No Association Between Donor Variables and Clinically Significant Outcomes, Reoperations, and Failure After Osteochondral Allograft Transplantation

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Background: Mismatch between osteochondral allograft (OCA) donor and recipient sex has been shown to negatively affect outcomes. This study accounts for additional donor variables and clinically relevant outcomes.

Purpose: To evaluate whether donor sex, age, donor-recipient sex mismatch, and duration of graft storage affect clinical outcomes and failure rates after knee OCA transplantation.

Study Design: Cohort study; Level of evidence, 3.

Methods: Patients undergoing knee OCA transplantation between 2003 and 2018 were prospectively followed. Inclusion criteria consisted of primary OCA transplantation and minimum 2-year follow-up. Patient descriptive data and allograft donor sex, age, and graft storage time before implantation were collected. Patients were evaluated for reoperation, failure, and achievement of clinically significant outcomes for International Knee Documentation Committee scores. Reoperation was defined as subsequent surgical intervention of the transplanted allograft, including second-look arthroscopy for graft evaluation, debridement, and loose body removal. Failure was defined as revision of the primary OCA transplantation or conversion to arthroplasty. A Kaplan-Meier curve determined cumulative survivability of OCA transplantations, and log-rank testing was used to compare survivorship between groups. Stepwise regression analysis was utilized to evaluate associations between donor variables and achievement of clinically significant outcomes, reoperation, and failure.

Results: A total of 372 patients undergoing OCA transplantation were included and followed for a mean 5.4 years (SD, 2.7; range, 2.0-16.3). Isolated OCA transplantation was performed in 45% of cases (169/372). A mismatch in donor and recipient sex was present for more female patients (90%) than male patients (10%; $P < .001$). Those who had a sex-mismatched graft more frequently underwent concomitant tibial tubercle osteotomy ($P = .034$). When controlling for patient sex, no other differences were seen between groups matched and mismatched by sex. Univariable and multivariable analysis found no significant difference in survival free from reoperation or failure on the basis of donor-recipient sex mismatch, donor age, or graft storage time before implantation.

Conclusion: In contrast to previous historical data, no donor variables were associated with inferior clinical outcomes in patients who underwent OCA transplantation. These data can help inform graft selection, expedient recipient selection, and outcome optimization after OCA transplantation.

Keywords: articular cartilage; knee; allografts

Focal cartilage defects of the knee are a commonly encountered source of pain, and when left untreated, these lesions may worsen and progress to generalized osteoarthritis.[21] Osteochondral allograft (OCA) transplantation is commonly used to restore focal cartilage defects and potential associated subchondral pathology.[17] This procedure has several advantages over common alternatives, such as autologous chondrocyte implantation, which provides a nonstructural hyaline-like cartilage that must grow and mature following a 2-stage procedure, and osteochondral autograft transplantation, which is usually limited to small isolated defects and has the potential disadvantage of harvest site morbidity.[41] OCA transplantation has

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consistently shown excellent improvements in patient-reported outcomes (PROs), with survival rates as high as 87%, 79%, 73%, and 68% at 5, 10, 15, and 20 years, respectively.[14]

Factors affecting surgical outcomes after knee OCA transplantation have been studied in the past but primarily examine patient-specific pre-, intra-, and postoperative factors. Increased body mass index (BMI), smoking, workers' compensation status, older age, and poor preoperative mental health have all been shown to negatively influence outcomes.[18,23,36,37,43] Patient sex in isolation has historically not shown a difference in PROs, reoperation rates, or failures.[16] Other factors have been investigated, such as preoperative activity level, symptom duration, previous knee procedures, medical comorbidities, concomitant knee lesions, size and location of cartilage defects, and concomitant procedures.

In contrast, OCA survival, as seen through the lens of graft-related risk factors, has received less attention. Within the available basic science literature, prolonged osteochondral allograft storage has been shown to negatively affect chondrocyte viability and cell density.[11,13,20] Recommendations advise implantation of fresh allograft within 42 days of storage, ideally between 24 and 28 days.[35] Clinical studies have recently shown that late implantation has been associated with as much as a 3.4-times greater chance of failure as compared with early implantation.[30]

In contrast to other solid-organ transplantations, which are matched by compatible human leukocyte antigen and blood group types, OCA transplantation does not historically take these factors into account and does not require patients to receive postoperative immunologic suppressive treatments. Cartilage transplantations have long been thought to be appropriate for allogenic transplantation, given their immunoprivileged status as an avascular and aneural tissue.[8,14] There is, however, growing evidence of human leukocyte antigen antibodies forming to the osseous component of the osteochondral graft, although the clinical significance of these antibodies is being elucidated.[12,29]

Other graft-related factors, such as concordant and discordant sex pairings between the donor and recipient, have been minimally studied for OCA transplantation. Donor-recipient sex plays an important role in various other solid-organ transplantations.[4,5,24,33,39] Sex mismatch was associated with an increased risk of pancreatic graft failure, and in heart transplantation, male recipients who received a female graft had increased 1-year mortality (odds ratio, 1.38; 95% CI, 1.31-1.44; $P < .001$).[2,27] Numerous anatomic, immunologic, and hormonal differences between the sexes have been proposed to explain the differences in outcomes seen in solid-organ transplantation.[3,25,44]

To our knowledge, the only published study to correlate outcomes from donor-recipient sex mismatching after OCA transplantation was Merkely et al[31] in 2022. They reported on a cohort of 154 patients at a minimum 2-year follow-up: 102 had same-sex donors while 52 had opposite-sex donors. Briefly, they found a significantly lower graft survival rate for different-sex donor transplants in comparison with same-sex transplants (63% vs 92%; $P = .01$) and a 2.9-times greater failure rate at 5 years ($P = .03$). Subgroup analysis of male-to-male transplantation demonstrated a significantly higher cumulative 5-year survival (94%; $P = .04$), whereas lower survival was found with male-to-female donorship (64%; $P = .04$). Ultimately, their study was sufficiently powered for overall conclusions based on donor-recipient sex mismatch but underpowered for subgroup analysis. The conclusions of their study are potentially profound—if other large series were to find similar clinically substantial outcome differences with sex mismatch, this would merit future efforts to match donors and recipients. However, these findings have yet to be comprehensively evaluated or replicated by another large-sample OCA investigation.

Given the relative paucity of available literature on this topic, the primary purpose of our study was to expand and test the hypothesis that sex-mismatched OCA transplantations increased the risk of failure. As a secondary outcome, we investigated other patient and lesion characteristics and their relationship to failure. We hypothesized that graft survival, reoperation rate, revision rate, and ability to achieve a Patient Acceptable Symptom State (PASS) would not be influenced by donor and recipient sex mismatch but would be driven by other established patient and lesion characteristics, such as age, BMI, defect size, and workers' compensation status.

METHODS

Patient Population

Before study initiation, approval was obtained from the local institutional review board at Rush University Medical Center. A prospectively collected database from a single institution was queried for patients who underwent

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primary OCA transplantation with a single surgeon between January 1, 2003, and January 1, 2018, with minimum 2-year follow-up. Patients were included regardless of the presence of concomitant procedures at the time of OCA transplantation. Patients were included who received multiple plugs in the same compartment (eg, a "snowman" allograft) or different compartments. Indications for OCA transplantation as well as concomitant procedures have been described.[16,28,40] Tibial tubercle osteotomies were generally performed for patients with patellofemoral lesions and a tibial tubercle–trochlear groove distance $\geq$20 mm. All patients underwent an arthroscopy before OCA transplantation. Inclusion criteria consisted of a primary OCA transplantation, a minimum 2-year follow-up, and the presence of allograft donor sex and age and date of allograft expiration. Exclusion criteria consisted of <2-year follow-up, inflammatory arthropathy, and revision OCA transplantation. Patients were evaluated for achievement of clinically significant outcomes as well as reoperation and failure.

International Knee Documentation Committee (IKDC) subjective score surveys were completed preoperatively and at 2-year minimum follow-up. A final postoperative PRO score of 62.1 was utilized for achievement of PASS for IKDC, as previously described.[7] Reoperation was defined as subsequent surgical intervention of the transplanted osteochondral allograft, including second-look arthroscopy for graft evaluation, debridement, and loose body removal. Failure was defined as revision cartilage procedure or conversion to unicompartmental or total knee arthroplasty (UKA and TKA, respectively).

Surgical Technique

All OCA transplantations were performed by the senior author, a fellowship-trained orthopaedic surgeon (B.J.C.) with a high-volume cartilage restoration practice.[10,17,19] Before fresh osteochondral allograft was ordered, staging arthroscopy was performed to assess the extent and location of symptomatic cartilage disease and the presence of concomitant ligamentous or meniscal injury. There was no intentional matching of donor and recipient sex preoperatively. Allografts were accepted per OCA availability and patient surgical scheduling logistics.

Briefly, under general anesthesia, patients were positioned supine on the operating table. After an examination under anesthesia, diagnostic arthroscopic surgery was performed to visually confirm the osteochondral defects and identify any other existing abnormalities. Concomitant procedures, such as meniscectomy, meniscal allograft transplantation, osteotomy, or ligament reconstruction, were performed first to prevent any iatrogenic injury to the newly restored articular cartilage. The goal of tibial tubercle osteotomies was to normalize the tibial tuberosity–trochlear groove distance to a range of 10 to 15 mm.[15] Fresh osteochondral allografts of the distal femur or patella (ie, 15-28 days after harvest) were thawed in room temperature saline on the back table. A majority of osteochondral allografts were obtained from JRF Ortho, which processes allografts within 48 hours of tissue recovery. After a swab culture was taken from the allograft, it was placed in an antibacterial nutrient medium. Once stored, allografts must be used within 28 days. In rare cases where an allograft could not be obtained, other suppliers were contacted (RTI Surgical or CryoLife). A lateral parapatellar arthrotomy with soft tissue lengthening or limited medial vastus-sparing arthrotomy was performed for exposure. For patellar defects, a lateral approach was employed and the patella was everted. A cannulated cylindrical sizing guide was placed over the defect to determine the diameter of donor allograft needed. A guide pin was inserted through the cannulated sizing guide in the center of the defect. The sizing guide was removed, and a cannulated bone reamer was placed over the guide pin to ream to a depth of 6 to 8 mm. Copious irrigation was utilized whenever reaming to prevent thermal necrosis. The reamer and guide pin were removed, and a small ruler was used to measure the depth of the 4 quadrants (3-, 6-, 9-, and 12-o'clock).

On the back table, the donor allograft was prepared, and a bushing was firmly held by an assistant over the desired harvest location. A donor harvester was used to create an allograft cylinder that matched the reamed diameter. Graft measurements were marked out on the donor plug, and the donor allograft was trimmed to the appropriate depth using an oscillating saw, rasp, and rongeurs. Pulsatile lavage with bacitracin-mixed saline was used for 2 minutes over the donor plug. The donor plug was then press-fit by hand, with care to ensure that the 12-o'clock position on the graft and recipient site was matched. An oversized tamp was used to gently impact the plug flush to the surrounding articular surface. After graft implantation and copious irrigation, layered wound closure was performed and a hinged knee brace applied.

Rehabilitation Protocol

Rehabilitation protocols differed between those undergoing patellar and distal femoral OCA transplantation.[40,42] Patients who underwent distal femoral OCA transplantation began heel-touch weightbearing between postoperative weeks 0 and 6. For the first 2 weeks, patients performed all activities while wearing a knee immobilizer brace, which was then removed. The brace was locked in full extension when not exercising. For postoperative weeks 0 to 2, exercise consisted of quad sets, patellar mobilization, calf pumps, and straight leg raises. When not bearing weight, knee flexion was limited to 0° to 90°. Patients progressed to full weightbearing as tolerated during weeks 6 to 8 postoperatively. Closed kinetic chain exercises were introduced gradually. After 12 weeks, elliptical biking and swimming were encouraged. At 6 to 12 months, a gradual return to functional activities was permitted. Patients were cleared by the attending physician to resume full activity by 8 months postoperatively. Minor adjustments were made to the rehabilitation protocol based on concomitant procedures performed.[10,17,19,42]

TABLE 1
Patient Characteristics and Intraoperative Variables: Osteochondral Allograft Transplantation, 2-Year Minimum Follow-up[a]

Variable	Allograft Donor-Recipient Sex, No. (%) or Mean ± SD		*P* Value
	Matched (n = 217)	Mismatched (n = 155)	
Sex			<.001[b]
Female	60 (28)	139 (90)	
Male	157 (72)	16 (10)	
Age, y	30.9 ± 9.7	31.5 ± 9.9	.673[c]
BMI, kg/m^2			
Male	27.9 ± 4.3	27.6 ± 4.2	.588[c]
Female	24.8 ± 3.8	25.7 ± 4.1	.217[c]
Laterality			.313[b]
Left	88 (40)	71 (46)	
Right	129 (59)	84 (55)	
Smoking status			.783[b]
Current	14 (6.5)	13 (8.4)	
Former	8 (3.7)	5 (3.2)	
Never	195 (90)	137 (88)	
No. of previous surgical procedures	2.61 ± 1.56	2.68 ± 1.40	.337[c]
MFC	115 (53)	75 (49)	.381[b]
LFC	92 (42)	65 (42)	.971[b]
Trochlea	26 (12)	14 (9.0)	.365[b]
Patella	24 (11)	25 (16)	.154[b]
Defect diameter, mm	19.9 ± 4.4	18.7 ± 3.7	.009[c]

[a]BMI, body mass index; LFC, lateral femoral condyle; MFC, medial femoral condyle.
[b]Pearson chi-square test.
[c]Wilcoxon rank sum test.

Statistical Analysis

Statistical analyses were performed using RStudio Version 4.1.1. Descriptive statistics for continuous variables were reported as means with standard deviations, whereas binomial variables were presented as frequencies and proportions. Chi-square and Fisher exact tests were utilized for comparing categorical variables. Shapiro-Wilk testing determined normality of the data, and Mann-Whitney *U* or independent samples *t* test was used accordingly for comparing continuous variables. Kaplan-Meier survival analysis was utilized to determine survival probabilities, which were compared between groups by log-rank testing.

A multivariable logistic regression was performed in a stepwise fashion to determine donor variable associations with achieving the PASS for the IKDC questionnaire, as well as reoperation and failure. Patient variables were assessed for inclusion in the regression models: age, athlete status, BMI, concomitant procedures (ligament or meniscal surgery, cartilage procedure at a separate location, or osteotomy), defect location and size, leg laterality, number of previous surgical procedures within the index knee, number of grafts placed, medical history (diabetes mellitus, hypertension, and thyroid disease), traumatic cause, sex, smoking status, symptom duration, and use of orthobiologics. Donor variables also assessed: age, sex, duration of graft storage (as a linear variable between 14 and 28 days), and a mismatch between donor and recipient sex. An a priori power analysis was performed according to an alpha of .05 and power of 0.80 to detect a survival difference based on a donor-recipient sex mismatch through univariable Cox regression analysis. Using previously reported hazard ratios of 2.87, 2.63, and 1.90, sample sizes were determined for the overall cohort (n = 98) and for subgroup analyses based on female (n = 167) and male (n = 610) recipients.

RESULTS

Patient Characteristics

Of 455 eligible patients undergoing OCA transplantation in the studied period, 372 met study inclusion criteria (82% follow-up) and were followed for a mean ± SD 5.4 ± 2.7 years (range, 2.0-16.3). At the time of surgery, the mean age and BMI were 31.2 ± 9.8 years and 26.6 ± 4.3 kg/m^2 (Table 1). At final follow-up, 129 patients (35%) had undergone repeat OCA transplantation–associated intervention, while 12% (44/372) met criteria for OCA failure.

Mean graft storage time before implantation was 24.3 ± 2.8 days (median, 25; range, 14-28). A mismatch between donor and recipient sex was noted for 139 of 199 (70%) female and 16 of 173 (9%) male patients, highlighting the relative preponderance (79.6%) of male OCA donors. A greater proportion of those with a recipient-donor sex

TABLE 2
Surgical Variables and Donor Characteristics[a]

Variable	Allograft Donor-Recipient Sex, No. (%) or Mean ± SD		
	Matched, N = 217	Mismatched, N = 155	*P* Value
Major concomitant procedure	119 (55)	84 (54)	.902[b]
Ligament repair or reconstruction	14 (6.5)	5 (3.2)	.164[b]
Meniscal allograft transplantation			
Lateral	53 (24)	40 (26)	.761[b]
Medial	40 (18)	20 (13)	.153[b]
Osteotomy			
Any	43 (20)	31 (20)	.965[b]
High tibial	22 (10)	8 (5.2)	.082[b]
Distal femoral	10 (4.6)	6 (3.9)	.730[b]
AMZ with TTO	11 (5.1)	17 (11)	**.034**[b]
Marrow stimulation	16 (7.4)	9 (5.8)	.552[b]
ACI	0 (0)	2 (1.3)	.173[c]
BMAC	21 (9.7)	23 (15)	.129[b]
Platelet-rich plasma	4 (1.8)	3 (1.9)	>.999[c]
Donor age, y	23.4 ± 6.4	22.0 ± 5.9	**.043**[d]
Days left before graft expiration	3.60 ± 2.82	3.85 ± 2.80	.408[d]
Subsequent reoperation	73 (34)	56 (36)	.688[b]
Graft failure	36 (17)	27 (17)	.849[b]
Revision OCA or TKA	25 (12)	19 (12)	.925[c]

[a]Bold indicates $P < .05$. ACI, autologous chondrocyte implantation; AMZ, anteromedialization; BMAC, bone marrow aspirate concentrate; OCA, osteochondral allograft; TKA, total knee arthroplasty; TTO, tibial tubercle osteotomy.
[b]Pearson chi-square test.
[c]Fisher exact test.
[d]Wilcoxon rank sum test.

mismatch were female (90% vs 10%; $P < .001$), had a younger allograft donor age (21.9 ± 5.8 vs 23.5 ± 6.4; $P = .043$), more frequently underwent concomitant anteromedialization with a tibial tubercle osteotomy (5% vs 11%; $P = .034$), and had a smaller defect size (18.7 ± 3.7 vs 19.9 ± 4.4 mm; $P = .009$) (Table 2). Women were more likely to have an elevated tibial tuberosity–trochlear groove distance and therefore undergo tibial tubercle osteotomy ($P = .03$). The difference in defect size was not significant when controlling for sex ($P \geq .173$).

Clinically Significant Outcomes

Final postoperative subjective IKDC scores were available for 232 patients (62%), of which 149 met criteria for the PASS (68%; 157/232). After patient variables predictive of achieving the PASS for the subjective IKDC questionnaire were assessed, performance of a major concomitant procedure, workers' compensation status, and trochlear OCA transplantation were included in the final model (Table 3). No donor variables were predictive of achieving the PASS.

Reoperations

At final follow-up, 129 patients (35%) had undergone repeat OCA transplantation–associated intervention (second-look arthroscopy for graft evaluation, articular cartilage debridement, or loose body removal). Among those in the mismatch and matched groups, 37% (56/149) and 35% (73/211) underwent a reoperation, respectively. Overall survival free from reoperation was 88.6%, 77.4%, 66.3%, and 57.3% at 1, 2, 5, and 10 years (Figure 1), with no significant difference in survival free from reoperation between those who did and did not have a recipient-donor sex mismatch ($P = .121$; hazard ratio [HR], 1.322 [95% CI, 0.756-1.881]) on univariable Cox regression analysis (Table 4). Recipient variables predictive of reoperation included concomitant anteromedialization osteotomy ($P = .036$), defect size ($P = .036$), and workers' compensation status ($P = .021$). No donor variables significantly predicted subsequent reoperation after univariable analysis and inclusion in the final model. Similarly, there were no significant differences in survival distributions upon subgroup analysis by patient (recipient) sex ($P = .189$; HR, 1.266 [95% CI, 0.890-1.801]).

Failures

A total of 12% (44/360) of patients met criteria for OCA transplantation failure at a mean 3.8 ± 2.9 years after index surgery (range, 0.6-12.8). The most common criterion met at the time of failure was TKA or UKA (50%; n = 22) or revision OCA transplantation (50%; n = 22). Survival free of failure (revision cartilage procedure or UKA/TKA) was 99.0%, 95.5%, 89.6%, and 80.4% at 1, 2, 5, and 10 years,

TABLE 3
Clinically Significant Outcomes for IKDC Subjective Form[a]

Variable Included in Model	*P* Value		Odds Ratio (95% CI)
	Univariable	Multivariable	
MCID			
Sex: female	**.008**	**.004**	**3.587 (1.535-9.023)**
No. of previous surgical procedures	**.010**	**.005**	**0.620 (0.440-0.859)**
Days in storage: linear[b]	.643	.739	1.025 (0.887-1.196)
Donor age	.078	.162	0.952 (0.887-1.020)
Donor sex: female	.100	.073	4.400 (1.041-30.810)
Donor-recipient sex mismatch	.631	.369	0.599 (0.188-1.819)
PASS			
Trochlear defect	**.014**	**.028**	**0.348 (0.132-0.891)**
Workers' compensation	**.023**	**.047**	**0.393 (0.154-0.993)**
Days in storage: linear[b]	.153	.192	0.932 (0.837-1.037)
Donor age	.210	.168	0.966 (0.918-1.015)
Donor sex: female	.200	.185	3.174 (0.705-9.012)
Donor-recipient sex mismatch	.342	.342	0.758 (0.428-1.345)
SCB			
Sex: female	**.003**	**.030**	**2.718 (1.393-5.402)**
Meniscal allograft transplantation	**.024**	**.004**	**0.471 (0.236-0.927)**
Days in storage: linear[b]	.194	.208	0.924 (0.818-1.047)
Donor age	.086	.101	0.954 (0.900-1.009)
Donor sex: female	.120	.083	2.615 (0.981-7.532)
Donor-recipient sex mismatch	.321	.282	0.619 (0.250-1.454)

[a]Regression analysis of variables associated with meeting MCID, PASS, and SCB for the IKDC. Variables were included in the final model if they achieved an alpha value <.15. Bold indicates $P < .05$. IKDC, International Knee Documentation Committee; MCID, minimal clinically important difference; PASS, Patient Acceptable Symptom State; SCB, substantial clinical benefit.
[b]Duration of graft storage was assessed as a linear variable (14-28 days of storage) or binomial variable (≥25 days).

TABLE 4
Stepwise Cox Regression for Reoperation[a]

Variable Included in the Final Model	*P* Value		Hazard Ratio (95% CI)
	Univariable	Multivariable	
ACLR	.149	.141	0.183 (0.009-1.213)
AMZ	.104	.036	2.436 (1.056-1.118)
Defect size	.110	.036	1.059 (1.003-1.118)
No. of previous surgical procedures	**.0008**	**.00005**	1.423 (1.205-1.700)
Workers' compensation	**.022**	**.021**	1.435 (1.211-1.721)
Donor age	.259	.400	1.016 (0.978-1.055)
Donor sex: female	.794	.997	0.999 (0.548-1.787)
Mismatch	.651	.830	1.053 (0.654-1.689)
Time to expiration[b]			
Linear, 14-28 d	.448	.532	1.028 (0.942-1.121)
Binomial, ≥25 d	.693	.783	0.947 (0.641-1.397)

[a]Stepwise Cox proportional hazards regression analysis of variables associated with undergoing a reoperation of the index cartilage defect. Variables were included in the model if their alpha value was <.15. Osteochondral allograft donor variables were subsequently added to the model and their *P* values and hazard ratios recorded. Bold indicates $P < .05$. ACLR, anterior cruciate ligament reconstruction; AMZ, anteromedialization.
[b]Duration of graft storage was assessed as a linear variable (14-28 days) or binomial variable (≥25 days).

respectively (Figure 2). The 5-year survivability was lowest for female-to-male OCA transplantations (78.8%), followed by male to male (87.9%), male to female (90.1%), and female to female (96.3%), with no significant difference in survival distributions between patients who had a sex-matched or sex-mismatched graft ($P = .569$). Similarly, there were no significant differences in survival distributions upon subgroup analysis by patient sex ($P = .428$).

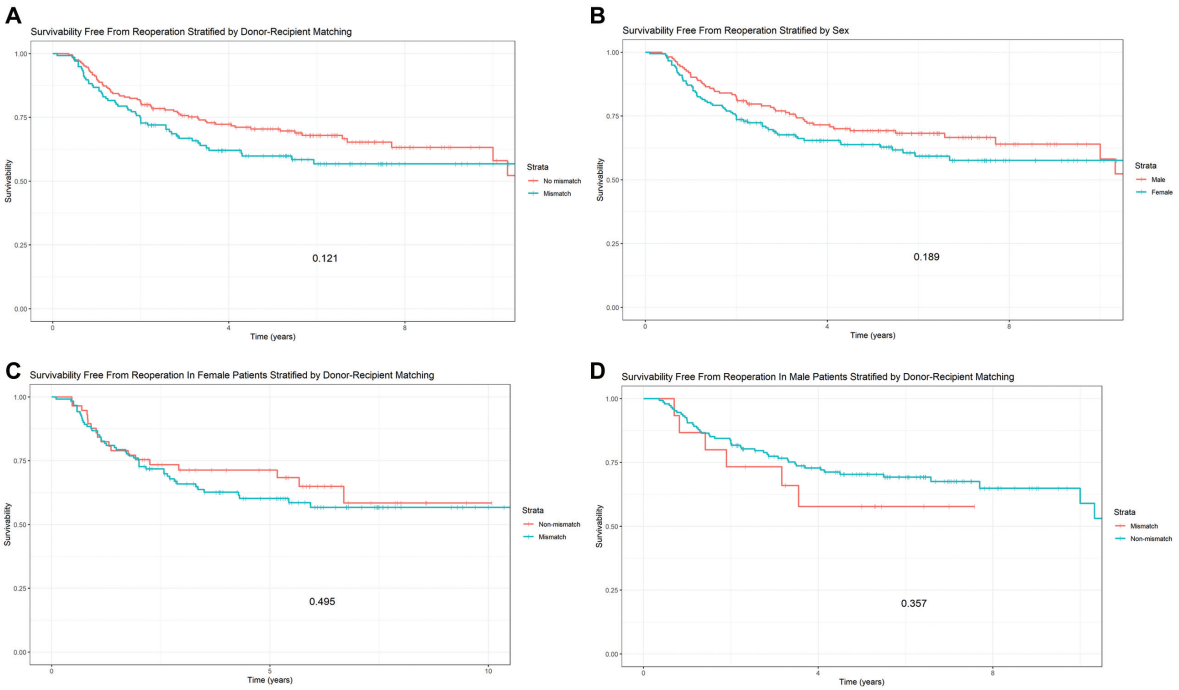

Figure 1. Kaplan-Meier survival analysis for reoperation was stratified as follows: (A) recipient-donor groups mismatched or matched by sex; (B) male and female patient sex; and subgroup analysis of (C) female and (D) male patients by recipient-donor groups mismatched or matched by sex. Overall survival free from reoperation was 88.6%, 77.4%, 66.3%, and 57.3% at 1, 2, 5, and 10 years, respectively. The log-rank test did not demonstrate a significant difference in survival distributions free from reoperation between those who did and did not have a recipient-donor sex mismatch.

TABLE 5
Stepwise Cox Regression for Failure[a]

Variable Included in Model	*P* Value		Hazard Ratio (95% CI)
	Univariable	Multivariable	
Diabetes mellitus	.080	**.018**	6.329 (1.364-29.368)
Concomitant LMAT	0.061	**.035**	0.393 (0.165-0.936)
No. of previous surgical procedures	**.002**	**.006**	1.212 (1.056-1.391)
Particulated juvenile cartilage	.091	.052	7.411 (0.984-55.803)
Symptom duration	**.0005**	**.002**	1.071 (1.024-1.120)
Donor age	.773	.491	1.018 (0.967-1.071)
Donor sex: female	.615	.941	0.969 (0.425-2.211)
Mismatch	.569	.752	1.106 (0.589-2.077)
Time to expiration[b]			
Linear, 14-28 d	.684	.542	1.034 (0.927-1.153)
Binomial, ≥25 d	.121	.065	0.523 (0.263-1.043)

[a]Stepwise Cox proportional hazards regression analysis of variables associated with undergoing a failure of the index cartilage defect. Failure was defined as a subsequent revision cartilage procedure or total or unicompartmental knee arthroplasty. Variables were included in the model if their alpha value was <.15. Osteochondral allograft donor variables were subsequently added to the model and their *P* values and hazard ratios recorded. Bold indicates $P < .05$. LMAT, lateral meniscal allograft transplantation.
[b]Duration of graft storage was assessed as a linear variable (14-28 days) or binomial variable (≥25 days).

Recipient variables predictive of failure included diabetes mellitus ($P = .018$), increased number of previous surgical procedures ($P = .006$), and longer symptom duration ($P = .002$). Concomitant lateral meniscal transplantation was, however, protective against subsequent failure ($P = .035$). No donor variables significantly predicted subsequent failure after univariable analysis and inclusion in the final Cox regression model (Table 5).

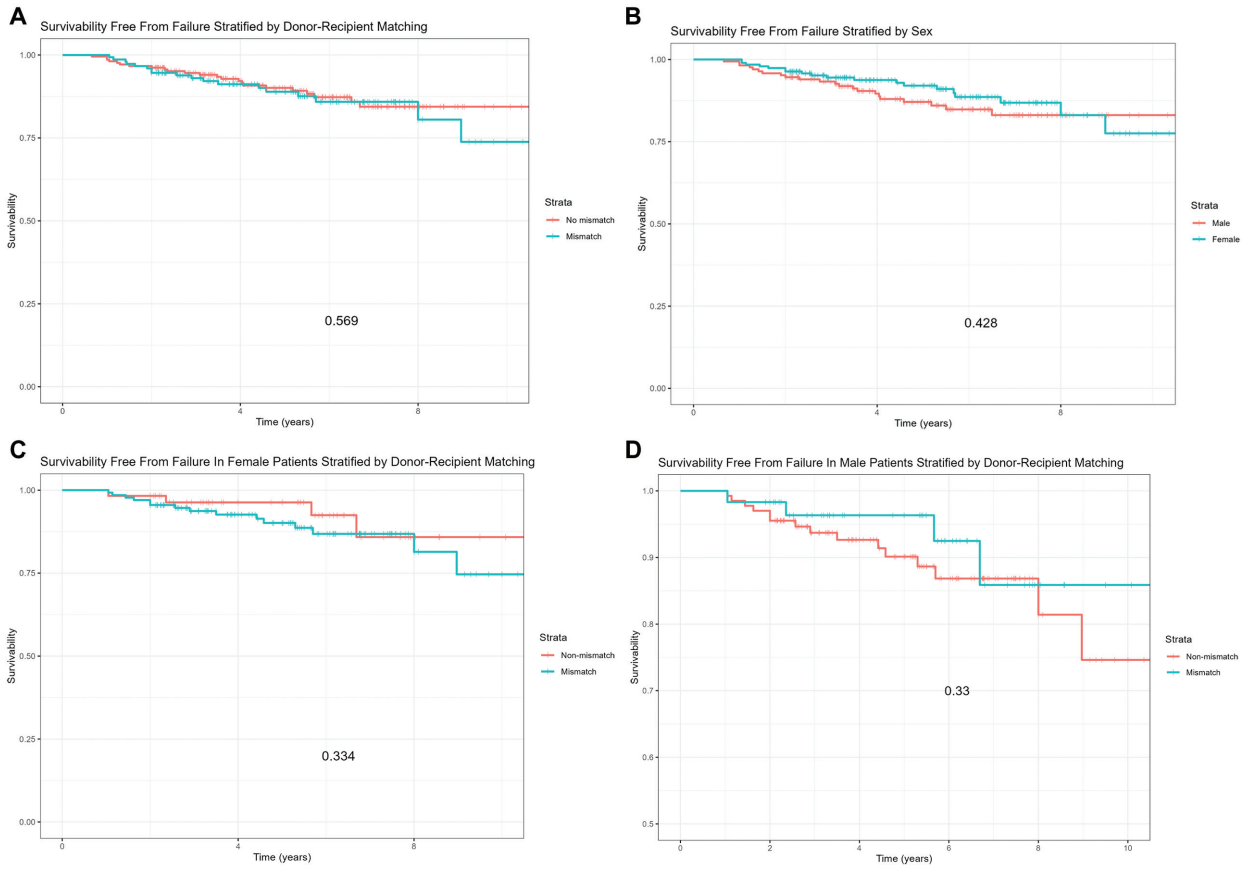

Figure 2. Kaplan-Meier survival analysis of failures after osteochondral allograft transplantation was stratified as follows: (A) recipient-donor groups mismatched or matched by sex; (B) male and female patient sex; and subgroup analysis of (C) female and (D) male patients by recipient-donor groups mismatched or matched by sex. Overall survival free from reoperation was 99.0%, 95.5%, 89.6%, and 80.4% at 1, 2, 5, and 10 years, respectively. The log-rank test demonstrated no significant difference in survival distributions between patients who had a sex-matched and sex-mismatched graft (P = .569).

DISCUSSION

The purpose of our study was to evaluate whether donor and recipient factors such as donor age, sex mismatch, and duration of graft storage affect clinical outcomes and failure rates after knee OCA transplantation. The primary finding from this investigation was that there is no substantial difference in terms of clinically significant outcomes, reoperations, or failures after OCA transplantation for patients who received a graft from a donor of the opposite sex. Additionally, donor age and graft storage time before implantation were not predictive of clinical outcomes.

While commonly described as immunoprivileged, osteochondral allografts have been shown to be antigenic, yet the clinical effect of this antigenic response remains unclear.[22] In a 2014 study, Hunt et al[22] described an increased prevalence of anti–human leukocyte antigen class I antibodies among patients who received relatively larger osteochondral allografts. Similar to the present study, patients were included with a 2-year minimum follow-up, and failure was defined as revision allografting or conversion to any form of arthroplasty. Ultimately, Hunt et al did not find an association between the presence of anti–human leukocyte antigen class I antibodies and subsequent failure or inferior PROs.

Recent clinical studies examining inferior outcomes with nonmatched allografts have focused on the role of sex mismatches, given the importance of this for the transplantation of other organs.[27,39,44] In liver transplantation, male recipients who had an allograft from a female donor demonstrated an increased risk of graft failure and mortality.[26] In those undergoing pancreas-kidney transplantation, those who received allografts from a female donor had inferior survivability.[9] In a large database study of 24,195 pancreas transplantations, Li et al[27] reported inferior graft survivorship in those with a sex-mismatched graft (HR, 1.09; $P < .001$). Conversely, various large case series and database studies have demonstrated no survivability difference when a donor-recipient sex mismatch is present.[1,32] Mechanisms by which mismatches portend to higher failure rates include sensitization to antigens expressed by the male sex, such as the H-Y antigen.[6] Specific to orthopaedics, Merkely et al[31] described increased

failure rates at a 2-year minimum among patients who received a sex-mismatched OCA. In their study, they found inferior cumulative 5-year survivorship among female patients who received a male graft (P = .04; HR, 2.63 [95% CI, 1.03-6.69]). Proposed mechanisms behind inferior survivability were multifactorial but included minor histocompatibility antigen H-Y, differences in graft radius of curvature, tissue architecture, histologic composition, and others. It should be noted that allografts in the study by Merkely et al were from the same supplier that provided most of the allografts in the present study (JRF Ortho), which helps to control for any possible differences in allograft cleansing and processing. Reoperation rates and association with CSOs were not examined by Merkely et al. The present study differs from that of Merkely et al in several notable aspects. While survival analyses were performed similarly to the present study, the failure definition differed in that it included subchondral collapse of the OCA on postoperative magnetic resonance imaging or arthroscopy. Several patients who did not meet criteria for failure did have evidence of partial graft collapse on second-look arthroscopy, yet at 2 years postoperatively after debridement, they achieved the PASS and had not undergone any subsequent reoperation. Additionally, in the study by Merkely et al, the covariates for multivariable regression analysis of failure were age, graft size, and BMI. These variables were chosen because they have been commonly associated with clinical outcomes. The present study did not find a similar association between sex-mismatched grafts and increased failure rates. Additionally, patients did not have a significant increase in reoperation rates or inferior PROs.

Apart from mismatches in donor sex, worse outcomes after OCA transplantation with increased graft storage time have been described. In a 2017 study, Nuelle et al[34] reported on 75 patients and assessed whether donor age and duration of OCA storage affected visual analog scale scores. Those with inferior scores tended to have grafts with longer storage times (P = .048). However, in their group, OCAs were held in storage up to 45 days, and only 31 patients had a minimum 2-year follow-up. The study did not assess reoperation and failure rates or the effect of donor sex on outcomes. Conversely, in a study of 111 patients at 2-year minimum follow-up, storage times between 25 and 28 days had a 3.4-times greater likelihood of failure as compared with $\leq$24 days.[30] Last, Schmidt et al[38] performed a matched-pair analysis comparing 75 patients who had allografts transplanted within <14 days of storage (mean, 6.3 days) versus those with 16 to 28 days of storage time (mean, 20.0 days). Those with a shorter storage time exhibited a higher rate of failure (defined as revision OCA transplantation or conversion to arthroplasty) than those stored for $\geq$16 days (P = .036), which may be attributed to the longer follow-up for patients in the early-transplant cohort (11.9 vs 7.8 years). This difference was not seen on Kaplan-Meier survivorship curves (P = .321), and no other differences in reoperation rates or postoperative PROs were identified. The present study similarly suggests noninferiority in patients who receive grafts with longer storage times, as graft storage beyond 25 days was not seen to significantly affect PROs, reoperations, and failures. However, our findings must be viewed in light of a relatively expedited time to transplantation. Therefore, the effect of prolonged storage times is not well represented in our sample, for which the longest time was 28 days.

The effect of donor age on outcomes after OCA transplantation is not well described. In the study by Nuelle et al,[34] there was no significant difference in donor age between those with a successful and unsuccessful outcome (mean, 22.7 and 22.0 years, respectively; P = .83). In the present study, a significant difference in donor age was noted between cohorts, with younger donors seen in the sex-mismatch cohort (P = .043). However, on univariate and multivariate analysis, donor age was not predictive of clinical outcomes.

Limitations

This study is not without limitations. Although we were adequately powered for the overall cohort survival analysis, we were not powered for the male recipient subgroup analysis. In the present study, most allograft donors were male and thus few male patients received a sex-mismatched graft. Radiographic findings were not utilized as part of the failure criteria in this study, which may limit comparisons to studies with alternative definitions of failure, such as progression of radiographic arthritis. Patients in this study were treated by a single surgeon at a high-volume institution, which potentially limits the generalizability of these findings for patients undergoing primary OCA transplantation at other institutions or nonacademic centers. Not all PROs were available for patients in this study, which may introduce a selection bias. Finally, all retrospective reviews are subject to the inherent biases related to recall and complete record keeping.

CONCLUSION

In contrast to previous historic data, no substantial survival difference was observed for sex-mismatched OCA donors and recipients in terms of reoperation or failure. Of note, increased PASS achievement was noted at final follow-up for female graft donors. These data can help inform graft selection, expedient recipient selection, and outcome optimization after OCA transplantation.

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