidence intervals (CIs) and follow-up >80%, and (4) arthroscopic ACL reconstruction. Exclusion criteria were case-control studies, case series, retrospective comparative studies or case reports, history of previous injury or surgery on the same side of the knee, and inadequate follow-up. Two investigators (S.W. C.Z.) examined the articles for inclusion. Disagreements were resolved through discussion among the authors. Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed for further guidance.[12,13]

Furthermore, articles’ full text was obtained and reviewed for its quality based on the *Cochrane Handbook for Systematic Reviews of Interventions*.[14] To determine the possibility of bias, 2 separate observers (S.W., Y.C.) independently examined selection bias, performance bias, attrition bias, detection bias, and reporting bias. Moreover, the level of evidence was determined for each eligible study (as given at http://handbook.cochrane.org/).

Data were extracted separately from the remaining high-quality studies that were all level of evidence I and II, including authors, simple size, age, autograft, allograft, and outcomes that covered the International Knee Documentation Committee (IKDC) score, Tegner score, Lysholm score, and adverse events. Any discrepancies between the extracted data were resolved by consensus.

Two comparisons were made between the group of autograft and nonirradiated allograft and the group of autograft and irradiated allograft and the observation, which contained the IKDC score, Tegner score, Lysholm score, and adverse events such as postoperative infection, arthritic progression, laxity (side-to-side difference >5 mm),[15] reoperation, hypoesthesia of the medial saphenous nerve territory, harvest site tenderness, or irritation. Statistical analysis was performed using Review Manager 5.3 (Cochrane Collaboration, Nordic Cochrane Centre, Copenhagen, Denmark). Dichotomous variables were analyzed using relative risks, and continuous variables were assessed using the mean difference. We reported both variables with 95% CIs and a *P* value <.05, which was considered statistically significant. Heterogeneity between studies was evaluated by the *Q* statistic (significance level of $P < .05$) and I^2 statistic (significance level of $I^2 > 50\%$). A random-effects method was adopted for

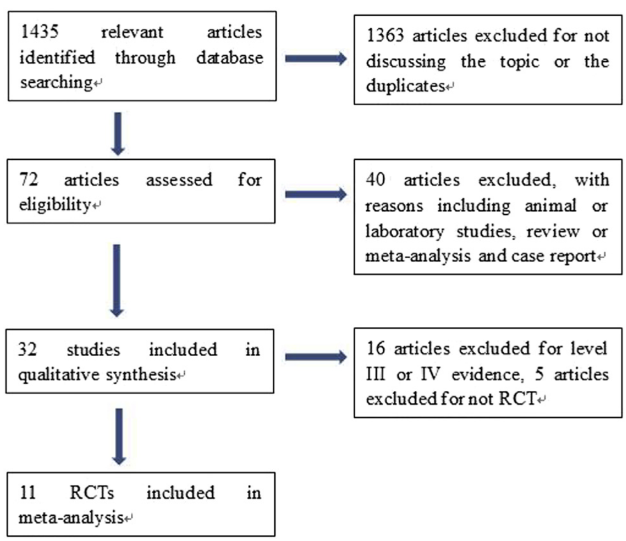

Fig 2. Trial flow. (RCT, randomized controlled trial.)

Table 1. Quality Assessment (Cochrane Risk of Bias Score and Jadad Scale [5 Points])

Authors	Study Design	Selection Bias	Performance Bias	Attrition Bias	Detection Bias	Reporting Bias	Jadad Scale (5 Points)	LOE
Li et al.[11]	RCT	+	+	±	+	+	2	II
Tian et al.[3]	RCT	+	−	−	−	+	3	II
Bottoni et al.[16]	RCT	+	+	±	+	+	5	I
Sun et al.[19]	RCT	+	−	−	−	+	3	II
Sun et al.[18]	RCT	+	−	±	−	+	3	II
Sun et al.[20]	RCT	+	−	+	−	+	3	II
Sun et al.[21]	RCT	+	−	±	−	+	3	II
Tian et al.[6]	RCT	+	−	−	−	+	3	II
Lawhorn et al.[17]	RCT	+	−	−	−	−	2	II
Yoo et al.[22]	RCT	+	+	±	−	+	5	I
Noh et al.[23]	RCT	+	+	±	+	+	2	I

−, high risk; +, low risk; ±, not sure; LOE, level of evidence; RCT, randomized controlled trial.

results pooling if the Q or I^2 value was statistically significant; otherwise, the fixed-effects model was used. In this study, the pooling result of IKDC score showed a statistical power of 89.1% with the available 279 patients for an approximate 3.84 point difference between groups (standard deviation = 10). The funnel plot and Egger test were performed for any publication bias of the pooling results on the IKDC score in the meta-analysis. In this study, the results of funnel plot suggested that there was no presence of publication bias in IKDC score analysis (Fig 1). This was also statistically supported by the Egger test ($P = .511$).

Results

A summary of the study selection process was performed and is shown in Figure 2. The literature search identified 1,435 relevant articles; 1,364 citations were discarded for not fitting the eligibility criteria. After the full text of the remaining 71 articles was verified, 11 studies[3,6,11,16-22] were later included in the quantitative analysis. All studies were randomized controlled trials in which 1,138 patients were enrolled (540 patients for autograft and 598 patients for allograft). The quality of involved studies was determined on the risk of bias, including selection, performance, attrition, detection, reporting bias, and Jadad scale (5 points) (Table 1).These studies were all randomized clinical trials, with 9 studies reporting a detailed randomization method and 2[11,23] declaring randomization. Two studies[16,22] adopted double-blind methods, and 4 studies[3,11,18,20] adopted single-blind methods. Most studies did a qualified follow-up and few patients died during the course of study, especially in the study of Noh et al.[23] However, Lawhorn et al.[17] reported a relatively larger number of patients lost to follow-up without a detailed explanation. All studies involved patients with the clinical outcome scores, and adverse events occurrence were reported with at least 24 months of follow-up. The characteristics of the included studies are summarized in Table 2, and the outcome measures are shown in Table 3.

A total of 1,172 patients were involved (465 autograft and 461 nonirradiated allograft patients; 141 autograft and 138 irradiated allograft patients). The average follow-up varied from 2 years to >10 years. The mean age of patients was between 22 and 32.8 years (range,

Table 2. Characteristics of the Included Studies

Author	No. patients per graft type	Mean Age, yr	Follow-up	Graft Type	Allosterilization
Bottoni et al.[16]	48/49	28.9 ± 5.8/29.2 ± 5.5	10.0-11.0 yr	Hamstring/posterior tibialis	Fresh frozen
Sun et al.[19]	76/80	31.7 ± 6.3/32.8 ± 7.1	4-8 yr	BPTP/BPTP	Fresh frozen
Sun et al.[21]	91/95	29.6 ± 6.9/31.2 ± 8.3	6-10 yr	Hamstring/hamstring	Fresh frozen
Lawhorn et al.[17]	54/48	16.4-53.4	2 yr	Hamstring/anterior tibialis	Fresh frozen
Yoo et al.[22]	68/64	30 (15-62)/24 (13-52)	32.8/34.5 mo	Hamstring/tibialis	Fresh frozen
Noh et al.[23]	33/32	23 (20-51)/22 (20-55)	28.1/31.6 mo	Hamstring/Achilles	Fresh frozen
Tian et al.[6]	62/59	30.5 ± 4.9/29.9 ± 6.1	4.0-5.5 yr	Hamstring/hamstring	Fresh frozen
Li et al.[11]	32/31	29.8 ± 7.9/30.5 ± 6.1	5-7 yr	Hamstring/anterior tibialis	2.5 Mrad irradiation
Tian et al.[3]	40/43	29.2 ± 6.9/28.62 ± 7.2	5.5-8.0 yr	Hamstring/hamstring	2.5 Mrad irradiation
Sun et al.[18]	33/34/32	29.7 ± 7.2/31.8 ± 6.9/30.1 ± 6.2	24-47 mo	BPTP/BPTP/BPTP	Fresh frozen/2.5 Mrad irradiation
Sun et al.[20]	36/31	30.9 ± 8.7/30.3 ± 7.9	41.5 ± 7.6/43.0 ± 7.1 mo	Hamstring/hamstring	2.5 Mrad irradiation

NOTE. Autograft/Allograft; Autograft/Irradiated allograft; Autograft/Allograft/Irradiated allograft.
BPTP, bone−patellar tendon−bone.

Table 3. Outcome Measures of the Included Studies

Author	Outcome Measures
Bottoni et al.[16]	IKDC and Tegner scores
Sun et al.[19]	IKDC, Lysholm, Tegner, and Cincinnati knee scores
Sun et al.[20]	IKDC, Lysholm, and Tegner scores; KT-2000 (MEDmetric, San Diego, CA)
Sun et al.[21]	IKDC, Lysholm, and Tegner scores; Lachman test; KT-2000
Lawhorn et al.[17]	Cincinnati knee score
Yoo et al.[22]	IKDC score, Lachman test
Noh et al.[23]	Lysholm and Tegner scores
Li et al.[11]	IKDC, Lysholm, and Tegner scores
Tian et al.[3]	IKDC, Lysholm, Tegner, and Cincinnati knee scores
Sun et al.[18]	IKDC, Lysholm, Tegner, and Cincinnati knee scores; Lachman test; KT-2000
Tian et al.[6]	IKDC, Lysholm, Tegner, and Cincinnati knee scores

IKDC, International Knee Documentation Committee.

13-62). The types of graft and sterilization are shown in Table 2. The total failure rates were 2.5% (autograft 2.3% with allograft 2.8%; autograft 2.1% with irradiated allograft 2.2%). There was no evidence indicating a difference in polled clinical outcomes between the autograft and nonirradiated allograft groups for the IKDC score (0.68; 95% CI, −1.16 to 2.53; $P = .47$; $I^2 = 0\%$; Fig 3A), Lysholm score (−0.75; 95% CI, −2.08 to 0.58; $P = .27$; $I^2 = 0\%$; Fig 3B), and Tegner score (0.13; 95% CI, −0.08 to 0.34; $P = .24$; $I^2 = 0\%$; Fig 3C).

The clinical adverse events (0.80; 95% CI, 0.56-1.16; $P = .24$; $I^2 = 0\%$; Fig 4) showed no significant differences between autograft and nonirradiated allograft. Adverse events included in this study were postoperative infection, arthritic progression, laxity (side-to-side difference >5 mm), reoperation, hypoesthesia of the medial saphenous nerve territory, harvest site tenderness, or irritation. Six patients in the allograft group revealed late infection through laboratory examinations; all were cured after conservative therapy. In the autograft group, 1 study reported 3 cases (3.2%) that developed hypoesthesia of the medial saphenous nerve territory and 2 cases (2.2%) with harvest site tenderness or irritation. Two comparisons including the Cincinnati knee score and Lachman test showed no significant difference, with $P = .46$ and $P = .564$, $P = .78$ and $P = .968$, respectively.

Meanwhile, compared with the irradiated allograft group, statistically significant differences in favor of autograft were observed for the IKDC score (3.84; 95% CI, 1.93-5.76; $P < .0001$; $I^2 = 0\%$; Fig 5A), Lysholm score (2.94; 95% CI, 0.66-5.22; $P = .01$; $I^2 = 0\%$; Fig 5B), and Tegner score (0.54; 95% CI, 0.20-0.87; $P = .002$; $I^2 = 0\%$; Fig 5C). In terms of adverse events occurrence, we observed a significant difference (0.20; 95% CI, 0.11-0.39; $P < .00001$; $I^2 = 0\%$; Fig 6) between autograft and irradiated allograft. Adverse events included postoperative infection, arthritic progression, laxity (side-to-side difference >5 mm), reoperation, hypoesthesia of the medial saphenous nerve territory, harvest site tenderness, or irritation. Two patients with a superficial wound infection in the irradiated allograft group were cured by antibiotic treatment. Two studies reported 2 (5.6%) and 3 (7.5%) cases of hypoesthesia of the medial saphenous nerve territory; 1 study (2.8%) reported harvest site tenderness or irritation in

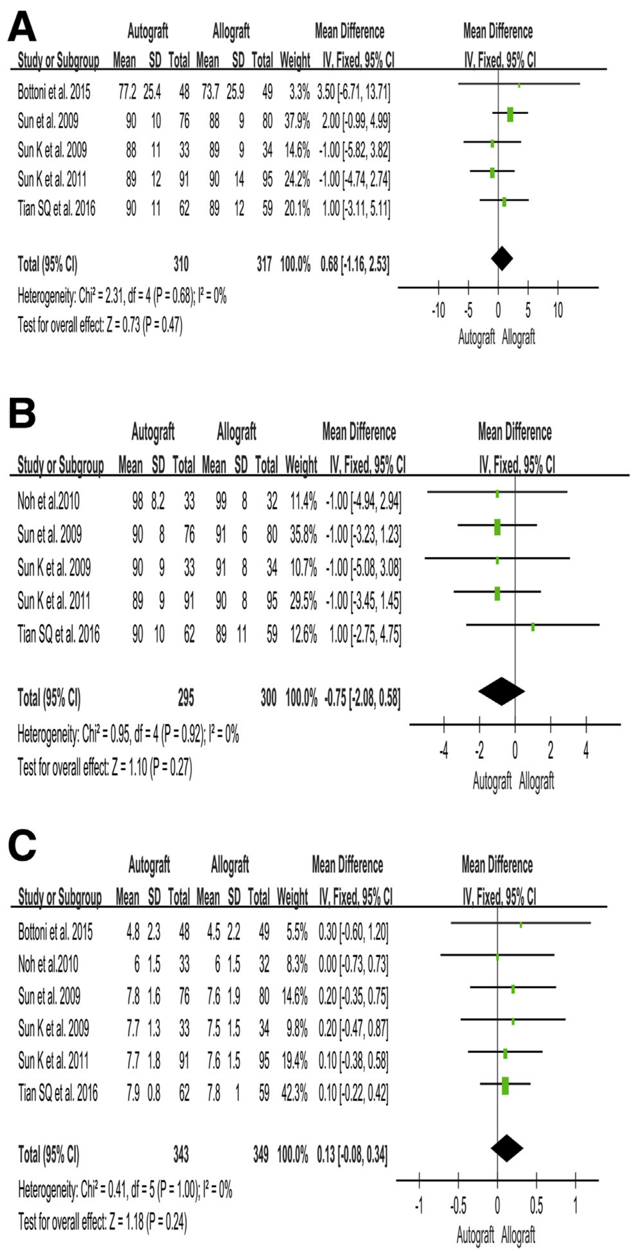

Fig 3. Clinical outcomes between autograft and nonirradiated allograft groups: IKDC (A), Lysholm score (B), and Tegner score (C). There were no statistical differences between autograft and nonirradiated allograft in the IKDC score, Lysholm score, and Tegner score. (CI, confidence interval; df, degrees of freedom; IKDC, International Knee Documentation Committee; IV, inverse variance; SD, standard deviation.)

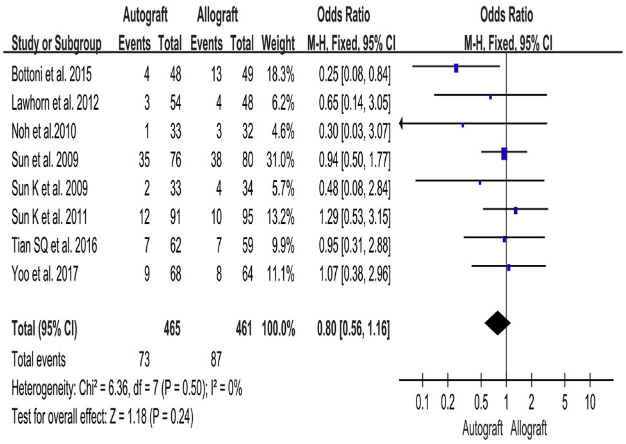

Fig 4. Clinical outcomes between autograft and nonirradiated allograft groups for adverse events occurrence. The odds ratio revealed no difference between autograft and nonirradiated allograft in adverse events occurrence. (CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel method.)

autograft, with 1 (3.2%) irradiated allograft recipient complaining of persistent localized discomfort that disappeared after reoperation. Two studies also observed a significant difference ($P < .001$) in antibiotic treatment and the Lachman test. One study reported longer mean postoperative duration of fever (37.2°C) in the irradiated allograft group (5.3 days vs 2.5 days, $P < .001$). Another study that focused on C-reactive protein and erythrocyte sedimentation rate also reported a statistical increase in the irradiated allograft group on the 3rd, 7th, and 14th days ($P < .05$) after surgery.

A series of sensitivity analysis was conducted and showed there was no particularly influential study among the selected studies. The pooled data gave consistent findings (Table 4).

Discussion

Analysis demonstrated that the irradiated allograft group had poorer performances in IKDC, Lysholm, and Tegner scores and a higher adverse events occurrence rate compared with the autograft group, which further indicated a potential negative effect caused by irradiation. Meanwhile, there was no statistically significant difference between autografts and nonirradiated allografts in IKDC, Tegner, and Lysholm scores or adverse events occurrence. These findings were consistent with previously published literature.[9,10,24,25] Poorer results with irradiated allograft were not only shown in IKDC, Lysholm, and Tegner scores and reoperation rate but also in arthritic progression, laxity (side-to-side difference >5 mm), knee discomfort, and other physical examination, which might play important roles in a patient's rehabilitation.

Previous studies have proposed that a high dose of irradiation could weaken the biological properties. Some studies have confirmed that the influence of irradiation is dose dependent.[26] Fideler et al.[27] reported the result of an in vitro experiment in which, after 2 Mrad irradiation, allograft strength could be reduced by 15%, and after 3 Mrad and 4 Mrad irradiation, the effect could be as high as 24% and 46%, respectively. Bhatia et al.[28] contrasted autografts and 1.2 Mrad

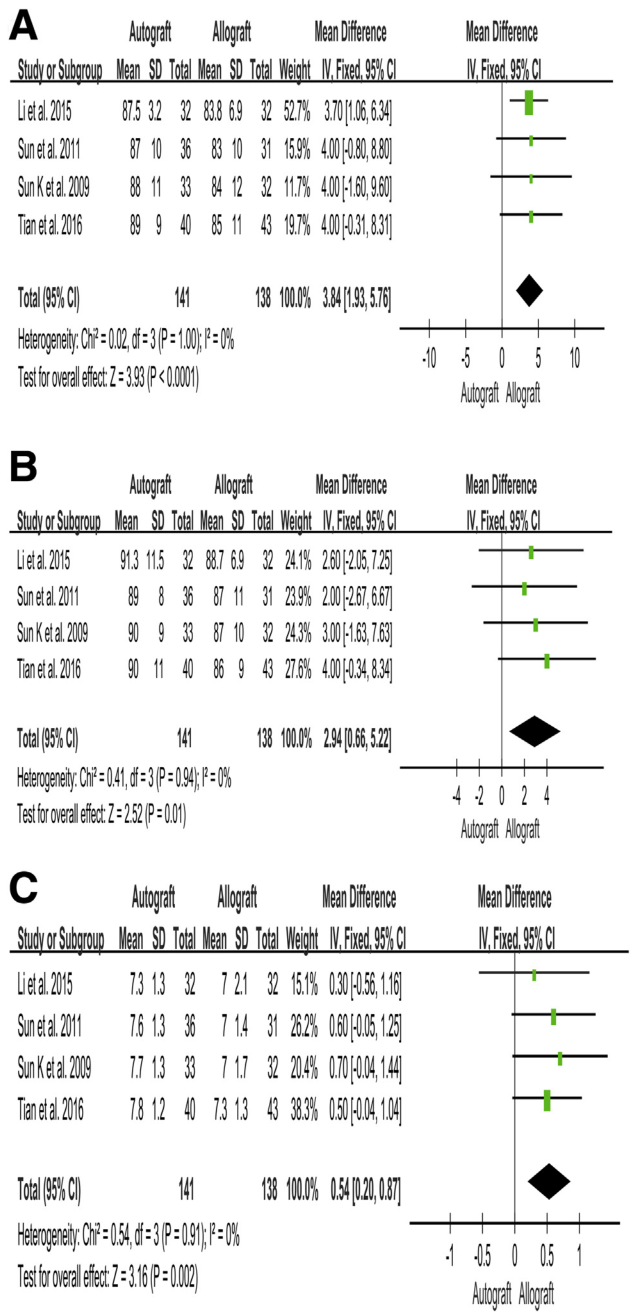

Fig 5. Clinical outcomes between autograft and irradiated allograft groups: IKDC score (A), Lysholm score (B), and Tegner score (C). The mean difference trended higher scores in the autograft group. (CI, confidence interval; df, degrees of freedom; IKDC, International Knee Documentation Committee; IV, inverse variance; SD, standard deviation.)

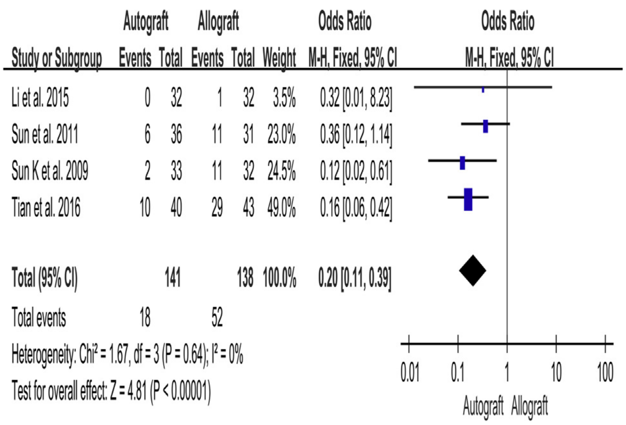

Fig 6. Clinical outcomes between autograft and irradiated allograft groups for adverse events occurrence. The odds ratio trended toward more adverse events occurring in the irradiated allograft group. (CI, confidence interval; df, degrees of freedom; IKDC, International Knee Documentation Committee; M-H, Mantel-Haenszel method.)

irradiated allografts in 48 New Zealand White rabbits. They found no obvious differences in maximum load and stiffness at 2 or 8 weeks after the surgery; however, Yanke et al.[29] found decreased graft stiffness by 20% after low-dose (1.0-1.2 Mrad) gamma irradiation.

Baldini et al.[30] contrasted 2.0 and 2.8 Mrad gamma irradiation and unprocessed allografts in vitro to determine differences in failure stress. They reported no statistically significant difference between the irradiated and nonirradiated groups, with an average load of 29,332.3 N and 2,427.3 N, respectively. This supports our report of an equal failure rate and that irradiation could influence the allograft's remodeling and revascularization process in a host. Although 1 study declared that electron beam irradiation had less influence than gamma irradiation,[31] Schmidt et al.[32,33] reported that electron beam irradiation could lessen biomechanical properties and affect the early remodeling process in sheep models. They found a delay in remodeling and revascularization with some negative changes in biomechanical properties in an electron beam group and cautioned against using irradiated allografts even at a low dose because of substantial changes in remodeling.

Mehta et al.[34] observed that the use of irradiation might lessen a graft's biological capacity in clinical practice. They advised caution and paying more attention to patient notification. Park et al.[5] stated a similar conclusion that nonirradiated allografts have better clinical outcomes than low-dose irradiated (<2.5 Mrad) allografts. In accordance with the U.S. Food and Drug Administration's request, sterility of grafts should be lower than 10^{-3}.[35] To reach this goal, some mechanical properties may have to be sacrificed. Spore-forming bacteria might require 2.1 Mrad irradiation, whereas non–spore-forming bacteria and fungi may require lower doses of 0.5 and 0.8 Mrad, respectively. Human immunodeficiency virus, however, appeared more tenacious; the effective dose varied from 1.5 to 4.0 Mrad, with some cases reporting as high as 5.0 Mrad, which could lead to extensive mechanical property damage.[7,29] At present, we have not come to a convincing agreement in a tissue-processing method, but a combination of physical methods such as irradiation, fresh-frozen preservation, freeze-drying preservation, supercritical carbon dioxide, and chemical methods such as antibiotics, hydrogen peroxide, and chemical washes have been used.[36] Meanwhile, the sterilizing dose was not consistent and was usually calculated by statistical extrapolation, experiencing the worst characteristics, or both.[37] For several decades, 2.5 Mrad was recommended as the terminal sterilization standard; however, the actual given doses of irradiation are still diverse.[38] As a result, the contrast in clinical cases could be more complex.

Limitations

There are several limitations in our study. First, there were only 2 studies that used the double-blind method; more clinical trials are needed.[39] There were 4 studies[18-21] performed by 1 group and 2 studies[3,6] performed by another group. We analyzed the patients' data and found a low risk in overlap, but the generalizability still needs to be discussed. The operation time varied from 2000 to 2011, mostly between

Table 4. Sensitivity Analysis

Outcomes	RR or Mean Difference (95% CI)	*P*	Test for Heterogeneity	No. of Patients	No. of Studies
IKDC	0.68 (−1.16 to 2.53)	.47	0.68	627	5
Lysholm score	0.75 (−2.08 to 0.58)	.27	0.92	595	5
Tegner score	0.13 (−0.08 to 0.34)	.24	1.00	692	6
Adverse events	0.80 (0.56-1.16)	.24	0.50	926	8
IKDC (Ir)	3.84 (1.93-5.76)	<.0001	1.0	279	4
Lysholm score (Ir)	2.94 (0.66-5.22)	.01	0.94	279	4
Tegner score (Ir)	0.54 (0.20-0.87)	.002	0.91	279	4
Adverse events (Ir)	0.20 (0.11-0.39)	<.00001	0.64	279	4

NOTE. (Ir) for autograft and irradiated allograft groups.
CI, confidence interval; IKDC, International Knee Documentation Committee; RR, relative risk.

2004 and 2008. Because techniques and related conceptions developed gradually, we analyzed the heterogeneity but saw no statistical significance; this needs further attention. Moreover, we tried to create some contrasts in different types of grafts; however, there were few data with little reference value. In addition, the allografts are often sterilized by 2 or more types of sterilization methods, leading to difficulty in respective counting. Irradiation dose range also did not have a common standard.[40] The average age of the patients was about 30 years, with the youngest at 13 and the oldest at 62 years; therefore, the conclusions might not be suitable for an older group.

Conclusions

Autograft offered greater advantages in functional outcomes and adverse events than irradiated allograft in ACL reconstruction; however, there were no significant differences between autograft and nonirradiated allograft in ACL reconstruction.

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