Severe Bone Marrow Edema Among Patients Who Underwent Prior Marrow Stimulation Technique Is a Significant Predictor of Graft Failure After Autologous Chondrocyte Implantation

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Background: Autologous chondrocyte implantation (ACI) is a well-established cartilage repair procedure; however, numerous studies have shown higher ACI graft failure rates after prior marrow stimulation techniques (MSTs).

Purpose: To identify which factors may predict decreased graft survival after ACI among patients who underwent a prior MST. A secondary aim was to investigate the specificity of these predictors.

Study Design: Case-control study; Level of evidence, 3.

Methods: In this review of prospectively collected data, the authors analyzed 38 patients who had failed prior MST surgery and subsequently underwent collagen-covered ACI (case group). The case group was divided into graft failure ACI (n = 8, 21%) and successful ACI (n = 30, 79%). Fourteen clinical variables were categorized and analyzed to determine predictors for failure of the ACI graft: age, body mass index, sex, defect characteristics (number, size, location, etiology, type), presence of kissing lesion, intraoperative presence of intralesional osteophyte, time between an MST and ACI, previous surgery, duration of the symptoms, and concomitant surgical procedure. Preoperative magnetic resonance imaging (MRI) was used to evaluate the severity of subchondral bone marrow edema (BME), graded I (absent) to IV (severe), and the presence of subchondral cyst, hypertrophic scarring, and intralesional osteophyte. The effects of these MRI findings on the graft survivor were also investigated. Concurrently, a control group without a prior MST was matched to investigate the specificity of the previously determined predictors. These patients were matched individually according to age, sex, body mass index, and outcome of the procedure (failure [n = 8] or successful [n = 30] per the case group).

Results: In the case group, the presence of preoperative severe BME was significantly higher among patients with failed ACI as compared with patients with successful ACI (P < .001). In the control group, the presence of severe BME was not significantly different between the failure and successful groups (P = .747). The ACI graft failure rate among patients with a prior MST and preoperative grade IV BME was 83.7% at 5 years postoperatively, resulting in a significantly lower survival rate as compared with patients with a prior MST and without severe BME (5-year graft failure rate, 6.5%; P < .001). All the other parameters did not differ significantly.

Conclusion: After a prior MST, the presence of grade IV BME by MRI was a predictive factor for graft failure among patients who then underwent second-generation ACI.

Keywords: autologous chondrocyte implantation; subchondral bone marrow edema; magnetic resonance imaging; marrow stimulation technique

Articular cartilage has limited inherent capacity for spontaneous healing after injury. Cartilage damage can lead to persistent symptoms, including swelling, pain, and loss of function, and may ultimately progress to symptomatic degeneration of the joint.2 To delay or avoid a prosthetic arthroplasty, multiple possibilities are available to restore the injured cartilage depending on patient and lesion characteristics: marrow stimulation techniques (MSTs), drilling, abrasion arthroplasty, and microfracture, as well as osteochondral autograft transplantation, osteochondral allograft transplantation, and autologous chondrocyte implantation (ACI).11

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MSTs are frequent first-line treatment options for symptomatic small-to-medium-size cartilage defects of the knee and may provide effective short-term functional improvement. \(^{15,16}\) Among them, microfracture is the most commonly performed cartilage repair technique: it is technically simple, has limited patient morbidity, and may provide satisfactory results. \(^{4,14,15}\) However, microfracture may still provide only short-term clinical improvement. \(^{16,17}\) In those cases where an initial MST fails, decision making on which subsequent technique to choose becomes increasingly difficult owing to alterations in the subchondral bone after an MST. \(^{5}\) ACI is a well-established cartilage repair procedure with a high satisfaction rate over a long-term follow-up. \(^{34,41,45}\) ACI is a commonly used secondary procedure after failed microfracture; however, recent studies demonstrated a 3- to 8-times higher failure and decreased satisfaction rate among patients who underwent an MST before ACI. \(^{29,30,43}\) Numerous studies have reviewed factors that are prognostic in determining the success of the ACI procedure, such as age, \(^{26,27}\) sex, \(^{26}\) body mass index (BMI), \(^{8}\) number of previous surgical procedures, \(^{26}\) duration of the symptoms, \(^{26,4,47}\) defect size, \(^{8}\) defect location, \(^{38,44}\) and presence of osteoarthritis (OA). \(^{5}\) However, there are no articles on the predictors of graft failure for the ACI procedure after a prior MST. Identifying the predictors of graft failure for ACI after an MST would be valuable. This is the purpose of this study. Furthermore, we investigated the specificity of this predictor to determine whether the associations are the same between patients with and without a history of an MST.

METHODS

Patient Cohort

Our institutional review board approved this study, and informed consent was obtained from all patients at the time when they were entered into the database (usually at the time of the index surgery). From June 2007 to November 2015, 436 patients underwent a second-generation (collagen covered) ACI procedure by the senior author (T.M.). Out of 436 patients, 82 underwent subsequent ACI after a failed prior MST. Indications for the treatment of cartilage defects with ACI were \(\geq 1\) full-thickness chondral defects of the knee with consistent history, physical examination, radiography, magnetic resonance imaging (MRI), and arthroscopy confirming that the defects accounted for the patient’s symptoms. Exclusion criteria for this study were any prior cartilage repair procedures besides an MST before ACI, concomitant anterior cruciate ligament reconstruction, sandwich ACI, meniscal allograft transplantation, and lack of preoperative MRI analysis. Patients with osteochondritis dissecans were also excluded from the study, to not confuse the indications for treatment of focal chondral defects and not osteochondral (Figure 1).

Index patient details were collected. Thirty-eight patients met the inclusion criteria. As a first step, to identify the potential predictors of ACI graft failure after an MST, we performed a study analysis of potential risk factors of the included 38 patients. On the basis of their ACI graft status, the 38 patients were divided into 2 groups: the successful group consisted of those patients whose ACI graft remained intact during the follow-up period, whereas the failure group was composed of patients with ACI graft failure. Subsequently, by conducting a case-control study, we aimed to investigate the specificity of the previously determined predictors by comparing the 38 patients with a prior MST (case group) with a matched control group of patients without a prior MST (control group) (Figure 1). These patients \((n = 38)\) were matched from the same ACI register \((436\) patients), individually according to age, sex, BMI, and procedure outcome (ACI graft failure or successful) (Table 1). The closest available match was used for age and BMI, but up to 2 years and 4.0 BMI deviation was accepted.

Surgical Procedure

The details of the ACI procedure were described previously in greater detail. \(^{16,32}\)

Briefly, chondral defects were debrided back to healthy cartilage and intact subchondral bone; defect sizes were measured and templated. The senior author used a type I/III bilayer collagen membrane derived from porcine perichondrium and skin (Bio-Gide; Geistlich Pharma). The membrane was then cut precisely to the template. Each membrane was then positioned at the site of the defect and secured with multiple 6-0 Vicryl sutures (Ethicon). The suture line was sealed with fibrin glue to be watertight, and the defect was injected full with autologous chondrocytes. Patients with defects on the weightbearing femoral condyles in the setting of \(\geq 2^\circ\) of malalignment from the neutral mechanical axis were treated with a concurrent valgus- or varus-producing corrective osteotomy to a neutral mechanical axis. Patients with patellofemoral defects with maltracking underwent a concomitant tibial tubercle osteotomy (TTO) and soft tissue balancing to correct maltracking. For those patients who underwent prior MST, if there were alterations of the subchondral bone,
Figure 1. Flowchart of the study. ACI, autologous chondrocyte implantation; ACL, anterior cruciate ligament; MRI, magnetic resonance imaging; MST, marrow stimulation technique.

### TABLE 1

**Patients' Characteristics Comparison Between Case and Control Groups**

<table>
<thead>
<tr>
<th></th>
<th>With Prior MST (n = 38)</th>
<th>Without Prior MST (n = 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graft failure</td>
<td>8 (21)</td>
<td>8 (21)</td>
</tr>
<tr>
<td>Age, y</td>
<td>36.4 ± 9.9</td>
<td>36.7 ± 8.8</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.12 ± 4.3</td>
<td>27.4 ± 6.5</td>
</tr>
<tr>
<td>Sex: female</td>
<td>15 (39.5)</td>
<td>15 (39.5)</td>
</tr>
<tr>
<td>Follow-up period, y</td>
<td>6.7 ± 2.5</td>
<td>6.3 ± 3.1</td>
</tr>
</tbody>
</table>

*BMI, body mass index; MST, marrow stimulation technique.

and MRI evaluation, near normal results (ie, minimal subchondral bone marrow edema [BME] and isotonic appearance of the ACI graft to the adjacent articular cartilage). Patients were restricted from inline impact activities (running) for 12 to 18 months, and cutting sports were allowed after 18 months. The ACI rehabilitation protocol considered each patient's surgical reconstruction, graft maturation, and previous activity level, which were reflected in individualized variations in the rehabilitation protocol.\(^{30}\)

**Definition of Graft Failure**

Graft failure was defined as surgical removal of >25% of the graft area, repeat ACI, additional surgical MST violating the subchondral bone of the treated defect, or prosthetic replacement.

**Assessed Variables**

In this study, 14 clinical variables were analyzed to determine their influence on failure of the ACI graft: (1) age in years; (2) BMI (kg/m²); (3) sex—female or male; (4) defect number; (5) defect size (mm\(^2\)) per knee; (6) defect location—medial tibiofemoral compartment, lateral tibiofemoral compartment, patellofemoral compartment; (7) origin—traumatic or other; (8) defect type—simple (single unipolar grade 3/4 lesion on femur or grade ≤2 on the tibia or patella), complex (multifocal unipolar grade 3/4 chondral lesions on femur, concurrent high tibial osteotomy or TTO, osteochondritis dissecans, unipolar lesions on tibia or patella), and salvage (bipolar focal chondral lesions, generalized chondromalacia grade ≥2)\(^{44}\); (9) presence of

**Postoperative Rehabilitation**

Motion was emphasized in the first 6 weeks with continuous passive motion, active and isometric straight-leg raises, stationary bike by 3 weeks, and touchdown weight-bearing. From 7 to 12 weeks, patients progressed from partial to full weight-bearing. Functional activities were allowed from 4 months onward, including bicycle, treadmill, elliptical trainer, outdoor distance walking, hiking, and swimming. Inline jogging was allowed at 12 to 14 months if the knee examination yielded normal results such as sclerosis or intraslesional osteophytes, these were removed as needed to the level of the adjacent subchondral bone with the use of a high-speed bur under constant cold irrigation (to avoid overheating the bone and surrounding cartilage), at which point the tourniquet was let down and the bleeding stopped before ACI.
kissing lesion; (10) presence of intralesional osteophyte based on operation note; (11) time between an MST and ACI—<6 months, 6-12 months, >12 months; (12) number of previous surgical procedures; (13) duration of the symptoms; (14) concomitant osteotomy—high tibial osteotomy, TTO, distal femoral osteotomy.

Magnetic Resonance Imaging

All 76 patients underwent preoperative MRI examination. MRI scans were evaluated by 2 independent orthopedic surgeons (T.O. and G.M.) who were blinded to case status. The reproducibility of these evaluations was high: interobserver reliability ranged from 0.844 to 0.935, and intraobserver reliability ranged from 0.856 to 0.947. Four patients had their MRI examinations performed elsewhere, and the images were not available to review directly; thus, the MRI reports were used instead. All 4 patients underwent an MST and were in the successful group. On the MRI reports, none of the patients had BME. Preoperative MRI evaluation of subchondral bone included the following sequences: sagittal, axial, and coronal T1, T2-weighted imaging, as well as fat-suppressed T1, T2 imaging. The presence of subchondral BME, intraskeletal osteophyte formation, subchondral cyst, or hypertrophic sclerosis was evaluated separately. Subsequently, the effects of these 4 radiographic variables were also investigated. BME was graded according to Henderson et al. as follows: absent, grade I; mild, grade II; moderate, grade III; and severe, grade IV (Figure 2).

Statistical Analysis

Patient characteristic results are reported as mean and SD. Normal distribution of the data was confirmed by utilizing the Shapiro-Wilk test. We compared the success and failure groups on select variables by using chi-square for the categorical variables and independent-samples t tests (or the Mann-Whitney U test when appropriate) for continuous variables to evaluate factors that might predict graft failure. Subsequently, Kaplan-Meier curves were performed with log-rank analysis to investigate the influence of those variables that showed statistical significance in the aforementioned analysis, to visualize their effects on graft longevity. In this study, no effort was made to adjust the alpha value at which tests were considered significant, given the hypothesis-generating nature of the work. All statistical tests were 2-tailed. A P value of .05 was used to determine statistical significance. Data were analyzed with SPSS (v 13.0; IBM Corp).

RESULTS

Patient Cohort

Complete baseline data of all 14 clinical variables defined in this study were available for 38 patients (Tables 2-4). Out of 38 patients, 8 were considered to have a graft failure (21.1%) at 8.5 years.

To show that our sample of 38 patients was representative of the MST ACI cohort, we evaluated the graft failure rate of the patients who underwent a prior MST but were excluded from the study (n = 44). There were no significant differences in the graft failure rate between the included and excluded patients treated with a prior MST before ACI (8 of 38 vs 7 of 44 patients failed, P = .548).

In the successful group of the case group (n = 30), 12 (40%) patients were female; the mean ± SD age at the time of the surgery was 35.5 ± 10.2 years; and the mean BMI was 27.4 ± 4.3 kg/m². The mean number of treated defects per knee was 2.4 ± 1.3, with an overall defect size of 12.6 ± 7.6 cm² per knee. Nine (30%) patients had complex defects, and 21 (70%) had salvage defects. Twenty-one patients (70%) had intraskeletal osteophytes based on the operative note (Table 2). In this group, 7 patients (23.3%) underwent TTO and ACI after a failed MST to the patellar defect. Three of the patellar defects were located on the medial patellar facet and central pole of the patella, 2 on the central pole, 1 on the central and lateral facet, and 1 on the inferior lateral facet of the patella. The mean time between an MST and ACI procedure was 4.6 ± 4.4 years (Table 3). During the follow-up period, 50% of the patients underwent reoperations in which the graft remained intact (Table 5).

In the failure group (n = 8), 3 (37.5%) patients were female; the mean age at the time of surgery was 37.6 ±
### TABLE 2

Patient Characteristics <sup>a</sup>

<table>
<thead>
<tr>
<th></th>
<th>Total (N = 38)</th>
<th>Successful (n = 30)</th>
<th>Failure (n = 8)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>36.4 ± 9.9</td>
<td>35.5 ± 10.2</td>
<td>37.6 ± 6.3</td>
<td>.663</td>
</tr>
<tr>
<td>BMI, kg/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>27.1 ± 4.3</td>
<td>27.4 ± 4.3</td>
<td>26.2 ± 4.8</td>
<td>.898</td>
</tr>
<tr>
<td>Sex: female</td>
<td>15 (39.5)</td>
<td>12 (40)</td>
<td>3 (37.5)</td>
<td>.898</td>
</tr>
<tr>
<td>No. of defects</td>
<td>91</td>
<td>72</td>
<td>19</td>
<td>.678</td>
</tr>
<tr>
<td>1</td>
<td>9 (23.7)</td>
<td>9 (30)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>15 (39.5)</td>
<td>9 (30)</td>
<td>6 (75)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>6 (15.8)</td>
<td>5 (16.6)</td>
<td>1 (12.5)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>6 (15.8)</td>
<td>5 (16.6)</td>
<td>1 (12.5)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2 (5.3)</td>
<td>2 (6.7)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>2.4 ± 1.2</td>
<td>2.4 ± 1.3</td>
<td>2.4 ± 0.9</td>
<td>.818</td>
</tr>
<tr>
<td>Size, mm</td>
<td>12.4 ± 8.4</td>
<td>12.6 ± 7.6</td>
<td>11.8 ± 11.3</td>
<td>.765</td>
</tr>
<tr>
<td>Kissing lesions</td>
<td>14 (38.8)</td>
<td>12 (40)</td>
<td>2 (25)</td>
<td></td>
</tr>
<tr>
<td>Tibiofemoral compartment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medial</td>
<td>4.2 ± 5.1</td>
<td>4.5 ± 5.5</td>
<td>3.1 ± 3.4</td>
<td>.214</td>
</tr>
<tr>
<td>Lateral</td>
<td>5.6 ± 4.1</td>
<td>1.8 ± 2.9</td>
<td>3.2 ± 4.3</td>
<td>.186</td>
</tr>
<tr>
<td>Patellofemoral compartment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Traumatic</td>
<td>6.0 ± 4.9</td>
<td>6.3 ± 4.5</td>
<td>5.3 ± 6.2</td>
<td>.927</td>
</tr>
<tr>
<td>Other</td>
<td>20 (52.3)</td>
<td>15 (41.7)</td>
<td>5 (62.5)</td>
<td>.588</td>
</tr>
<tr>
<td>Defect</td>
<td>18 (47.3)</td>
<td>15 (41.7)</td>
<td>3 (37.5)</td>
<td>.476</td>
</tr>
<tr>
<td>Simple</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Complex</td>
<td>12 (31.6)</td>
<td>9 (30)</td>
<td>3 (37.5)</td>
<td>.685</td>
</tr>
<tr>
<td>Salvage</td>
<td>26 (68.4)</td>
<td>21 (70)</td>
<td>5 (62.5)</td>
<td>.685</td>
</tr>
<tr>
<td>Intrallesional osteophyte</td>
<td>26 (68.4)</td>
<td>21 (70)</td>
<td>5 (62.5)</td>
<td>.685</td>
</tr>
<tr>
<td>Previous surgery</td>
<td>2.5 ± 1.5</td>
<td>2.4 ± 1.5</td>
<td>3 ± 1.3</td>
<td>.152</td>
</tr>
<tr>
<td>Previous MST</td>
<td>36 (96.7)</td>
<td>28 (93.3)</td>
<td>8 (100)</td>
<td></td>
</tr>
<tr>
<td>MFX</td>
<td>28 (93.3)</td>
<td>8 (100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drilling</td>
<td>1 (2.8)</td>
<td>1 (3.3)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Abrasion arthroplasty</td>
<td>1 (2.8)</td>
<td>1 (3.3)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Duration of the symptoms, y</td>
<td>6.1 ± 5.5</td>
<td>6.5 ± 6.1</td>
<td>4.8 ± 2.8</td>
<td>.449</td>
</tr>
</tbody>
</table>

<sup>a</sup>Data are provided as no. (%) of patients or mean ± SD. BMI, body mass index; MFX, microfracture; MST, marrow stimulation technique.

### TABLE 3

Time Between Procedures <sup>a</sup>

<table>
<thead>
<tr>
<th>Time Between</th>
<th>Total</th>
<th>Successful</th>
<th>Failure</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MST and ACI, y</td>
<td>4.7 ± 4.3</td>
<td>4.6 ± 4.4</td>
<td>4.9 ± 3.9</td>
<td>.884</td>
</tr>
<tr>
<td>&lt;6 mo</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>6-12 mo</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>&gt;12 mo</td>
<td>30</td>
<td>22</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>MST and MRI, y</td>
<td>4.1 ± 3.9</td>
<td>3.9 ± 4.1</td>
<td>4.9 ± 3.6</td>
<td>.533</td>
</tr>
<tr>
<td>MRI and ACI, y</td>
<td>1.2 ± 1.2</td>
<td>0.7 ± 0.7</td>
<td>1.1 ± 1.2</td>
<td>.196</td>
</tr>
</tbody>
</table>

<sup>a</sup>Data are provided as no. of patients or mean ± SD. ACI, autologous chondrocyte implantation; MRI, magnetic resonance imaging; MST, marrow stimulation technique.

6.3 years; and the mean BMI was 26.2 ± 4.8 kg/m<sup>2</sup>. The mean number of treated defects per knee was 2.37 ± 0.9, with an overall defect size of 11.8 ± 11.3 cm<sup>2</sup> per knee. Three (37.5%) patients had complex defects, and 5 (62.52%) had salvage defects. Among these patients, 5 (62.52%) had intrallesional osteophytes (Table 2). In this group, 1 patient (12.5%) underwent TTO and ACI after a failed MST to the medial patellar facet chondral defect. The time between an MST and ACI procedure was 4.9 ± 3.9 years (Table 3).

There were no significant differences in the patient characteristics and defect type at baseline between the success
and failures within the case group (Table 2). Additionally, there were no significant differences in the presence of concomitant osteotomies done at the time of ACI (Table 4) or in the time between an MST and ACI between the success and failures (Table 3). Until the ACI graft failed, 87.5% of patients underwent reoperations in which the ACI graft remained intact (Table 5). Out of the 8 failed cases, 1 required arthroscopic chondroplasty; 1, revision ACI; 3, osteochondral allograft transplantation; and 3, partial or total knee arthroplasty during the follow-up period (Table 6).

In the matched control group of patients who underwent ACI without a prior MST, the mean follow-up period was 6.3 ± 3.1 years. The same variables were analyzed in this group, except the time between an MST and ACI. None of the remaining 13 variables showed a significant difference in the matched control group between the successful group and failure group.

Radiographic Outcomes

There was no significant difference between the groups in the time between an MST and MRI (successful group, 3.9 ± 4.1 years; failure group, 4.9 ± 3.6 years; P = .533) and in the time between MRI and ACI (successful group, 0.7 ± 0.7 years; failure group, 1.1 ± 1.2 years; P = .195).

In the successful group, BME scores were graded as II for 7 patients (23.3%), III for 5 patients (16.7%), and IV for 1 patient (3.3%). The grade IV BME was unipolar. Two patients presented both subchondral cyst and BME. Intraligamental osteophyte (n = 4, 11.1%) and hypertrophic sclerosis (n = 2, 5.6%) were detectable with BME (3 intraligamental osteophytes, 1 hypertrophic sclerosis) or without BME (1 intraligamental osteophyte, 1 hypertrophic sclerosis).

In the failure group, all preoperative MRI scans showed BME grade II for 1 patient (12.5%), grade III for 2 patients (25%), and grade IV for 5 patients (62.5%). Out of 5 patients with grade IV BME (Figure 3), 4 had unipolar BME and 1 had bipolar BME (Table 7). The proportion of patients without any BME (grade 1) was significantly higher in the successful group. There was a significant difference in the presence of grade IV BME between the groups (P < .001). Subchondral cyst, hypertrophic sclerosis, and intraligamental osteophyte were not statistically significant between the groups (Table 7).

In the matched control group, 5 patients (16.7%) had grade IV BME in the successful group (n = 30), and 1 patient (12.5%) had grade IV BME in the failure group (n = 8). Out of
TABLE 7
Radiographic Outcomesa

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Successful</th>
<th>Failure</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BME grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>17 (39.4)</td>
<td>17 (56.7)</td>
<td>0</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>II</td>
<td>8 (21.0)</td>
<td>7 (23.3)</td>
<td>1 (12.5)</td>
<td>0.504</td>
</tr>
<tr>
<td>III</td>
<td>7 (18.4)</td>
<td>5 (16.7)</td>
<td>2 (25)</td>
<td>0.589</td>
</tr>
<tr>
<td>IV</td>
<td>6 (15.8)</td>
<td>1 (3.3)</td>
<td>5 (62)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hypertrophic sclerosis</td>
<td>2 (5.3)</td>
<td>2 (5.6)</td>
<td>0</td>
<td>0.453</td>
</tr>
<tr>
<td>Cyst</td>
<td>5 (13.2)</td>
<td>2 (5.6)</td>
<td>3 (37.5)</td>
<td>0.133</td>
</tr>
<tr>
<td>Intralesional osteophyte</td>
<td>21 (55.2)</td>
<td>17 (56.7)</td>
<td>4 (50)</td>
<td>0.736</td>
</tr>
</tbody>
</table>

aData are provided as no. (%) of patients. Bold indicates P < .05. BME, bone marrow edema.

![Images of MRI scans](image)

**Figure 3.** Representative examples for grade IV bone marrow edema (BME). (A1, A2) Images show the coronal and sagittal views of unipolar grade IV BME on the medial femoral condyle. (B1, B2) Images show the axial and sagittal views of unipolar grade IV BME on the patella. (C1, C2) Images demonstrate coronal and sagittal views of bipolar grade IV BME on the medial compartment of the knee joint. (D1, D2) Images show the axial and sagittal views of bipolar patellofemoral grade IV BME.

Of these 5 patients in the successful group, 4 had unipolar grade IV BME, and 1 had bipolar patellofemoral BME. In the failure group, the grade IV BME was bipolar patellofemoral. In this matched control group, there was no significant difference in the presence of grade IV BME between the successful and failure groups (P = .747). Of the 8 graft failures, 1 required revision ACI; 2, osteochondral allograft transplantation; and 5, partial or total knee arthroplasty during the follow-up period.

In 4 cases, all underwent a prior MST and were in the successful group, and the MRI examination was performed in a different hospital for which only the report of the radiologist was available. None of them had BME on MRI (grade I). An analysis was conducted to investigate how the exclusion of these 4 patients would influence our results. A significant difference in the presence of grade IV BME between the groups (P < .001) was maintained after the removal of these 4 patients.

**Survival Analysis**

None of the previously categorized 14 clinical variables had a significant effect on graft survival rate. However, ACI graft failure rate among patients with preoperative grade IV BME was 83.7% at 5 years postoperatively, which
Figure 4. Kaplan-Meier survival curves. Survival rate with and without bone marrow edema (BME) before autologous chondrocyte implantation in patients with a prior marrow stimulation technique. The endpoint was defined as failure of the graft.

Figure 5. Kaplan-Meier survival curves. Survival rate with and without bone marrow edema (BME) before autologous chondrocyte implantation in patients without a prior marrow stimulation technique (control group). The endpoint was defined as failure of the graft.

showed a dramatic and statistically significant difference as compared with patients without preoperative grade IV BME (P < .001) (Figure 4).

In the control group, however, ACI graft failure rate among patients with preoperative grade IV BME was 21.4% at 5 years, which was similar to that of patients without preoperative grade IV BME (P = .740) (Figure 5).

DISCUSSION

The purpose of the present study was to identify those variables that predicted decreased graft survival after ACI among patients who underwent a prior MST. In this review of a prospectively collected data set, we analyzed 38 patients with failed prior MST surgery who subsequently underwent second-generation ACI, and we compared them with a matched control group that did not undergo a prior MST to ACI. Our results showed significant differences in the study group between the successful and failed cases of ACI in the presence of grade IV BME (P < .001). All the other parameters (14 clinical variables and 3 radiographic variables) did not predict graft failure. In the matched control group of 38 ACI patients with no prior MST, the presence of grade IV BME did not predict graft failure. Our current study demonstrated that grade IV BME is a predictor of graft failure for patients undergoing an MST before ACI. In particular, when grade IV BME was present after an MST, the 5-year failure rate was 83.7%, and when it was present without a prior MST, the 5-year failure rate was 6.5% (P < .001).

MSTs are widely used procedures and include subchondral drilling, abrasion arthroplasty, and microfracture. These techniques demonstrate good to excellent results in 60% to 80% of patients with low morbidity, a comparatively quick recovery, and a low complication rate. However, outcomes are poor and unpredictable for lesions in the patellofemoral compartment or when the size of the defect is >4 cm².

Another limitation of MSTs procedures is their durability. The long-term durability of an MST has been shown to decline from 18 to 36 months. Moreover, revision cartilage repair procedures with ACI demonstrate a higher failure rate and worse functional outcomes after a prior failed MST. Numerous studies have shown postoperative changes in the subchondral bone plate after a prior MST. Animal studies have demonstrated osteocyte necrosis after microfracture, as well as changes in the subchondral bone in 30% to 50% of animals treated with microfracture, such as sclerosis, thickening of the subchondral bone, subchondral cysts, and osseous overgrowth, resulting in the formation of intralesional osteophytes. These findings are similar to those seen in chronic defects, which have yielded lower success rates after any type of cartilage repair. Generally, BME is recognized as a nonspecific reaction of the bone to trauma and acute and chronic repetition from overload. Therefore, BME may represent a multitude of differential diagnoses, such as traumatic bone contusions, stress fractures, degenerative lesions, inflammation, ischemic lesions (avascular necrosis), infection (septic osteomyelitis), metabolic lesions, neoplastic lesions, or iatrogenic lesions. Although BME is an expression of different noncharacteristic pathologies in summary, it overall reflects increased metabolism and remodeling of the subchondral bone.

Numerous studies have investigated the appearance of BME in patients with OA and have noted that the presence of BME is linked to pain and stiffness. The severity of OA is associated with BME and the increased rate of progression of OA. Although the cause of the subchondral changes in OA is still unknown, 1 hypothesis is subchondral remodeling processes from stress fractures owing to chronic overload that is reflected as BME on MRI.
Roemer et al\textsuperscript{49} reported that in patients with OA, BME might lead to alterations in the subchondral osseous plate with eventual weakening and deformity of the osseous articular contour. BME observed in our study may be similar to that in patients with OA. The fact that patients with OA demonstrate worse outcomes with cartilage repair procedures suggests that the altered subchondral bone may be responsible for lessened outcomes in the OA knee as well as lesions after prior failed MSTs.\textsuperscript{5}

The presence of pre- and postoperative BME after an ACI procedure, based on data in the literature, is controversial. Niemeyer et al\textsuperscript{47} discovered worse functional outcomes 1 year after ACI in patients with severe preoperative subchondral edema. However, their study did not discuss the nature of prior cartilage procedures on the presence or absence of preoperative BME. The negative influence of severe BME on the clinical outcomes of ACI is in line with our findings confirmed by our longer-follow-up study of patients with ACI with a prior MST. However, in our study, there was no negative effect of severe BME on graft survival rates in patients without a prior MST. Knowing about baseline prior procedures in the Niemeyer et al study would have been useful.

Ebert et al\textsuperscript{52} reported no association between the severity of preoperative subchondral BME with postoperative pain, symptoms, or postoperative graft failure as assessed by MRI. None of their patients had a prior MST.

Niethammer et al\textsuperscript{13} found postoperative BME as a risk factor of revision surgery after third-generation ACI. In their study, 19.9\% of the ACI procedures were conducted as a second-line procedure after a prior MST or ACI. Filardo et al\textsuperscript{13} could not demonstrate any correlation between the presence of postoperative edema and worse clinical scores. The previous surgical procedures for their patient population (n = 116) were heterogeneous, with only 3 patients who underwent a prior MST.

Given the fact that BME can be associated with chronic inflammation and fibrosis,\textsuperscript{8} it is plausible that after an MST, the MRI sign of this chronic alteration behind the severe BME is subchondral fibrosis. MST procedures may cause the subchondral bone to heal with subchondral sclerosis and mechanical stiffness, which affect the overlying cartilage.\textsuperscript{23-25} In our case failure group, 1 patient had bipolar grade IV BME, as opposed to 2 in the control group (1 in the failure group and 1 in the successful group). All these patients underwent concomitant osteotomy to unload the restored cartilage. Bipolar lesions usually represent degenerative change and previously demonstrated worse outcomes after ACI.\textsuperscript{45} However, current articles report good clinical outcomes addressing these lesions.\textsuperscript{31,40,42} A recent study\textsuperscript{40} demonstrated that the survival rate of ACI for patients who had bipolar cartilage lesions in the tibiofemoral compartment is 84\% at 8.3 years. Moreover, in the current study, the majority of the grade IV BME in the case failure group was unipolar (80\%); therefore, we believe that the appearance of grade IV BME after an MST is a predictor of graft failure of the subsequent ACI regardless of whether it is uni- or bipolar.

Accordingly, grade IV BME after an MST may represent an MRI sign of damaged, sclerotic subchondral bone and marrow space, leading to decreased ACI graft survivorship. To identify the exact histological abnormalities behind grade IV BME, future studies are required, including histological assessment with biopsies.

A recent study demonstrated that the outcomes after an MST with osteochondral allograft transplantation (OCA) were comparable with those of primary OCA.\textsuperscript{19} The OCA technique removes the damaged, abnormal subchondral bone that is substituted by the donor bone and cartilage surface. Sandwich ACI can be utilized as an alternative, with concurrent subchondral bone grafting and ACI, particularly if the bony deficiency is >6 mm.\textsuperscript{33} In those cases in which preoperative severe BME is apparent, OCA or sandwich ACI may replace the entire “osteochondral unit” that is abnormal or damaged.

There are several limitations to our study. In 4 cases, all underwent a prior MST and were in the successful group. MRI examination was performed in a different hospital for which only the report of the radiologist was available. However, none of these 4 cases had BME on their MRI (grade I), and after their exclusion, a significant difference was maintained between the groups for the presence of grade IV BME (P < .001) (see Table 7). We believe that our results are accurate and not the consequence of these 4 patients.

Second, the time between the MRI examination and the ACI procedure was not standardized, although there was not a significant difference between the groups (P = .195). Future studies would standardize the preoperative interval between MRI and ACI. Finally, our study was performed on a relatively small sample of 38 patients who had a prior MST and MRI and not the entire group of patients with a prior MST, although there were no significant differences in graft failure rates between the included patients (8 of 38 failed) and the excluded patients (7 of 44 failed; P = .548). Further studies with a large sample size are warranted, as in this study there were only 8 failures in each substudy, and a multivariate logistic regression was not possible.

CONCLUSION

In conclusion, the present study identified the presence of severe grade IV BME after an MST as a highly predictive finding for graft failure (5-year failure rate, 83.7\%) among patients who underwent second-generation ACI. However, in the matched control group without a prior MST, the presence of severe BME was not a predictor of graft failure (5-year failure rate, 21.4\%). Fourteen other variables studied showed no statistical significance associated with post-procedural graft failure. Treating surgeons should carefully assess the subchondral bone on the preoperative MRI before revision cartilage surgery after a failed MST. Addressing the subchondral bone with a sandwich ACI or OCA may be necessary when the MRI shows severe BME preoperatively. In this way, treatment of the osteochondral unit is addressed and not just the surface repair when prior bone penetration has occurred. Further studies are required to validate the results of our study.
REFERENCES


