

# Intra-articular Bone Marrow Aspirate Concentrate for Knee Osteoarthritis: 7-Year Outcomes and Predictors of Treatment Success in 50 Knees

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## Article

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# Abstract

Total knee arthroplasty volumes continue to rise, particularly in younger patients with advanced osteoarthritis who lack durable joint-preserving alternatives. Evidence for bone marrow aspirate concentrate (BMAC) beyond four years, and reliable predictors of response, have been lacking. We prospectively followed 50 knees with Kellgren-Lawrence grade II-IV knee osteoarthritis in 35 patients after a single intra-articular BMAC injection using the reorientation technique; 49 knees entered analysis. IKDC improved from  $57.0 \pm 13.4$  to  $74.1 \pm 14.9$  and WOMAC from  $36.8 \pm 23.9$  to  $16.3 \pm 19.5$  at seven years (both  $p < 0.001$ ), with gains achieved within the first year and maintained thereafter. Eleven knees were converted to arthroplasty, giving a 7-year TKA-free survival of 64%. Baseline symptom severity did not distinguish failures from successes (WOMAC  $p = 0.494$ ; IKDC  $p = 0.143$ ). Two readily assessable baseline variables did: extension deficit ( $7.2^\circ \pm 5.6^\circ$  vs  $1.1^\circ \pm 2.6^\circ$ ;  $p = 0.002$ ) and BMI ( $27.1 \pm 4.7$  vs  $24.4 \pm 3.9$  kg/m<sup>2</sup>;  $p = 0.05$ ). In the 36 knees without these features, 7-year TKA-free survival reached 80%. One minor, self-limiting complication occurred. This longest reported follow-up for intra-articular BMAC demonstrates a durable, low-risk effect governed by patient selection rather than disease severity.

## Introduction

Knee osteoarthritis (OA) is the most common chronic joint disease and a leading cause of disability worldwide, with total case numbers rising by more than 132% between 1990 and 2020[1] and knee OA cases in individuals aged 55 years and older more than doubling over a similar period, with further increases projected through 2050[2]. This growing burden is mirrored by a parallel rise in total knee arthroplasty (TKA): procedure volumes continue to climb across OECD countries, while the patient population is trending progressively younger; more than half of all knee replacements are now performed in individuals under the age of 65[3]. This mirrors earlier findings from three national joint replacement registries (Sweden, Australia, and the United States), which similarly reported an increase in knee replacement volumes[4].

As an alternative to surgical intervention, injection therapy is well established, yet the past years have seen a marked shift in its landscape: multiple randomised controlled trials and meta-analyses of the last years indicated that intra-articular platelet-rich plasma (PRP) and Cellular based therapy (CBT), such as bone marrow aspirate concentrate (BMAC) yield superior clinical outcomes compared with hyaluronic acid or corticosteroids[5]. This shift is reflected in the evidence review of the UK National Institute for Health and Care Excellence (NICE), among the most rigorous and widely adopted health-technology assessment bodies internationally: In the year 2022 NICE evidence recommended “stem cell therapy” over hyaluronic acid (HA), corticosteroids (CS), and placebo due to better effects regarding activity and pain[6]. In 2024, the European Society for Sports Traumatology, Knee Surgery and Arthroscopy (ESSKA) presented the ESSKA-ORBIT consensus at the ICRS World Congress in Catania - a formal statement by 77 European experts in regenerative medicine endorsing cellular-based therapies (CBT) for knee osteoarthritis, published in 2025[7]. In 2025, the German AWMF S3 guideline likewise endorsed regenerative measures-specifically platelet-rich plasma (PRP)-while similarly withdrawing its support for

the routine use of intra-articular hyaluronic acid in knee osteoarthritis[8]. The evidence base has continued to evolve. A recent EFORT review highlighted the growing role of regenerative therapies in orthopaedic practice[9].

A first attempt to identify criteria for appropriate patient selection was made in 2023 by Smith, who stated, that those with lower pain levels, or high pain levels with previous surgery, could be predicted to benefit from a single intra-articular BMAC injection[10]. In 2026 the ESSKA-ICRS consensus provided more granular guidance on indications and patient-specific determinants of outcome, including age and body mass index[11]. Nevertheless, clear indications and models predicting the outcome of cell-based therapies remain almost entirely lacking[11]. In principle, imaging, radiomics, biomechanics, multi-omics, and product-quality attributes could be integrated to define meaningful endotypes and support responder prediction in regenerative medicine in knee arthritis; to date, however, such models are largely confined to PRP, while validated AI-based tools for MSC-, BMAC-, MFAT-, and EV-based therapies are still missing in the year 2026[12].

Having previously reported the first prospective four-year study worldwide of reorientation-technique BMAC injection in severe (KL grade III-IV) knee OA-with significant IKDC and WOMAC gains, a 95% success rate, and no conversions to arthroplasty[13] we now extend this work in an expanded cohort. The present study additionally includes consecutively enrolled KL grade II patients and prolongs follow-up to seven years, with a particular focus on patient-specific predictors of outcome. To our knowledge, this is the longest follow-up published worldwide for intra-articular BMAC injection using the reorientation technique and focusing on prediction variables.

Therefore the aim of the current study was to (a) prospectively evaluate the long-term clinical outcome of patients with osteoarthritis of the knee following a single injection of bone marrow aspirate concentrate (BMAC) intra-articularly using the reorientation technique and (b) to identify outcome predictors.

## Material and Methods

This prospective multi-center cohort study was approved by the Ethics Committee of the Medical University of Graz (EK#: 31–152 ex 18/19). All procedures followed the relevant guidelines and the Declaration of Helsinki, and informed consent was obtained from all participants or their legal guardians. 50 knees of 35 patients (see Table 1) were prospectively enrolled from 2019–2022 in the following two centers in Austria: The Institute for Regenerative Medicine and the Private Clinic Leech. The following inclusion criteria were used:

- Age between 40 and 90 years
- Arthritis Grade II-IV according to the Kellgren-Lawrence classification
- Failure after at least 12 months of conservative treatment (patients not responsive to physiotherapy, NSAIDs, intraarticular injective treatment or scheduled for knee arthroplasty)

- Patients physically and mentally able to comply with the study requirements and with scheduled follow-up.

The following exclusion criteria were considered:

- Patients lacking understanding capacity
- Previous knee trauma within 24 months
- Intra-articular injection in the past 12 months
- Knee surgery in the last 24 months
- Untreated knee instability
- Malalignment of the leg-axis  $> 15^{\circ}$
- History of malignant neoplasia or rheumatic disease
- Presence of metabolic disorders including diabetes, thyroid metabolic diseases, history of alcohol or drug abuse; body mass index  $< 17$  or  $> 40$ , Vitamin D deficiency of  $< 30$  ng/ml
- Persistent history of bone marrow edema bigger than 2cm in diameter over 12 months.
- Malignant diseases of the bone marrow

Table 1  
Patient demographics (50 knees, 35 patients)

| Parameter                                             | Value                                    |
|-------------------------------------------------------|------------------------------------------|
| <b>Sex</b> (male / female)                            | 32 / 18                                  |
| <b>Age</b> , years (mean $\pm$ SD, range)             | 61.0 $\pm$ 14.3 (36–94)                  |
| <b>Height</b> , cm (mean $\pm$ SD, range)             | 175.0 $\pm$ 9.4 (150–196)                |
| <b>Weight</b> , kg (mean $\pm$ SD, range)             | 77.8 $\pm$ 17.1 (50–128)                 |
| <b>BMI</b> , kg/m <sup>2</sup> (mean $\pm$ SD, range) | patients, mean: 25.1 $\pm$ 4.3 (18–40)   |
| < 20                                                  | 5                                        |
| 20–24                                                 | 22                                       |
| 25–30                                                 | 15                                       |
| $\geq$ 30                                             | 5                                        |
| <b>Coronal deformity of patients</b>                  | 22 patients, mean 2.6° $\pm$ 3.4° (0–11) |
| Mean Varus (degrees)                                  | 5 patients, mean 1.2° $\pm$ 2.6° (0–10)  |
| Mean Valgus (degrees)                                 |                                          |
| <b>Leg extension deficit</b>                          | patients, mean: 2.6° $\pm$ 4.4° (0–15)   |
| 0°                                                    | 35                                       |
| 1–4°                                                  | 1                                        |
| 5–9°                                                  | 5                                        |
| 10°                                                   | 7                                        |
| > 10°                                                 | 2                                        |
| <b>Kellgren-Lawrence</b> grade I / II / III / IV      | 0 / 12 / 16 / 22                         |

## Procedure

A single experienced surgeon performed all procedures with the patient supine under sedoanalgesia. After surgical preparation of the ipsilateral iliac crest and knee, a 2 mm stab incision was made in the ventral iliac crest and 60 mL of bone marrow aspirate was collected with an Arthrex Angel needle using the previously published reorientation technique[14], where the bone marrow aspirate (BMA) was collected from 2 different entry points (2cm apart from each other) in three different positions in 2cm depth each. The BMA was then anticoagulated with citrate. The aspirate was concentrated in the Arthrex Angel centrifuge (<https://www.arthrex.com/de/orthobiologie/arthrex-angel-system>) at a 7% concentration factor for 15 minutes, yielding 5 mL of BMAC, which was injected intra-articularly through

a lateral suprapatellar approach; bilateral cases were treated on both knees in the same session and bilateral harvest.

Patients were discharged the same day, with NSAIDs for pain and cryotherapy as needed for 1–2 days. Full weight-bearing was allowed immediately, sports were paused for 1 to 2 weeks, and neither thromboprophylaxis nor structured physiotherapy was prescribed.

## Patients' evaluation

Clinical evaluation took place on the postoperative day and at week six, and thereafter annually. Treatment safety was evaluated by recording all complications and adverse effects, assessed by the physician at each follow-up visit or reported by the patient between visits. Complications were classified as serious if they involved death, a life-threatening state, hospitalization, further intervention, or lasting impairment, and as minor if limited to pain, swelling, hematoma, or temporary restriction of daily activities.

Primary outcome parameters were the International Knee Documentation Committee (IKDC) score and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).

Secondary parameters - used for prediction analysis -were two SF-36 items (Q1: "How would you rate your current state of health?"; Q2: "How would you rate your current state of health as compared to last year?"), walking distance, age, sex, weight, height, BMI, extension deficit, ROM, varus / valgus, history of previous injections, anamnesis of arthritis in the family, every single item of IKDC and WOMAC questions (pain at night, etc...) and days postoperatively.

Treatment failure was defined as the need, on the index knee, for a further surgical procedure (e.g., total knee arthroplasty) or a repeat injection (corticosteroid, hyaluronic acid, PRP, etc.) prompted by persistent or worsening symptoms.

Treatment success was defined as the absence of knee arthroplasty. As the success of a medical procedure should be sustainable - ideally until the end of life - patients who died without requiring any further intervention (repeat injection or total knee arthroplasty) were also counted as treatment successes, but are reported separately. Although this may appear unusual at first glance, it should be emphasized that death is an unavoidable competing outcome: At the age of 61, a patient with knee osteoarthritis in Austria carries an approximately 9% risk of dying from causes unrelated to the procedure by year 7, a risk that only grows as patients age.

In order to compute prediction, all parameters were recorded both preoperatively and postoperatively at each time point.

## Statistical analysis

Continuous variables are reported as mean  $\pm$  standard deviation, categorical variables as frequencies and percentages. Paired t-tests compared preoperative with postoperative IKDC, WOMAC, and secondary outcome scores.

Pearson's correlations assessed possible associations between primary and all secondary parameters. Baseline predictors of failure (age, sex, BMI, extension deficit) were compared between patients who did and did not convert to TKA using independent-samples t-tests, with Welch correction applied where Levene's test indicated unequal variances. Kaplan-Meier-test: Log-rank tests were used to compare treatment survival between strata of baseline extension deficit and BMI. No correction for multiple comparisons was applied. Normality was confirmed with the Kolmogorov-Smirnov test and homogeneity of variance with Levene's test for all comparisons. Analyses were performed in IBM SPSS Statistics 28, with the significance level set at  $p < .05$ .

## Results

### Secondary parameters - Prediction analysis

Extension deficit and high BMI at baseline were both strong and significant predictors of failure: Patients who progressed to TKA had baseline WOMAC and IKDC scores comparable to those who did not ( $p = 0.50$  and  $p = 0.14$ ). They differed, however, in two respects:

- a greater extension deficit ( $7.2^\circ \pm 5.6^\circ$  vs.  $1.1^\circ \pm 2.6^\circ$ ;  $p = 0.002$ ) and
- a higher baseline BMI ( $27.1 \pm 4.7$  vs.  $24.4 \pm 3.9$  kg/m<sup>2</sup>;  $p = 0.05$ ).

Age and BMI both hardly correlated with the baseline WOMAC ( $r = .18$ ,  $p = .25$ , and  $r = .21$ ,  $p = .18$ ) and IKDC ( $r = -.31$ ,  $p = .04$ , and  $r = -.15$ ,  $p = .34$ ) scores, but correlated negatively with the final IKDC score ( $r = -.52$  and  $r = -.66$  respectively, both  $p < .001$ ); WOMAC showed weaker but directionally similar correlations ( $r = .30$ ,  $p = .06$ , and  $r = .31$ ,  $p = .05$ ).

No correlation was found between the two SF36 questions and walking distance preoperatively ( $r = -.22$ ,  $p = .15$ , and  $r = .21$ ,  $p = .17$ ), but a strong correlation was found postoperatively ( $r = .84$  and  $r = .80$ ,  $p < .001$ ). At the latest follow-up, the correlation disappeared ( $r = .03$ ,  $p = .84$ , and  $r = .09$ ,  $p = .54$ ). Both SF36 values and walking distance differed significantly between baseline and first follow-up ( $p = .40$  and  $p = .004$  and  $p = .005$ ) with higher wellbeing and distance postoperatively, but only walking distance also did at the latest follow-up ( $p < .001$ ).

A weak correlation was found between KL-grade of arthritis and postoperative WOMAC ( $r = .32$ ,  $p < .04$ ).

No correlation was found between coronal deformity (varus and valgus malalignment) and all other primary and secondary parameters with each other.

### Secondary parameters - descriptive analysis

Overall pain during activity was reduced by 75%, and no patient reported persistent night pain, with the exception of those subsequently converted to knee arthroplasty.

Stiffness improved. Patient activity (walking distance, pain-free time, and activity level) approximately doubled, see Table 2.

**Table 2. Secondary outcome parameters** of 49 knees at the 7-year follow-up after BMAC injection (“mesenchymal stem cell therapy”) in reorientation technique.

|                                                                                                                              | pre- | postoperatively |
|------------------------------------------------------------------------------------------------------------------------------|------|-----------------|
| <b>Pain (0 = no pain, 4 = extreme pain)</b>                                                                                  |      |                 |
| Pain while walking                                                                                                           | 1.8  | 0.5             |
| Pain during the night                                                                                                        | 1.2  | 0.8             |
| Pain during sitting                                                                                                          | 1.0  | 0.5             |
| <b>Stiffness (0 = no stiffness, 4 = extreme stiffness)</b>                                                                   |      |                 |
| Morning stiffness                                                                                                            | 2.0  | 1.1             |
| After sitting                                                                                                                | 1.9  | 1.1             |
| <b>Physical activity (0 = no limitation, 4 = extreme limitation)</b>                                                         |      |                 |
| Walking down stairs                                                                                                          | 2.4  | 1.2             |
| Walking up stairs                                                                                                            | 1.8  | 0.5             |
| Get in/out of the car                                                                                                        | 1.6  | 0.7             |
| Severe household work                                                                                                        | 2.3  | 1.0             |
| Light household work                                                                                                         | 1.3  | 0.4             |
| Activity                                                                                                                     | 2.1  | 2.7             |
| <i>2 = walking, light household activities; 3 = moderate activities like running, jogging, moderate household activities</i> |      |                 |
| <b>Pain (0 = always, 10 = never)</b>                                                                                         |      |                 |
| Pain                                                                                                                         | 3.7  | 6.9             |
| <b>Functionality (0 = unable to perform daily activities, 10 = no limitations)</b>                                           |      |                 |
| Functionality                                                                                                                | 5.4  | 7.4             |
| <b>Walking distance (0 = apartment only, 5 = unlimited)</b>                                                                  |      |                 |
| Walking distance                                                                                                             | 3.6  | 4.6             |
| <i>1 = Home, 2 = &lt; 1 km, 3 = 1-2 km; 4 = &gt; 2 km; 5 = unlimited</i>                                                     |      |                 |

## Treatment failure and Success rate

Eleven of 49 knees were ultimately converted to total knee arthroplasty at mean 38 months mean (range 12-82 months). The 7 year TKA-free survival rate is therefore 64% (19 knees of 30 followed knees still without TKA). This included also all obese patients and all patients with knee extension deficit.

Five patients died of causes unrelated to the procedure; these knees were censored at the time of death, having survived free of arthroplasty for the remainder of the patients' lives. This equals approximately 10% "success rate" at year seven, since the procedure lasted until the patients' life.

*In an exploratory subgroup* 4 patients were excluded due to elevated BMI ( $>31 \text{ kg/m}^2$ ) and 9 further patients were excluded due to a significant extension deficit ( $> 10^\circ$ ). In these selected 36 knees, the number of knee arthroplasties was reduced significantly; only 4 knees required arthroplasty at 48 months mean (30-82 months), consecutively leading to a higher success rate of 80% at year 7 (16 knees of 20 followed knees still without TKA). All 5 patients who had deceased unrelated to the operation were in this group, their procedure lasted until the end of their life without the need for an implant.

Kaplan-Meier treatment survival curves (freedom from TKA) and cumulative mortality are shown for all patients and for the exploratory subgroup in Figure 6.

## **Complications**

One patient developed a small subcutaneous hematoma (2 cm in diameter) at the harvest site, which compressed the lateral femoral cutaneous nerve and produced a transient sensory deficit that resolved within several days. No other adverse events were recorded.

## **Discussion**

On the one hand total knee arthroplasty volumes continue to rise[3,4], and on the other hand a growing share of procedures is now performed in younger patients[3], reflecting a larger population of younger patients with advanced osteoarthritis who need durable joint-preserving options, yet have few. This is the gap our study addresses: we prospectively followed 50 knees over 7 years with Kellgren-Lawrence grade II-IV osteoarthritis treated with a single intra-articular injection of bone marrow aspirate concentrate using the reorientation technique, to our knowledge the longest such follow-up reported worldwide. This is furthermore, the first clinical long-term study worldwide to emphasize on patient selection: We found out, BMI and extension deficit are negatively correlated with favourable outcome.

The positive effect of the single BMAC injection in the reorientation technique was substantial and durable: IKDC and WOMAC improved within the first year and did not decline thereafter. The improvement was sustained throughout the seven-year observation period, with 64–80% of knees (depending on indication) remaining free of arthroplasty, a single minor complication, and no serious adverse events. Crucially, baseline symptom severity did not separate the patients who ultimately required arthroplasty from those who did not; however, a greater extension deficit, and a higher BMI did.

Response therefore appears to be governed more by patient selection than by disease severity. This bears immediate clinical relevance for physicians and patients, given that the state-of-the-art therapeutic regimen has changed substantially over the past 3 years:

By 2026, the most influential guidelines across the globe (NICE, ESSKA, AWMF, ICRS) had converged on positioning regenerative therapies ahead of hyaluronic acid for knee osteoarthritis[6–8,11]. However, to date, no large-scale evidence has established the long-term superiority of cellular-based therapies (CBT) over PRP. No study has directly compared BMAC and PRP over a comparable follow-up period. Notably, about one third of our patients had already received prior PRP injections without lasting benefit, hinting that BMAC may offer a more durable response than earlier PRP and HA treatments. This observation, however, cannot establish superiority without a controlled comparison. Whether the more than three-fold higher CD34 + cell yield achieved with the reorientation technique[14] contributes to the more durable effect observed here remains a hypothesis rather than a demonstrated mechanism, and dedicated comparative studies would be needed to test it.

Most prior studies of intra-articular BMAC report outcomes at only 12 to 24 months. The longest prospective follow-up before our four-year report[13] was that of Kon et al., who documented stable results at 24 months using a combined subchondral and intra-articular technique, without the reorientation approach applied here[15]. Mariani et al. found that a single BMAC injection led to meaningful clinical improvement and safety in a retrospective series of 55 patients treated with a single BMAC injection, with a mean follow-up of 57.6 months (range 18 to 111 months); however, the cohort was limited to Kellgren-Lawrence grade II and III disease, with no grade IV patients included, limiting its comparability to our grade II/III/IV population[16]. The only long-term evidence, Hernigou et al.'s 15-year study, reported arthroplasty avoidance in 80% of subchondrally versus 30% of intra-articularly treated knees[17]. Despite substantial methodological differences, it confirms that a durable biological effect is achievable - which our data now extend to the intra-articular route over seven years. Notably, these findings were contradicted by a recent double-blind randomised controlled trial reporting that adding a subchondral injection not only failed to improve outcomes but yielded significantly worse WOMAC and IKDC scores at 12 months than the intra-articular route alone[18]. This reinforces the case for the simpler intra-articular technique and obviates the need for intraosseous puncture.

Even the cautious 2025 Cochrane review found low-certainty evidence of a short-term benefit for stem cell injections in knee OA, while noting the absence of any long-term outcome data[19]. This gap is precisely what our study addresses, providing durable outcomes at up to seven years.

Two baseline factors accounted for most failures in our cohort, both readily identifiable preoperatively by the orthopaedic surgeon: knees converted to arthroplasty showed a greater extension deficit ( $7.2^{\circ} \pm 5.6^{\circ}$  vs  $1.1^{\circ} \pm 2.6^{\circ}$ ;  $p = 0.002$ ) and a higher BMI ( $27.1 \pm 4.7$  vs  $24.4 \pm 3.9$  kg/m<sup>2</sup>;  $p = 0.05$ ) than those remaining TKA-free. This pattern accords with Muthu et al., who reported that obese patients sustained the benefit of BMAC for a shorter period than normal-weight patients [20]. It also aligns with the 2026 ESSKA-ICRS consensus, which applied the RAND/UCLA appropriateness method: an international expert panel rated

144 clinical scenarios for point-of-care cell-based therapy in knee OA and identified BMI and age as key determinants of appropriateness, adopting a BMI of 35 kg/m<sup>2</sup> as the threshold for most indications[11]. Regarding BMI, our findings align with the consensus, however, the number of overweight and obese patients was limited in our cohort, not a single patient with a BMI over 35.

Notably, this is the first study to identify extension deficit as a predictor of BMAC failure, with a threshold effect around 10°: Survival free of arthroplasty followed a clear dose-response gradient (Fig. 4): Knees with full extension (0°) remained at ~ 91% through year 7, and those with a minor deficit ( $\leq 9^\circ$ ) declined only to ~ 66%. By contrast, knees with a 10° deficit fell to ~ 43% from year 4 onward, and every knee exceeding 10° had converted by year 4 (0% survival). A fixed deficit of  $\geq 10^\circ$  thus marks a clinically meaningful tipping point-likely reflecting more advanced structural disease that a single injection can no longer offset.

However, game theory raises the question of whether selecting thinner patients (BMI < 31) without a relevant extension deficit (< 10°) truly benefits the public and the individual patient. At first glance, we were able to improve the 7-year TKA-free survival rate from 64% to 80%, meaning that only 4 instead of 11 TKAs had to be implanted. The leverage of BMI is smaller than that of extension deficit: only one of the 4 patients (25%) excluded for a BMI > 31 accounted for a saved prosthesis, compared with five of the 9 (56%) patients excluded for an extension deficit of 10° or more. On closer inspection, however, it must be acknowledged that the selected group of 36 patients was obtained by excluding 13 of the originally 49 patients (due to an extension deficit of  $\geq 10^\circ$  and a BMI of  $\geq 31$ ). Had these 13 patients been treated with a TKA upfront, a total of 13 + 4 = 17 TKAs would have been required at year seven, rather than the 11 we actually performed. It therefore has to be noted that patient selection may improve one's own statistics while offering no benefit from a public health perspective. Ideally, our findings may help to convince patients to lose weight and mobilise their knees. These findings can inform the process of obtaining informed consent, allowing patients to be told that the best outcomes – high clinical scores together with a high probability of clinically relevant improvement – are to be expected in those with a BMI below 31 and no more than a mild extension deficit, while even obese patients still have an approximately 50% chance of avoiding total knee arthroplasty in the long term.

The link between elevated BMI and BMAC outcome hints that treating osteoarthritis in such patients may increasingly demand a metabolic, almost internist's, perspective alongside the surgical one. Pharmacological approaches to obesity-related OA could complement patient selection: metformin has been associated with lower knee replacement risk and reduced pain in type 2 diabetes[21], and a co-twin study points to a possible causal role in lowering OA incidence[22].

Age followed a different pattern. It was not associated with treatment failure in our study -older patients were no more likely to require arthroplasty - yet age correlated moderately and inversely with the final IKDC score ( $r = -0.55$ ,  $p < .001$ ): older patients achieved a lower absolute level of function, even when the treatment did not fail. Notably, however, the ESSKA-consensus paper[11] weighted age as an equally or

even more decisive exclusion criterion than BMI, a position we do not share. We would question an age-based cutoff for four reasons:

- First, the assumed age-related decline in regenerative capacity is not supported by the data: bone marrow-derived CD34 + stem cell numbers remain essentially stable up to at least 80 years[23,24], and age did not predict failure in our cohort.
- Second, it is precisely elderly patients who are often unfit for arthroplasty because of cardiac or pulmonary comorbidity-for whom a minimally invasive, day-case injection may be the only joint-preserving option. In these patients death is a competing risk.
- Third, in older patients a single injection need only last for their remaining lifetime: 10% of our patients, predominantly those over 65, died of unrelated causes without ever requiring arthroplasty.
- Older patients (65 years and older) are increasingly under-served, as pandemic-era backlogs disproportionately affected this group[3]. BMAC injection represents a low-threshold, complication-free treatment option for this patient group.

For elderly patients, a one-time joint-preserving injection may be enough, making them a key indication group. We therefore see no biological or clinical rationale for restricting BMAC by age alone.

How does BMAC compare with TKA?

Primary knee arthroplasty offers excellent long-term durability, with a pooled analysis of worldwide arthroplasty register data reporting an implant survival of approximately 94% at ten years[25]. Returning to the widening gap identified above, a growing cohort of younger patients with advanced disease but few durable joint-preserving options, these survival figures must be read in the following context: TKA offers excellent implant survival overall[26], but patients treated before age 55 face a lifetime revision risk of up to 35%, compared with about 5% after age 70[27]. Large registry data confirm this pattern: patients aged 50–65 years face nearly double the risk of implant failure compared with older patients[28], a trend also seen in other national registries[29]. Every year gained at a younger age is a year the prosthesis remains at risk. Regenerative therapies occupy exactly this space: a low-risk, joint-preserving intervention that can defer arthroplasty without foreclosing it as a later option. When read alongside the ESSKA-ICRS appropriateness thresholds, our findings suggest that BMAC delivers the greatest value precisely where TKA is least favourable: in younger, normal-weight patients with no or only mild extension deficit. In this group, arthroplasty carries a disproportionate lifetime failure risk, making joint preservation the more rational first step. In patients with obesity and knee extension deficit, by contrast, the biological rationale for BMAC itself weakens, as the inflammatory environment associated with high BMI and low ROM is thought to compromise cell quality and regenerative potential, consistent with the ESSKA-ICRS rating of BMI > 35 kg/m<sup>2</sup> as inappropriate for cell-based therapy[11]. We therefore agree - based on our own findings - that a BMI of 31 is too low a threshold, since it would increase the overall number of arthroplasties.

Several limitations apply. The cohort is small, at 50 knees, which limits the power of subgroup analyses. There is no control arm. Survivor bias is a genuine concern, since those remaining in follow-up are likely a healthier and more motivated subset. We had no patient with BMI over 35. These limitations were acknowledged in the 4-year report[13] and remain unchanged.

According to the ESSKA consensus and current guidelines, cell-based therapies represent a valuable low-risk option once conventional injectables such as corticosteroids or hyaluronic acid and PRP have failed, and are increasingly regarded as a meaningful second-line step in the treatment algorithm[7]. The considerable heterogeneity in protocols, cell sources, and preparation techniques complicates their translation into routine practice and underlines the pressing need for high-level comparative trials and standardised guidelines, a gap already highlighted by the 2018 AAOS/NIH consensus conference on orthobiologics[30].

In summary, a single intra-articular BMAC injection using the reorientation technique provided clinically meaningful improvement sustained over seven years, with treatment survival reaching 64%-80%, depending on patient selection. Combined with a low complication rate and the option of subsequent TKA, bone marrow derived cellular based therapy represents a reasonable intervention in knee OA without severe extension deficit-particularly in younger patients not yet suited for arthroplasty and in the very elderly.

In conclusion, outcome after BMAC depends on patient selection, not disease severity: extension deficit ( $p = .002$ ) and BMI ( $p = .05$ ) raised 7-year TKA-free survival from 64% to 80%, while other baseline scores carried no prognostic value.

## **Declarations**

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## **Author Contribution**

P.S. , R.K., I.S., C.P. wrote the main manuscript text and H.L. prepared figures and did the statistics. All authors reviewed the manuscript.

## **Data Availability**

The datasets used and/or analysed during the current study available from the corresponding author on reason-able request.

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## Figures

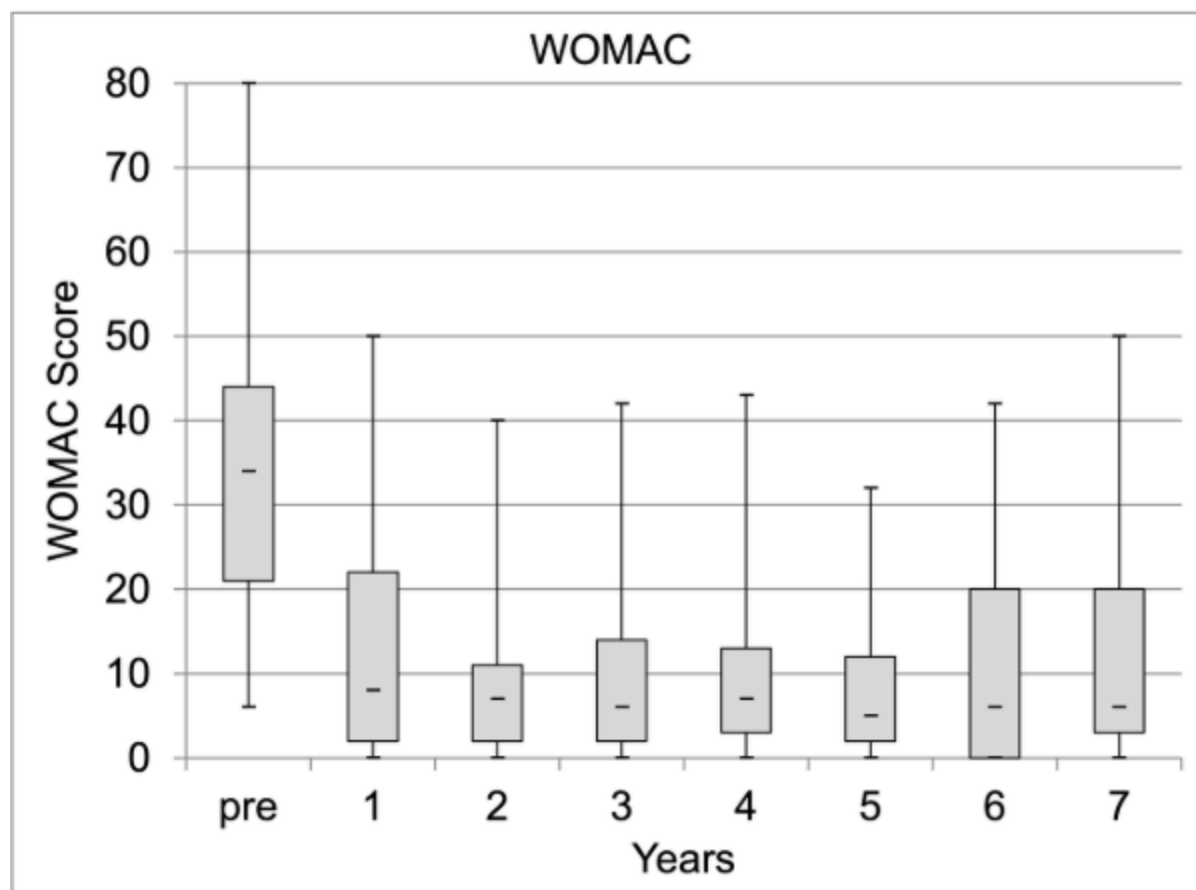


Figure 1

**WOMAC scores at baseline and each annual follow-up (years 1-7).** Boxes show median, the 25th-75th percentile, whiskers the 5th-95th percentile. Follow-ups differed significantly from baseline ( $p < .001$ , paired  $t$ -test). Including patients later converted to TKA.

IKDC improved from mean  $57.0 \pm 13.4$  (range 34-83) to  $76.3 \pm 13.2$  (range 45-100), then sat at  $74.1 \pm 14.9$  (range 52-95) at the 7-year follow-up ( $p < .001$ ) with no significant attrition of the effect over time:

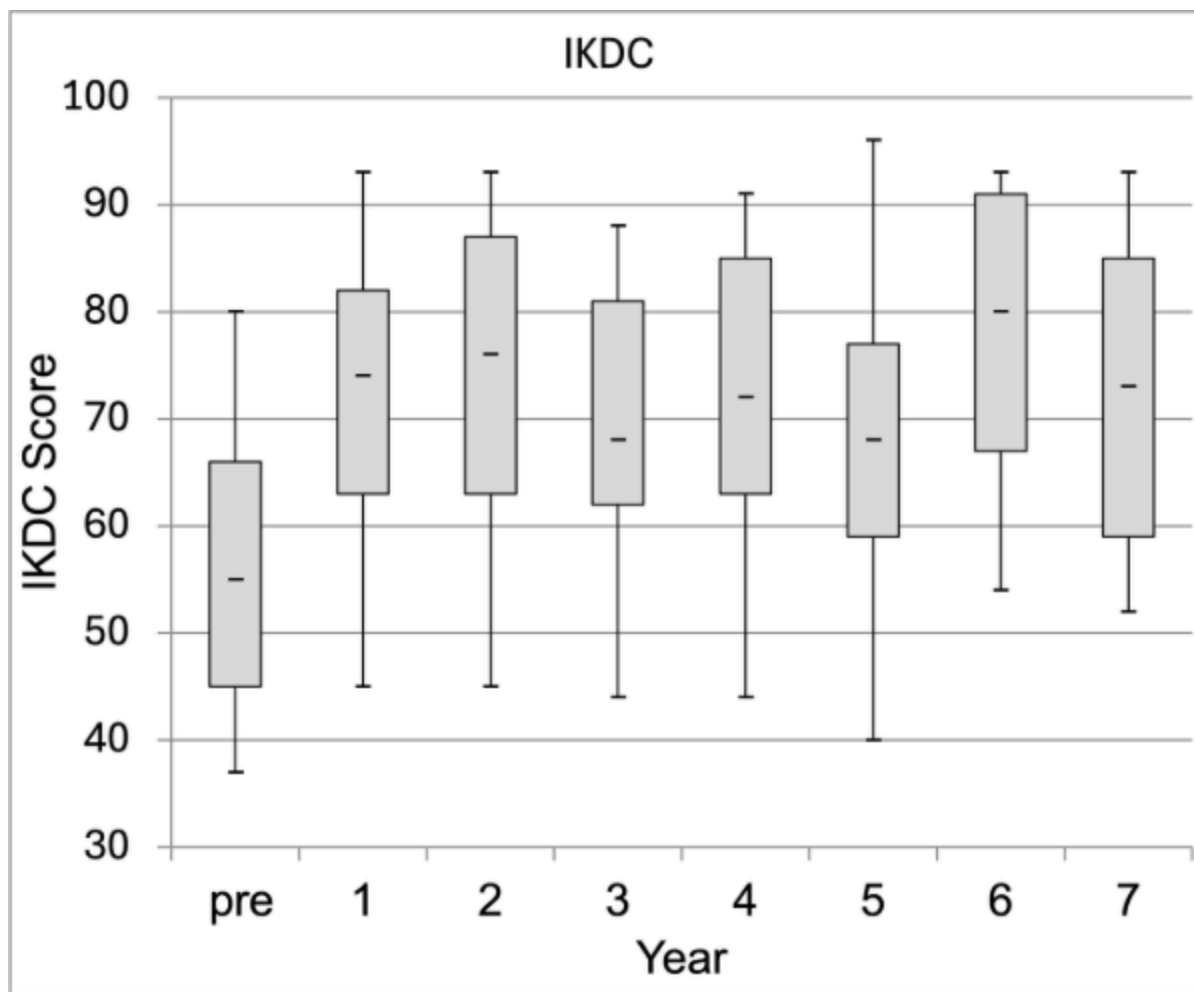


**Figure 2**

***IKDC scores at baseline and each annual follow-up (years 1-7).*** Boxes show mean, the 25th-75th percentile, whiskers the 5th-95th percentile. Follow-ups differed significantly from baseline ( $p < .001$ , paired  $t$ -test). Including patients later converted to TKA.

Note: IKDC and WOMAC scores included all patients; that is, outcome data from patients who subsequently underwent arthroplasty were included up to their date of operation.

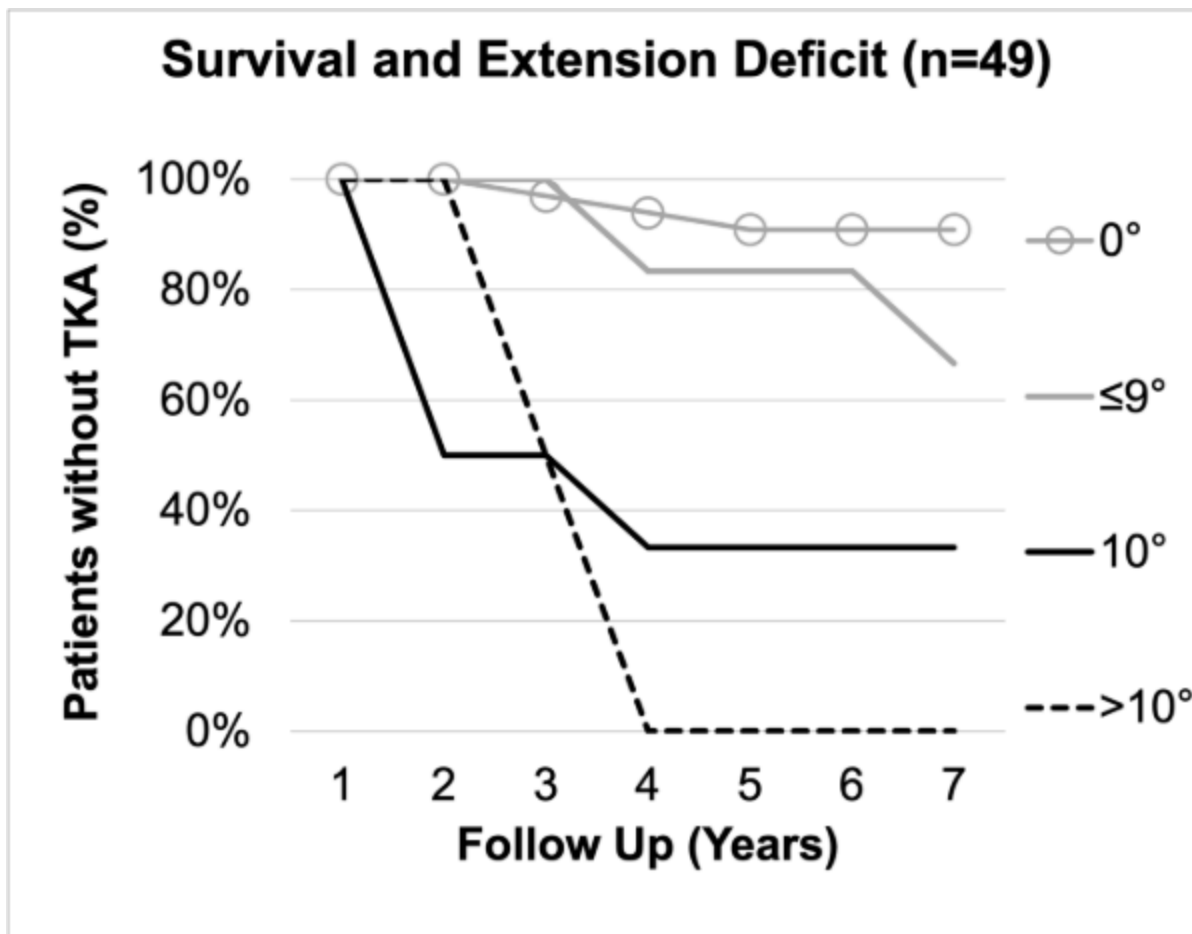


Figure 3

**Figure 4. TKA-free Kaplan-Meier survival stratified by baseline extension deficit: Failure versus Success:**  
 $7.2^\circ \pm 5.6^\circ$  vs  $1.1^\circ \pm 2.6^\circ$ ;  $p = .002$ .

## Survival and BMI (n=49)

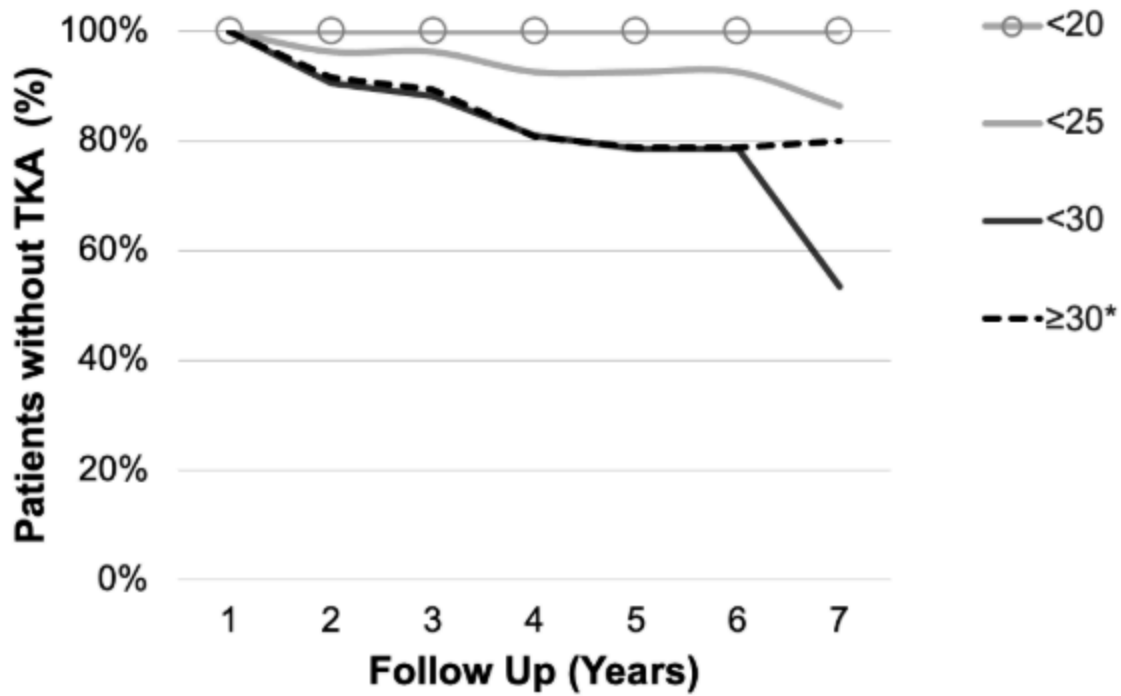


Figure 4

**TKA-free Kaplan-Meier survival stratified by baseline extension deficit:** Failure versus Success:  $7.2^\circ \pm 5.6^\circ$  vs  $1.1^\circ \pm 2.6^\circ$ ;  $p = .002$ .

## Success (no TKA) over time

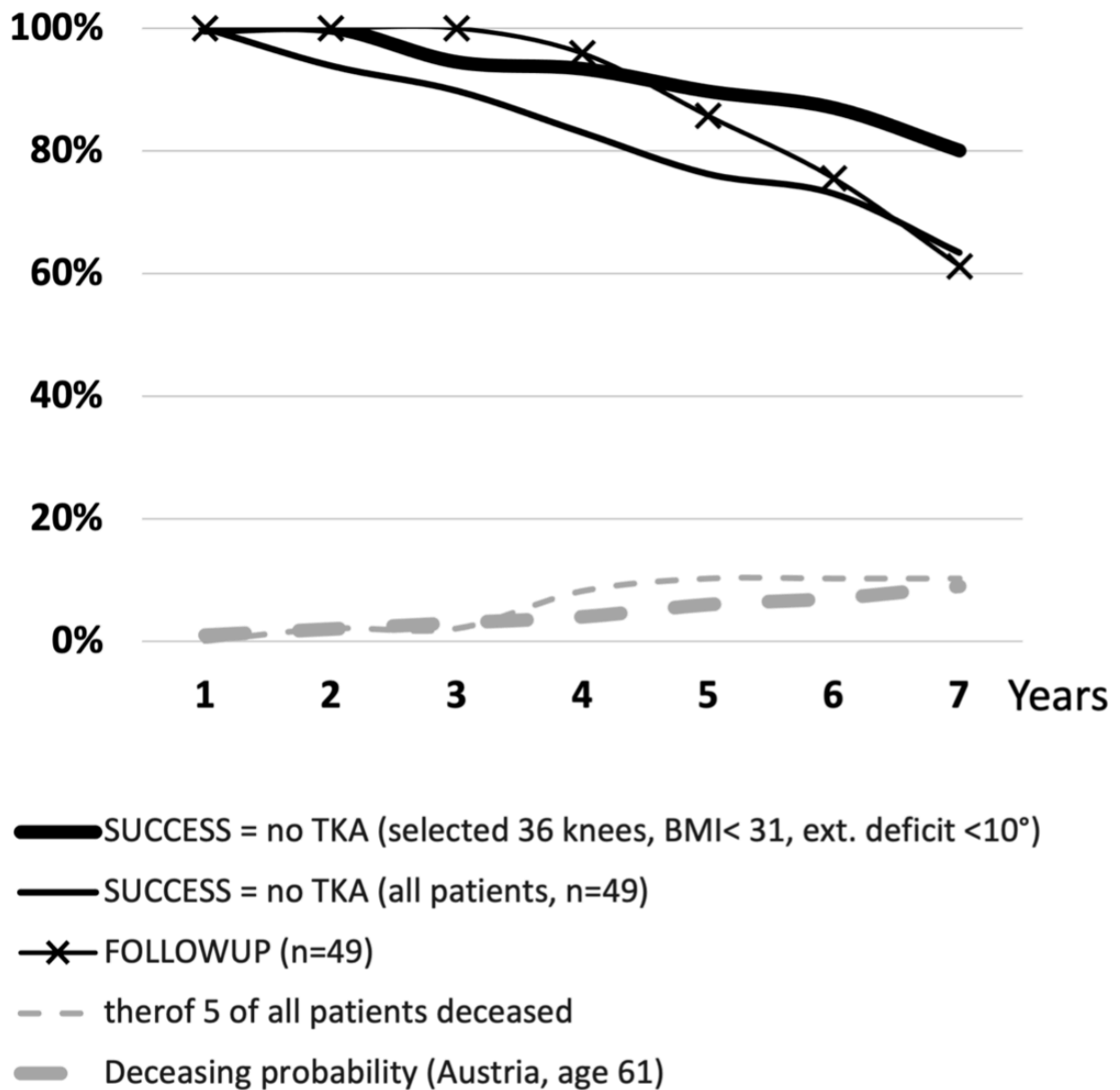


Figure 5

Figure 5. TKA-free Kaplan-Meier survival stratified by BMI: Failure versus Success:  $27.1 \pm 4.7$  vs  $24.4 \pm 3.9$  kg/m<sup>2</sup>;  $p = .05$ .

\* limited number of knees with BMI  $\geq 30$  (n=5)