Incidence, Timing, and Risk Factors for 5-Year Revision Surgery After Autologous Chondrocyte Implantation in 533 Patients

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Background: Autologous chondrocyte implantation (ACI) can be used to treat focal, full-thickness chondral defects of the knee. However, there is limited large-sample evidence available regarding the incidence, timing, and risk factors for revision surgery after ACI.

Purpose: To assess the 5-year incidence, timing, and risk factors for revision surgery after ACI in a large national cohort.

Study Design: Case series; Level of evidence, 4.

Methods: The 2010-2020 PearlDiver database was queried for patients aged 20 to 59 years who underwent primary ACI of the knee without previous chondral procedures or knee arthroplasty. Revision surgery was defined as subsequent revision ACI, osteochondral allograft transplantation, osteochondral autograft transfer, unicompartmental knee arthroplasty, or total knee arthroplasty within 5 years. Kaplan-Meier analysis was used to assess both incidence and timing of revision surgery. Risk factors evaluated for revision surgery included patient age, sex, body mass index (BMI), Elixhauser Comorbidity Index (ECI) score, and previous or concomitant bony realignment procedures.

Results: In total, 533 patients underwent primary ACI and met inclusion criteria. The 5-year incidence of revision surgery was 10.3%, with 63% of revisions occurring in the first 2 years after surgery. Risk factors associated with revision surgery included female sex (odds ratio, 2.58; 95% CI, 1.22-5.45; $P = .013$) and BMI $\geq$35 (odds ratio, 2.24; 95% CI, 1.01-4.94; $P = .047$). There was no relationship between age, ECI score, or previous or concomitant bony realignment procedures and revision surgery at 5 years ($P > .05$).

Conclusion: In an analysis of 533 patients who underwent ACI, 10.3% required a subsequent articular cartilage procedure or conversion to knee arthroplasty in the first 5 postoperative years. Revision surgery was greatest in the first 2 postoperative years. Female sex and severe obesity (BMI, $\geq$35) were associated with increased risk of revision surgery, while age, ECI score, and previous or concomitant bony realignment procedures were not. These findings suggest that treatment of chondral defects of the knee with ACI is associated with durable outcomes at the 5-year follow-up.

Keywords: autologous chondrocyte implantation; 5-year survivorship; revision surgery; risk factors

Chondral and osteochondral lesions of the knee are common, with a reported prevalence of up to 66% in patients undergoing knee arthroscopy.[2,11,19,25] The avascular nature of articular cartilage limits the capacity of these lesions for self-repair.[43] Consequently, these defects, if untreated, may lead to progression to osteoarthritis and the need for total knee arthroplasty (TKA) at an early age.[32,35] Surgical treatments for symptomatic, focal chondral defects have included debridement, microfracture, osteochondral allograft transplantation (OCA), and osteochondral autograft transfer (OAT).[20,22,24]

Autologous chondrocyte implantation (ACI) was first reported as an alternative approach to treat symptomatic focal, full-thickness chondral defects and osteochondral lesions of the knee in 1994.[8,36] ACI is a 2-stage, cell-based cartilage repair procedure that begins with an arthroscopic biopsy of healthy chondral tissue followed by in vitro culture expansion; an open or arthroscopic procedure is then employed to implant the cultured chondrocytes into the cartilage defect. This procedure aims to restore joint

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function and reproduce the hyaline-like articular cartilage surface. Since it was first reported, ACI has been increasingly employed, particularly in younger, active patients with defects exceeding 2.5 cm^2.[10,41]

Metrics used to assess outcomes after ACI have varied from the assessment of postoperative knee pain and/or functional scores to magnetic resonance imaging (MRI) and overall graft survivorship rate, with estimates of procedural failure (ie, poor functional outcomes, graft delamination, reoperation) ranging from 8% to 25% at a minimum of 4 years.[‖] These variable definitions of procedural efficacy complicate assessment of ACI success and graft durability. The need for a subsequent salvage procedure addressing the same articular surface is a clear indication of ACI failure. Specifically, repeat ACI, reimplantation of graft tissue (OCA/OAT), unicompartmental knee arthroplasty (UKA), or TKA unequivocally indicates an unsuccessful clinical outcome garnered from the index procedure. However, studies that have assessed such salvage (failure-defining) procedures have been limited by relatively small sample sizes and resultant single-digit numbers of salvage procedures. Previous studies have reported between an 8.1% and 19% ACI failure rate at 5 years and beyond, with samples of 58 to 110 total patients (2-11 failures); in those studies, clinical and radiographic metrics were combined to assess outcomes.[12-16,44]

To the authors' knowledge, there are no large studies that have evaluated treatment failure after ACI as indicated by failure-defining surgical revision, including revision ACI, OCA, OAT, UKA, or TKA. Therefore, the purpose of this study was to assess the 5-year incidence, timing, and risk factors for revision surgery after ACI in a large national cohort.

METHODS

Study Population

A retrospective study was performed with data from the January 2010 to April 2020 M91Ortho PearlDiver database (PearlDiver Technologies), a commercially available administrative US database containing 91 million patients. All data in the database are de-identified and Health Insurance Portability and Accountability Act compliant. Given that all data are de-identified in the PearlDiver database, our institutional review board deemed this study "not human research" and thus provided an exemption.

Inclusion criteria were primary ACI surgery (Current Procedural Terminology [CPT]–27412) and age 20 to 59 years at the time of surgery. Exclusion criteria were a history of OCA (CPT-27415 or CPT-29867), OAT (CPT-27416 or CPT-29866), UKA (CPT-27446), TKA (CPT-27447), chondroplasty (CPT-29877), or microfracture (CPT-29879) before index ACI. The use of cartilage repair procedures or arthroplasty before ACI has been associated with higher ACI failure rates[30,40]; thus, patients receiving these previous procedures were excluded from analysis to more accurately characterize the effects of primary ACI surgery alone.

Age was stratified among the data set in 10-year divisions: 20 to 29, 30 to 39, 40 to 49, or 50 to 59 years old. Sex was directly abstracted from the data set (male or female). Body mass index (BMI) categories were determined based on queries for the relevant International Classification of Diseases, 9th and 10th Revision codes and classified as <20, 20 to 24.9, 25 to 29.9, 30 to 34.9, or ≥35.0. The Elixhauser Comorbidity Index (ECI) is a comorbidity index including 31 unique conditions designed to predict inpatient mortality. Based on comorbidity data, the ECI score was calculated for each patient and categorized as a score of 0, 1 to 3, or >3.

The number of patients who received bony realignment procedures concomitantly or up to 1 year before index ACI was tabulated. Previous or concomitant bony realignment procedures included femoral shaft osteotomy (CPT-27450), proximal tibial osteotomy (CPT-27455 or CPT-27457), and tibial tubercle osteotomy (CPT-27418).

ACI Surgical Revision

Revision surgery was assessed within the first 5 postoperative years after ACI. Revision surgeries included secondary ACI (CPT-27412), OCA (CPT-27415 or CPT-29867), OAT (CPT-27416 or CPT-29866), UKA (CPT-27446), or TKA (CPT-27447).

Statistical Analysis

Kaplan-Meier analysis was used to determine the cumulative incidence of revision surgery during the 5-year period after index ACI. In addition, the incidence of revision surgery in each postoperative year was tabulated. All patients in the cohort were included in the analysis of revision surgery. The Kaplan-Meier function of the PearlDiver software censored patients who lacked further follow-up at the time point when data became unavailable (eg, because of change in insurance coverage, no further physician follow-up, or death). The incidence of surgical revision in each year after index ACI and the number of patients available for follow-up at each year were abstracted from Kaplan-Meier analysis.

[‖]References 5, 12, 14, 23, 28, 37, 40, 42, 44, 45.

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TABLE 1
Patient Characteristics and Comorbidities for Cohort Undergoing ACI[a]

	Value
Sample size	533 (100)
Age, y	37.6 ± 10.3
20-29	135 (25.3)
30-39	168 (31.5)
40-49	149 (28.0)
50-59	81 (15.2)
Sex	
Male	245 (46.0)
Female	288 (54.0)
BMI	
Underweight (<20)	4 (0.8)
Normal (20-24.9)	369 (69.2)
Overweight (25-29.9)	44 (8.3)
Obese (30-34.9)	34 (6.4)
Severely obese (≥35)	82 (15.4)
Region	
Midwest	130 (24.4)
Northeast	111 (20.8)
South	213 (40.0)
West	76 (14.3)
Unknown	3 (0.6)
Insurance	
Commercial	491 (92.1)
Medicaid/unknown	42 (7.9)
ECI score	1.6 ± 1.9
0	193 (36.2)
1-3	271 (50.8)
>3	69 (12.9)
Bony realignment procedure	
No	431 (80.9)
Yes	102 (19.1)

[a]Data are presented as number (%) or mean ± SD. Bony realignment procedures included femoral shaft osteotomy, proximal tibial osteotomy, and tibial tubercle osteotomy performed concomitantly or up to 1 year before ACI surgery. ACI, autologous chondrocyte implantation; BMI, body mass index; ECI, Elixhauser Comorbidity Index.

The effect of patient characteristics and comorbidities on the risk of surgical revision was evaluated via multivariate logistic regression, controlling for age, sex, BMI, ECI score, and previous or concomitant bony realignment procedures. Adjusted odds ratios (ORs) and 95% CIs were calculated.

All statistical analyses were performed using the Pearl-Diver software or GraphPad Prism Version 9 (GraphPad Software). Significance was defined as $P \leq .05$.

RESULTS

Study Population

A total of 533 patients who underwent primary ACI and met inclusion criteria were identified. The mean (±SD) age was 37.6 ± 10.3 years, 54.0% of patients were female, the mean ECI score was 1.6 ± 1.9, and 15.4% of patients were categorized as severely obese (BMI, ≥35). Bony realignment procedures (femoral shaft osteotomy, proximal tibial osteotomy, or tibial tubercle osteotomy) were performed concomitantly or up to 1 year before ACI in 102 patients (19.1%) (Table 1). The numbers of patients available for follow-up at 1, 2, 3, 4, and 5 years postoperatively were 440, 366, 325, 279, and 241 patients, respectively.

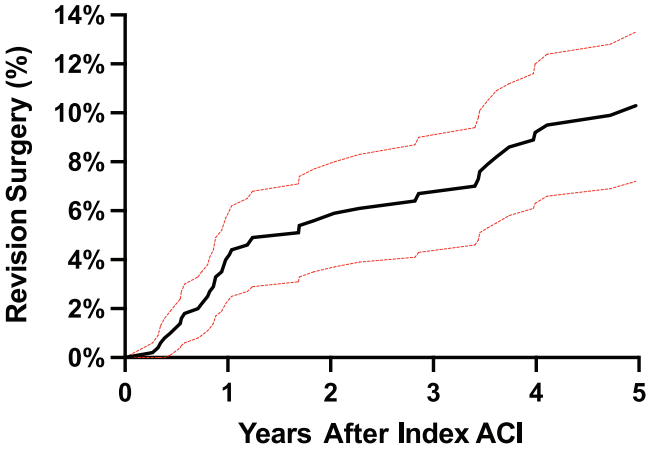

Figure 1. Five-year cumulative incidence of revision surgery after primary autologous chondrocyte implantation (ACI), with 95% CI estimates (depicted as dotted lines). Revision surgeries included procedures identified via Current Procedural Terminology codes for secondary ACI, osteochondral allograft transplantation, osteochondral autograft transfer, unicompartmental knee arthroplasty, or total knee arthroplasty within 5 years after index ACI. The cumulative 5-year incidence of revision surgery was 10.3% (41 failures).

ACI Revision Surgery and Timing

ACI revision surgery over time is depicted as cumulative incidence of surgical revision via Kaplan-Meier analysis in Figure 1. Over 5 years, 41 patients required surgical revision (progression to revision ACI, OCA, OAT, UKA, or TKA), for a cumulative 10.3% (95% CI, 7.2%-13.3%) incidence of revision.

The majority of surgical revisions occurred in the first (n = 19; 46.3%) and second (n = 7; 17.1%) postoperative years, collectively accounting for 63.4% of all surgical revisions over the 5-year time frame assessed. The proportions of revision procedures in subsequent years were 9.8% (year 3), 19.5% (year 4), and 7.3% (year 5).

Risk Factors for ACI Revision

The results of the logistic regression analysis performed to identify risk factors for revision surgery are presented in Table 2. Female sex was significantly associated with risk of surgical revision (OR, 2.58; 95% CI, 1.22-5.45; P = .013). Severe obesity (BMI, ≥35.0) (OR, 2.24; 95% CI, 1.01-4.94; P = .047) was also significantly associated with increased risk of surgical revision. There was no relationship between age, ECI score, or previous or concomitant

TABLE 2
Multivariate Regression Analysis With Adjusted Odds Ratios for Surgical Revision Within 5 Years of ACI[a]

	Total, N	Revision, n	Revision, %	OR	95% CI	*P* Value
Age, y						
20-29	135	7	5.2	—	—	—
30-39	168	13	7.7	1.37	0.52-3.60	.52
40-49	149	14	9.4	1.53	0.58-4.04	.39
50-59	81	7	8.6	1.40	0.45-4.36	.57
Sex						
Male	245	10	4.1	—	—	—
Female	288	31	10.8	2.58	1.22-5.45	**.013**
BMI						
Normal (20-24.9)	369	22	6.0	—	—	—
Overweight (25-29.9)	44	4	9.1	1.22	0.39-3.85	.73
Obese (30.0-34.9)	34	3	8.8	1.18	0.32-4.29	.80
Severely obese (≥35.0)	82	12	14.6	2.24	1.01-4.94	**.047**
ECI score						
0	193	10	5.2	—	—	—
1-3	271	23	8.5	1.39	0.63-3.09	.41
>3	69	8	11.6	1.59	0.56-4.52	.38
Bony realignment procedure						
No	431	32	7.4	—	—	—
Yes	102	9	8.8	1.26	0.56-2.82	.57

[a]The number of total patients and the number of patients with reoperations (ACI treatment failures) in each category are depicted, along with odds ratios (ORs), 95% CIs, and *P* values for significant association with surgical revision after ACI. For BMI, standard categories are depicted. Bony realignment procedures included femoral shaft osteotomy, proximal tibial osteotomy, or tibial tubercle osteotomy performed concomitantly or up to 1 year before ACI surgery. Boldface type indicates statistical significance ($P \leq .05$). Dashes indicate referent categories for regression analysis. ACI, autologous chondrocyte implantation; BMI, body mass index; ECI, Elixhauser Comorbidity Index.

bony realignment procedures and risk of undergoing ACI surgical revision at 5 years ($P > .05$ for each).

DISCUSSION

The present study, which employed the largest ACI cohort to date, identified a relatively low rate of subsequent articular cartilage salvage restoration and arthroplasty procedures after primary ACI, which totaled 10.3% at 5 years. These results affirm the durability of ACI as shown in smaller studies.[12-15,23] Second, this study found that in the 5-year postoperative period, the first 2 years carried a greater risk for reoperation (63% of all revisions) than did years 3 through 5 (37% of all revisions). Finally, this study identified female sex and severe obesity (BMI, ≥35) as significant risk factors for surgical revision after ACI. Despite the increasing use of ACI to treat isolated full-thickness chondral defects of the knee, studies of the mid- and long-term efficacy of ACI have previously been limited to small single-center studies with a paucity of multiyear or sufficiently powered evidence to better understand treatment failure.[12-16,44]

When defining surgical revision, this study employed a clinically relevant definition—namely, revision articular cartilage restoration procedures (ACI, OCA, OAT) or conversion to knee arthroplasty (UKA, TKA). The need for such procedures unequivocally indicates failure of the index ACI surgery. Previous studies have assessed ACI failure via radiologic evidence of graft delamination, loss of graft tissue on MRI scans, or arthroscopic assessment, with or without adverse clinical outcomes such as recurrent clinical symptoms.[12,14,17,44,46] Few studies have used conversion to cartilage restoration procedures (ACI, OCA, OAT) or arthroplasty (UKA, TKA) to define treatment failure.[14,23,44] While functional scores and radiologic metrics are meaningful, the present study's use of failure-defining revision surgery provides another clinically relevant metric that is meaningful to both the patient and the physician in a tangible way.

The ACI 5-year failure rate of 10.3% found in the present study is similar to that exhibited in previous, smaller studies. In a study of 37 ACI procedures, Ebert et al[13] reported an 8.1% (n = 2) ACI failure rate at a minimum of 5 years, with failure defined as delaminated grafts, repair sites devoid of repair tissue, or subsequent TKA. Studies extending beyond a 5-year follow-up have found similar incidences of failure, ranging from 8.2% failure (9/110 patients) at a mean of 7.5 years (failure defined as structural graft failure combined with subsequent UKA or TKA)[23] to 9.1% failure (9/99 grafts) at 10 years (failure defined as graft delamination or a graft bed devoid of any repair tissue)[14] and to 10.9% failure (7/64 patients) at 10 years (failure defined as delaminated grafts, repair sites devoid of repair tissue, or conversion to TKA).[12] In a case series of 58 patients, Ogura et al[44] found 19% failure (11/58 patients) at a 5-year follow-up after ACI, with failure defined as persistent or recurrent clinical symptoms in conjunction with MRI or arthroscopic evidence of graft delamination, revision cartilage repair, or conversion to

TKA. This higher failure rate likely resulted from the inclusion of radiographic criteria, in addition to revision cartilage and arthroplasty surgeries, to define failure. Overall, the findings in the current study of >500 ACI procedures agree with those of previous studies that have reported high survivorship of ACI.[12-14,16,23,44]

The large database employed in the present study enabled a time-based analysis of ACI revision surgery. Previous studies, with very small failure cohorts, have not obtained adequate power to perform such time-based analyses. We found that the majority of revisions (63%) occurred within the first 2 years postoperatively, with a substantial predominance in the first year. On the other hand, ACI survivorship into the third through fifth years postoperatively portended a decreased risk of subsequent surgical revision procedures. Smaller studies have suggested that functional scores, MRI findings, and survivorship tend to be relatively constant (with some noted improvements in functional scores) for grafts surviving beyond the 2-year mark.[12,14,44] Supporting this literature, our findings suggest that close monitoring of clinical symptoms is especially important during the first 2 postoperative years.

In addition to analyzing the timing of revision surgery, this study assessed whether patient characteristics and comorbidities were associated with increased risk of revision surgery. Via multivariate analysis, female sex conferred a significantly greater risk of revision relative to male sex, with women accounting for 76% of ACI revisions (women comprised 54% of the overall cohort). This agrees with previous findings that have associated female sex with higher rates of failure after ACI[27,33] and cartilage repair surgeries overall.[18,21] In a study of sex differences in ACI outcomes, Kreuz et al[29] suggested that higher graft failure in female patients, especially those with patellofemoral abnormalities, could be due to decreased proprioception and imbalances in muscle forces. However, the precise explanation is not well elucidated, and this finding merits further exploration.

Assessing BMI, we found that severe obesity (BMI, ≥35) was associated with a significantly higher incidence of revision surgery on multivariate analysis. Previous studies have found BMI ≥25 (overweight or obese) and BMI ≥30 (obese) to be associated with higher rates of failure and worse functional outcomes after ACI,[26,33] but the evidence has been limited. In other procedures of the knee, including microfracture[38] and UKA,[3,49] obese patients have demonstrated higher failure rates compared with nonobese patients. Furthermore, excessive body mass has been associated with osteoarthritis progression and cartilage turnover in the knee,[39] leading to greater joint reactive forces and increased cartilage rim deformation at the base of chondral defects.[7,31,34] In fact, recognizing unfavorable outcomes after ACI in severely obese patients, multiple large insurers regard severe obesity (BMI, ≥35) as grounds for denying coverage for ACI.[1,4] The present study firmly supports previous data suggesting that severe obesity portends a significantly higher incidence of ACI failure. Further investigation into the effects of BMI on outcomes after primary ACI is warranted, but these findings suggest that caution should be exercised when considering ACI for the severely obese patient population.

We found no association between age and risk of ACI revision surgery. Generally, ACI is indicated for patients younger than the age of 40 years, particularly given the need for a different approach for multiple, limiting degenerative joint changes present in many older patients.[41] Specifically, studies have found an increased risk of surgical revision after ACI and inferior functional outcome scores in patients older than 40 years.[30,33] However, we found no significant effect of age on the need for revision surgery on multivariate analysis. Our inability to identify a relationship between age and ACI failure may be related to a desire of clinicians and patients to postpone UKA or TKA into the sixth decade for patients requiring such interventions, which in turn would diminish perceived revision rates in patients on the higher end of the age spectrum for ACI (despite those patients having a poor functional outcome). Some patients in our cohort older than 40 years of age may instead have focal, full-thickness cartilage defects in the absence of any other defects and thus represent good ACI candidates (in contrast to older patients with multicompartmental degenerative changes). Regardless of the explanation, ACI is durable in patients aged <40 years, and more data are needed to evaluate the long-term durability of this surgery for older patients.

ECI score was also not associated with a greater risk of revision surgery. The relationship between ECI score and ACI revision surgery has not been previously explored, and certain individual component comorbidities—including severe obesity (as we found)—may be associated with worse outcomes. Because ECI is a heterogeneous index composed of 31 different comorbidities, it is impossible to ascertain the effect of individual, potentially relevant comorbidities in driving poor outcomes. However, it is reasonable to believe that patients in a poorer state of health with more comorbidities would be likely to have less favorable surgical outcomes and therefore be more likely to require surgical revision. Further investigation into the effect of multiple medical comorbidities on ACI outcomes is warranted.

Finally, we found that previous or concomitant bony realignment procedures did not affect the likelihood of ACI revision surgery. Many patients with chondral defects undergo both a primary cartilage restoration procedure and a synergistic procedure either concomitantly or in a staged fashion. Synergistic procedures include osteotomies (distal femoral osteotomy, high tibial osteotomy, or tibial tubercle osteotomy) to biomechanically offload the cartilaginous surface.[23,45] These procedures may be used in conjunction with primary ACI, and as a result, the present paper did not include these procedures in its definition of failure.[9] We did, however, include the presence of any tibial or femoral osteotomies (concomitantly or up to 1 year before index ACI) in our multivariate analysis. Previous studies have documented improved ACI durability when an osteotomy was used to address underlying malalignment.[5,6,44,47,48] Although we did not identify an effect of these procedures on the need for revision surgery after ACI, this finding does not preclude a potential effect of bony realignment procedures on functional outcomes.

The present study has several notable strengths. First, the advantages of the PearlDiver database include its diverse, nationally representative patient population, which covers the nation geographically and incorporates diverse insurance plans, including commercial insurance, Medicare, Medicaid, and self-pay. This diversity supports the generalizability of the findings presented. In addition, the large number of patients included in this study enabled analysis of time to revision after ACI, which has not been evaluated in previous literature.

There are several well-documented limitations inherent to large national databases such as PearlDiver and the retrospective nature of this study. First, when using PearlDiver, the accuracy of the data is directly related to the accuracy and specificity of the coding process, as International Classification of Diseases and CPT codes were used to identify the patients for this study. For this reason, we were unable to stratify patients based on the specific generation of ACI employed (ie, first, second, or third generation) and the graft site (eg, femoral condyle, patella, and trochlea). Therefore, this analysis provides a broad overview of the need for revision surgery after all types of ACI. Second, as data from this national administrative database are based on insurance claims data, variables are limited to those coded within the database, and factors such as patient-specific surgical indications, patient-reported outcomes, and radiologic data are not documented. Thus, our metric of failure included only failure-defining revision surgeries, as defined by CPT codes. Our inability to collect clinical outcome scores and incorporate radiographically confirmed graft delamination (specifically, cases that did not progress to surgical revision) suggests that we may have underestimated ACI clinical failure rates. Still, such metrics as graft delamination, while well reported in the literature, do not necessarily correlate with impaired function and thus may not necessitate surgical revision. For this reason, we believe that our metric of failure-defining salvage procedures at 5 years represents a valid and clinically relevant benchmark to assess ACI durability. Third, for various reasons (eg, change in insurance coverage, no physician follow-up, <5 years elapsed since index ACI surgery, or death), a number of patients lacked full 5-year follow-up. In total, 241 of the 533-patient cohort remained revision-free with follow-up available to 5 years. Of note, however, the Kaplan-Meier function used to calculate revision rates censored patients at the time of final follow-up, enabling us to provide a reliable estimate of revision rates at 5 years. Finally, as noted, our follow-up was limited to 5 years. Longer follow-up might identify an effect of other characteristics on ACI failure and would provide meaningful information concerning long-term durability.

CONCLUSION

In an analysis of 533 patients who underwent ACI, 10.3% required a subsequent articular cartilage procedure or conversion to knee arthroplasty in the first 5 postoperative years. Revision surgery was greatest in frequency in the first 2 postoperative years. Female sex and severe obesity (BMI ≥35) were associated with increased risk of surgical revision, while age, ECI score, and previous or concomitant bony realignment procedures were not. These findings suggest that treatment of chondral defects of the knee with ACI is associated with durable outcomes at the 5-year follow-up.

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