

Sex does not influence the long-term outcome of matrix-assisted autologous chondrocyte transplantation

Manuela Salerno¹  | Luca Andriolo² | Lucia Angelelli² | Roberto Buda³ | Cesare Faldini⁴ | Alberto Ferruzzi⁴ | Francesca Vannini⁴ | Stefano Zaffagnini² | Giuseppe Filardo¹

¹Applied and Translational Research Center, IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy

²Clinica Ortopedica e Traumatologica 2, IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy

³Clinica Ortopedica e Traumatologica, Ospedale SS Annunziata, Chieti, Italy

⁴Clinica Ortopedica e Traumatologica 1, IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy

Correspondence

Luca Andriolo, Clinica Ortopedica e Traumatologica 2, IRCCS Istituto Ortopedico Rizzoli, via G.C. Pupilli 1, Bologna 40136, Italy.

Email: lucas.andriolo@gmail.com

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Abstract

Purpose: Regenerative techniques for articular cartilage lesions demonstrated heterogeneous clinical results. Several factors may influence the outcome, with sex being one of the most debated. This study aimed at quantifying the long-term influence of sex on the clinical outcome obtained with a regenerative procedure for knee chondral lesions.

Methods: Matrix-assisted autologous chondrocyte transplantation (MACT) was used to treat 235 knees which were prospectively evaluated with the International Knee Documentation Committee (IKDC), EuroQol visual analogue scale, and Tegner scores at 14-year mean follow-up. A multilevel analysis was performed with the IKDC subjective scores standardised according to the age/sex category of each patient and/or the selection of a match-paired subgroup to compare homogeneous men and women patients.

Results: At 14 years, men and women showed a failure rate of 10.7% and 28.8%, respectively ($p < 0.0005$). An overall improvement was observed in both sexes. Women had more patellar lesions and men more condylar lesions ($p = 0.001$), and the latter also presented a higher preinjury activity level ($p < 0.0005$). Men had significantly higher IKDC subjective scores at all follow-ups (at 14 years: 77.2 ± 18.9 vs. 62.8 ± 23.1 ; $p < 0.0005$). However, the analysis of homogeneous match-paired populations of men and women, with standardised IKDC subjective scores, showed no differences between men and women (at 14 years: -1.6 ± 1.7 vs. -1.9 ± 1.6).

Conclusion: Men and women treated with MACT for knee chondral lesions presented a significant improvement and stable long-term results. When both sexes are compared with homogeneous match-paired groups, they have similar results over time. However, women present more often unfavourable lesion patterns, which proved more challenging in terms of long-term outcome after MACT.

Level of Evidence: Level II.

Abbreviations: ACI, autologous chondrocyte implantation; ACL, anterior cruciate ligament; AMIC, autologous matrix-induced chondrogenesis; EQ-VAS, EuroQol visual analogue scale; IKDC, International Knee Documentation Committee; MACT, matrix-assisted autologous chondrocyte transplantation; OA, osteoarthritis.

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KEYWORDS

cartilage regeneration, gender, knee, long-term follow-up, matrix-assisted autologous chondrocyte transplantation, sex

INTRODUCTION

Articular cartilage lesions are a frequent condition characterised by pain and functional disability. [74] Untreated chondral lesions lead to long-term degenerative changes [1, 2], finally leading to osteoarthritis (OA), with a remarkable social burden [3, 4]. Cartilage limited self-healing capacity represents a challenge for the orthopaedic surgeon, who ideally aims at restoring the articular surface with a hyaline-like cartilage resembling the physiological tissue [5]. To address these lesions, regenerative techniques—like autologous chondrocyte implantation (ACI) and its evolution matrix-assisted autologous chondrocyte transplantation (MACT)—have been developed. These regenerative approaches have been extensively studied, demonstrating good clinical results stable over time [6–13]. However, not all patients with proper indication benefit the same and a clinical profiling approach led to discovery of several negative prognostic factors on the final outcome [14]. Conclusive evidence has been published for some of these factors, like degenerative aetiology and OA, while others present more controversial results. One of the most debated aspects is sex [14–20].

Sexual dimorphism has been described for several orthopaedic conditions [21, 22], and also for cartilage surgery different results have been reported based on sex. Lower clinical results have been observed in women at mid-term follow-up both after MACT [23] and after autologous matrix-induced chondrogenesis (AMIC) [19]. Women also experienced more failures than men after cartilage surgery, ranging from microfractures to chondrocyte-based treatments [18, 24, 25]. On the other side, other authors did not find sex as a predictor of failure after ACI [26], and a systematic review analysing ACI results at mid-term follow-up demonstrated that patient's sex was not related to the clinical outcome [27]. Some authors reported even better clinical results for women compared to men after cartilage surgery, including MACT, AMIC and osteochondral scaffold [28, 29]. Even within the same study on a large population of 5000 patients treated with different knee cartilage procedures results were controversial: women showed a higher postoperative knee injury and osteoarthritis outcome score (KOOS) increase, but also lower absolute KOOS values, a higher revision rate and higher subjective dissatisfaction [28]. The contradictory findings may be due to the limitations of the previous studies, some presenting large numbers but heterogeneous patients,

some documenting only short- to mid-term follow-ups not suitable to fully understand the impact of patient sex on the results over time, others having too small patient cohorts to properly investigate subgroups based on sex.

The aim of this study was, therefore, to evaluate at long-term follow-up the influence of sex on the clinical outcome of a large cohort of patients treated with MACT for knee cartilage lesions.

MATERIALS AND METHODS**Patient selection and surgical treatment**

To address the study aim, this follow-up study (Level of Evidence, 2) investigates at long-term a series of patients whose mid-term results were previously published in the *American Journal of Sports Medicine* [18]. Between 2000 and 2006, patients with a symptomatic focal grades III–IV (ICRS evaluation) cartilage lesion involving femoral condyles, trochlea, and patella were treated after approval of the Ethics Committee of the Istituto Ortopedico Rizzoli in Bologna. Exclusion criteria: untreated malalignment or instability, previous/combined complete meniscectomies (>50%), bipolar ('kissing') lesions, diffused OA, previous intra-articular fractures, and other general medical conditions (e.g., diabetes, rheumatoid arthritis). Patients with axial deviation or an anterior cruciate ligament (ACL) lesion underwent a combined surgical procedure of realignment or ACL reconstruction in the same surgical session with cartilage harvesting. All patients were treated by surgeons of two specialised groups of the same institution experienced in regenerative procedures with the MACT technique in two steps as previously described [18]. Briefly, in the first step, a 150–200 mg biopsy sample of healthy cartilage taken from a nonweight-bearing knee area (intercondylar notch) was obtained for chondrocyte cell culture and subsequent seeding onto the hyaluronan-based scaffold (Hyaff 11; Fidia Advanced Biopolymers Laboratories). In the second one, the resulting bioengineered tissue (Hyalograft C; Fidia Advanced Biopolymers Laboratories) was cut to fit the defect and then was placed into the prepared lesion without the need of any fixation method because of the intrinsic adhesive properties of the hyaluronan scaffold. The scaffolds were implanted arthroscopically [30] or through a miniarthrotomy approach, based on the lesion location and the surgeon's preference [23].

Data collection and follow-up evaluation

Of the 250 knees documented at mid-term follow-up [18] 235 were available for the long-term analysis, while 15 patients (6%) were lost to follow-up (lost contact, $n = 14$; death, $n = 1$). There were 169 lesions in men and 66 in women. Among these patients, two cohorts of males and females with homogeneous characteristics were subsequently extracted by a blinded independent statistician to perform a match-paired comparative analysis. The selected cohorts comprised 50 males and 50 females with similar age, body mass index, mechanism of injury, lesion site and size and rate of previous or combined surgery. Patients' characteristics of the general population and homogeneous match-paired groups are reported in Table 1.

The operation was considered to have failed if the patient needed a re-operation because of symptoms related to the primary defect, regardless of the interval between first surgery and reoperation, and the last evaluation before the reoperation was reported at every subsequent follow-up. Patients were evaluated before surgery, at short-term (1 and 2 years), at mid-term (minimum 5-year, 8.4 ± 1.5 mean final follow-up, range: 5–9), and finally at long-term follow-up. The final mean follow-up was 14.3 ± 3.4 years (range: 10–22). The mean age of men and women at final follow-up was 44.9 ± 11.0 and 47.5 ± 12.2 , respectively. The clinical outcome at final follow-up was evaluated with the International Knee Documentation Committee (IKDC)

subjective score, EuroQol visual analogue scale (EQ-VAS), and Tegner score by a phone interview.

The analysis entailed different levels: after the analysis of the raw data, another analysis was performed on the IKDC subjective scores standardised for each patient at each follow-up according to their corresponding sex and age category in a healthy population, as demonstrated by Anderson et al. [31]. In this paper, the authors showed that IKDC subjective scores in the healthy population varies according to different age and sex groups, with a decrease in maximum obtainable scores for older patients and women both with and without a history of knee problems. In parallel, homogeneous subgroups selected among all patients were compared in a match-paired analysis. Finally, a further analysis level focused on comparing sex-based results in the two homogeneous match-paired groups evaluated with standardised scores.

Statistical analysis

All continuous data were expressed in terms of the mean and the standard deviation of the mean. One-way analysis of variance with the Scheffé post-hoc pairwise analysis was performed to assess differences among groups when the Levene test for homogeneity of variances was not significant ($p < 0.05$); otherwise, the Mann–Whitney test (two groups) or the Kruskal–Wallis test with the nonparametric post-hoc

TABLE 1 Patients' characteristics at surgery.

	Total group ($n = 235$)			Match-paired group ($n = 100$)		
	Men ($n = 169$)	Women ($n = 66$)	p Value	Men ($n = 50$)	Women ($n = 50$)	p Value
Age, mean \pm SD	30.8 ± 10.7	32.6 ± 12.0	NS	32.9 ± 10.1	33.9 ± 11.0	NS
BMI, mean \pm SD	24.8 ± 2.8	22.9 ± 3.7	<0.0005	24.6 ± 2.4	23.4 ± 3.7	NS
Mechanism of injury, %			NS			NS
Degenerative	49.7	60.6		66.0	62.0	
Nondegenerative	50.3	39.4		34.0	38.0	
Traumatic/OCD	26.0/24.3	19.7/19.7		12/22	20/18	
Lesion site, %			0.001			NS
Condyles	80.5	68.2		76.0	76.0	
Patella	10.6	28.8		22.0	22.0	
Trochlea	8.9	3.0		2.0	2.0	
Defect size, mean \pm SD, cm^2	3.0 ± 1.6	3.2 ± 1.6	NS	2.8 ± 1.2	3.2 ± 1.6	NS
Previous surgery, %	59.8	65.2	NS	70.0	74.0	NS
Combined surgery, %	40.2	33.3	NS	42.0	28.0	NS
Tegner preinjury score, mean \pm SD	6.7 ± 1.9	4.9 ± 1.9	<0.0005	6.3 ± 2.1	4.5 ± 1.8	<0.0005

Note: Characteristics of the general groups and match-paired groups. The selection process produced two homogeneous groups, with the only difference being the higher preinjury activity level in men.

Abbreviations: BMI, body mass index; OCD, osteochondritis dissecans.

pairwise least significant difference test was used. The Spearman rank correlation was used to assess the correlation between continuous variables and the scores. The Kaplan–Meier survival analysis was used to estimate the failure rate; the Log rank test was used to assess the influence of sex on the survival. The Pearson χ^2 test, evaluated by exact methods was performed to investigate the possible factors associated with dropouts. Logistic regression with backward Wald method was performed as multivariate analysis to identify any parameter independently influencing the possibility of a dropout. The subgroup for the match-paired analysis was made using propensity score matching (factors considered were chosen using logistic regression and weighted according to $W_i = \frac{\min(1 - e_i, e_i)}{Z_i e_i + (1 - Z_i)(1 - e_i)}$ where Z_i were the factors and e_i the odds ratio of the logistic regression. The chosen factors were then site, aetiology, previous surgery, associated surgery, age and size). The appropriateness of the sample size was confirmed by considering the standardised IKDC at the final follow up: for a minimal clinically important difference of one points and a standard deviation of 1.7 points 100 cases for the matched pairs would guarantee an error $\alpha = 0.05$ with a power of 0.82. For all tests, $p < 0.05$ was considered significant. Statistical Analysis was carried out by the Statistical Package for the Social Sciences (SPSS) software version 15.0 (SPSS Inc.).

RESULTS

In this long-term follow-up study, 15 patients were lost to follow-up respect to the mid-term evaluation, representing a 6% dropout rate. Fisher's exact test and logistic regression, performed to identify possible

factors associated with dropouts, demonstrated that these patients did not differ from non-dropouts for sex or basal scores and other characteristics, thus bias and attrition in the study results were very unlikely [32].

The cumulative survival analysis at the latest follow-up showed a failure rate of 10.7% in men and 28.8% in women, with a significantly higher failure rate in women ($p < 0.0005$) (Figure 1).

In the general population, an overall postoperative improvement of all the evaluated scores was observed at all follow-ups in both sexes. EQ-VAS scores were significantly higher in men than in women at long-term follow-up (82.5 ± 15.4 vs. 74.4 ± 16.8 , respectively, $p < 0.0005$), with both sexes showing a significant decrease of the score at the last follow-up ($p = 0.008$ for men, $p = 0.022$ for women). Similarly, the activity level at final follow-up, evaluated with the Tegner score, was significantly higher in men than in women (4.5 ± 1.9 vs. 2.9 ± 1.4 , respectively, $p < 0.0005$), even though the scores in men dropped significantly at the last follow-up ($p < 0.0005$), remaining instead lower but stable in women (Table 2).

Regarding the IKDC subjective raw data in the general population, a significant increase was observed after surgery both in men and in women up to the last follow-up (Table 2). At the long-term follow-up, men obtained significantly higher scores than women (77.2 ± 18.9 vs. 62.8 ± 23.1 , respectively, $p < 0.0005$) (Figure 2).

After IKDC subjective scores standardisation [31] in the general population, the difference observed between sexes decreased compared to the previous analysis on raw data, but men still had higher scores compared to women at each follow-up (at final follow-up: -1.3 ± 1.7 vs. -1.9 ± 1.6 , respectively; $p = 0.001$). At 14 years, both women and men had stable scores compared to the mid-term follow-up (Figure 3).

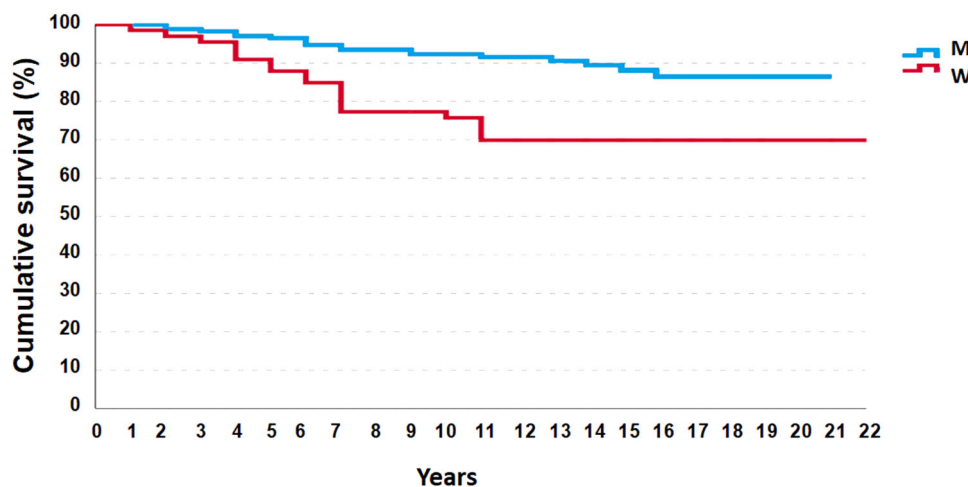


FIGURE 1 Men's and women's failure rate. Kaplan–Meier survival curve of women (red line) and men (blue line) in the general population (169 M, 66 W). Women had a significantly higher failure rate ($p < 0.0005$).

TABLE 2 Scores evaluated over time in the general population.

	Baseline	1 year	Improvement	2 years	Improvement	Mid-term follow-up	Improvement	Final follow-up	Improvement
IKDC, mean ± SD									
M	41.9 ± 14.2	74.0 ± 16.7 ^a	53.9 ± 28.5	78.3 ± 17.7 ^a	61.9 ± 29.8	79.9 ± 18.6 ^a	64.2 ± 32.8	77.2 ± 18.8 ^a	78.5 ± 17.7
W	33.6 ± 14.7	60.8 ± 18.4 ^a	39.8 ± 28.4	67.2 ± 19.7 ^a	49.3 ± 31.1	64.3 ± 20.5 ^a	44.9 ± 34.3	62.8 ± 23.1 ^a	64.6 ± 22.0
Sex comparison, <i>p</i> value	<0.0005	<0.0005	0.001	<0.0005	0.004	<0.0005	<0.0005	<0.0005	<0.0005
EQ-VAS, mean ± SD									
M	62.7 ± 20.6	83.1 ± 13.2 ^a	20.4 ± 21.2	84.2 ± 12.4 ^a	21.5 ± 22.2	86.1 ± 13.6 ^a	23.4 ± 24.6	82.5 ± 15.4 ^{a,b}	19.7 ± 26.3
W	57.9 ± 19.7	75.3 ± 16.9 ^a	17.4 ± 18.9	79.7 ± 15.1 ^a	21.8 ± 21.9	78.6 ± 15.3 ^a	20.8 ± 21.5	74.4 ± 16.8 ^a	16.5 ± 25.5
Sex comparison, <i>p</i> value	NS	0.001	NS	NS	NS	<0.0005	NS	<0.0005	NS
Tegner, mean ± SD									
M	2.1 ± 1.5	4.7 ± 2.0 ^a	2.6 ± 2.4	5.3 ± 2.3 ^a	3.2 ± 2.7	5.3 ± 2.2 ^a	3.2 ± 2.5	4.5 ± 1.9 ^{a,b}	2.4 ± 2.4
W	1.4 ± 1.1	2.8 ± 1.4 ^a	1.7 ± 1.4	3.1 ± 1.6 ^a	1.7 ± 1.6	3.0 ± 1.5 ^a	1.6 ± 1.7	2.9 ± 1.4 ^a	1.5 ± 1.4
Sex comparison, <i>p</i> value	<0.0005	<0.0005	<0.0005	<0.0005	<0.0005	<0.0005	<0.0005	<0.0005	0.013

Note: IKDC, EQ-VAS, and Tegner scores in the general population (169 M, 66 W).

Abbreviations: EQ-VAS, EuroQol visual analogue scale; IKDC, International Knee Documentation Committee.

^aSignificant improvement respect to baseline;

^bWorsening respect to 2-year or mid-term follow-ups.

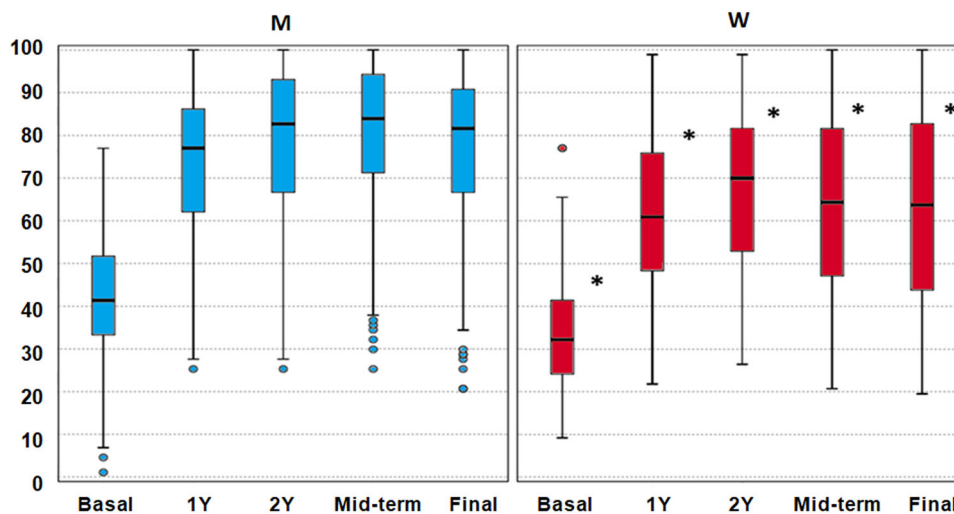


FIGURE 2 International Knee Documentation Committee (IKDC) subjective score over time in the general population. Post-surgical improvement of IKDC subjective score in men and women of the general population (169 M, 66 W) from before the operation to the follow-ups at 1, 2 years, mid-term, and final follow-up. Women had significantly lower scores ($p < 0.0005$, M vs. W). *Statistically significant difference between sexes.

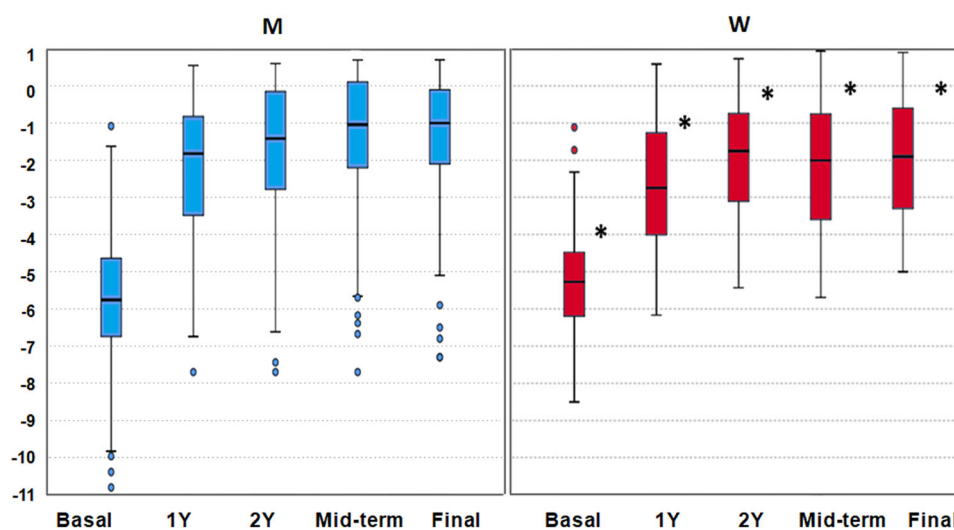


FIGURE 3 Standardised International Knee Documentation Committee (IKDC) subjective score over time in the general population. Post-surgical improvement of the IKDC subjective score in men and women of the general population (169 M, 66 W) from before the operation to the follow-ups at 1, 2 years, mid-term, and final follow-up after standardisation according to the mean score obtainable for each specific healthy patient category [31]. Women had significantly lower scores ($p = 0.031$ before the operation; $p = 0.020$ at 1 year; $p = 0.038$ at 2 years; $p = 0.001$ at 8 years; $p < 0.0005$ at 14 years, M vs. W). *Statistically significant difference between sexes.

The match-paired comparison of IKDC subjective scores between the homogenous groups of 50 men and 50 women confirmed that men still had significantly better IKDC subjective scores compared to women at all follow-ups except at 2 years (at final follow-up: 73.0 ± 19.8 vs. 61.7 ± 22.8 , respectively, $p = 0.010$). At 14 years, both women and men had stable scores (Figure 4).

The last level of analysis involving the homogeneous match-paired populations of men and women, with IKDC subjective scores standardised for their corresponding age and sex category [31], showed no differences

between sexes at all follow-ups. At final follow-up, both men and women had stable scores (at final follow-up: -1.6 ± 1.7 vs. -1.9 ± 1.6 , respectively) (Figure 5). The three-level analysis is graphically represented in Figure 6.

DISCUSSION

The main finding of this study is that hyaluronic acid-based MACT offers stable results at long-term follow-up in a large cohort of patients affected by cartilage

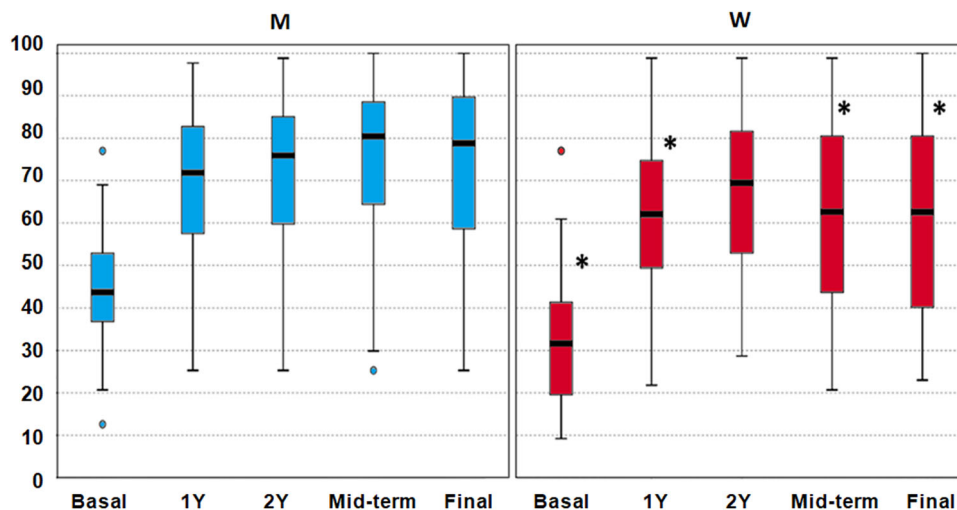


FIGURE 4 International Knee Documentation Committee (IKDC) subjective score over time in the match-paired subgroups. Post-surgical improvement of IKDC subjective score in men and women of the match-paired population (50 M, 50 W) from before the operation to the follow-ups at 1 year, 2 years, mid-term, and final follow-up. Women had significantly lower scores ($p < 0.0005$ before the operation; $p = 0.013$ at 1 year; $p = 0.006$ at 5 years; $p = 0.010$ at 14 years, M vs. W) except at 2 years (n.s.). *Statistically significant difference between sexes.

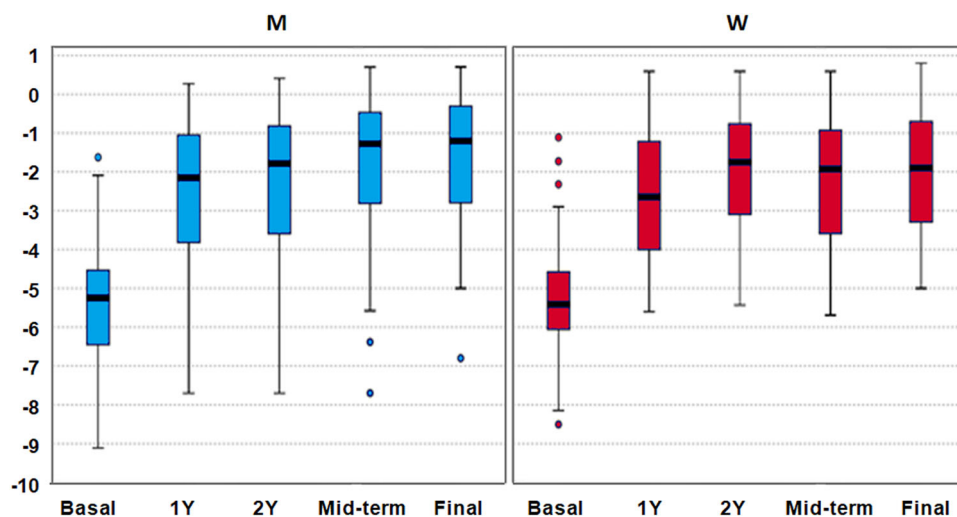


FIGURE 5 Standardised International Knee Documentation Committee (IKDC) subjective score over time in the match-paired subgroups. Post-surgical improvement of IKDC subjective score in men and women of the match-paired population (50 M, 50 W) from before the operation to the follow-ups at 1 year, 2 years, mid-term, and final follow-up after the standardisation according to the mean score obtainable for each specific healthy patient category [31]. No statistically significant differences were found between sexes.

lesions, providing the same chance of success for men and women with matched patient and lesion characteristics. However, women present more often unfavourable clinical conditions, leading to overall lower clinical results and a higher failure rate than men at long-term follow-up.

Chondrocyte-based techniques, like ACI, have been reported in the literature with overall good clinical results at long-term follow-up [34]. In particular, one of the first long-term reports of Peterson et al. showed that patients had a significant improvement of clinical scores and a 92% satisfaction rate [35], and another large study of Minas et al. found good to excellent

results in 78% of patients, with a failure rate of 25% [36]. Results on a smaller patient population showed a 63% survival rate up to 20 years after ACI and significant and sustained improvements in almost all clinical outcomes [10]. More recently, long-term data are emerging also for the new generation MACT. Different authors found a statistically significant increase of the clinical scores [37–40], or stable results [6, 33, 41, 42] at long-term follow-ups. However, the understanding of sex-related differences is limited to a small number of studies reporting controversial results. Besides, contrasting information on the final outcome after cartilage surgery are reported in the current

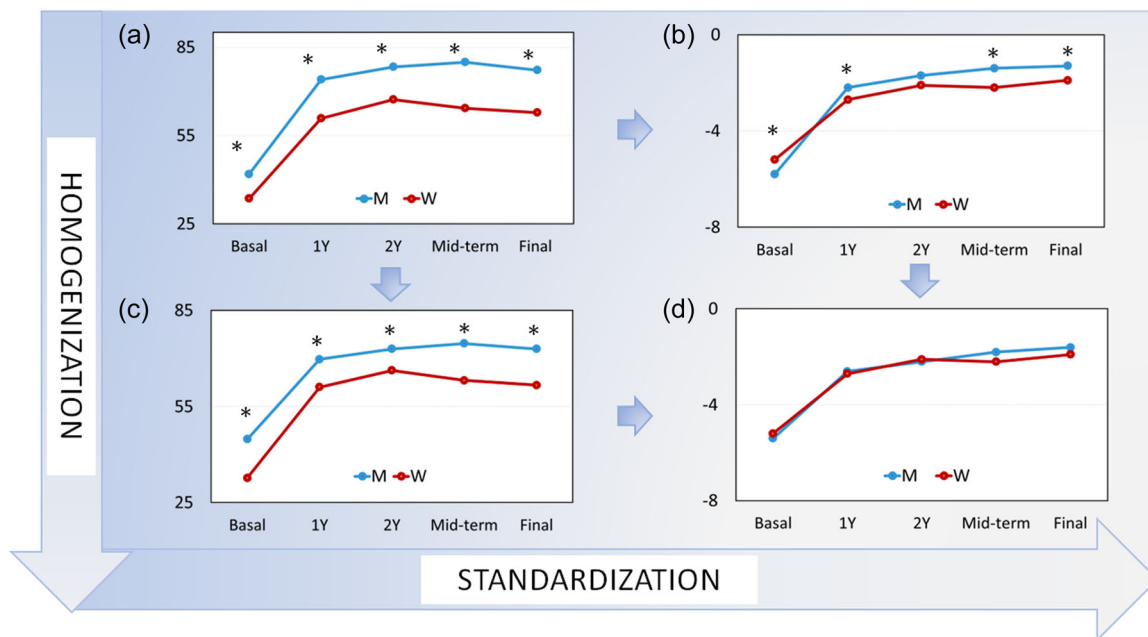


FIGURE 6 Multilevel analysis of the International Knee Documentation Committee (IKDC) subjective score. The analysis has been performed at different levels, starting from raw scores of the general population who underwent matrix-assisted autologous chondrocyte transplantation surgery (a), which were then standardised according to patients' age and sex category (b). Afterwards, raw scores (c) and standardised scores (d) were compared between two selected match-paired subgroups of 50 homogeneous patients each. Women presented lower scores in the general population. However, when match-paired men and women groups with standardised scores were compared, no significant differences based on sex were detected. *Statistically significant difference between sexes.

literature, making sex one of the most debated negative prognostic factors. Berruto et al. reported better results for men in a cohort of 32 patients treated with ACI or MACT and evaluated at 13 years of follow-up [43]. Also Kon et al. reported lower results at 10 years of follow-up for women in 32 patients treated with MACT for cartilage lesions of the patellofemoral joint [42]. On the other side, other studies did not observe any difference in clinical scores at long-term follow-up, but reported an increased likelihood of failure for women after cartilage procedures [6, 24, 45]. In summary, while different series documented the overall results at long-term follow-up, there is still a lack of gender-specific data and analysis to clarify the role of sex in determining the long-term treatment outcome.

This study performed a long-term evaluation of a large series, previously studied at mid-term follow-up [18], both in terms of surgical success over time and of sex role in the final outcome after MACT treatment. In that study, 250 patients were analysed aiming at understanding if the literature-reported differences between men and women could be explained by either sex- or gender-related factors. In fact, even if they are often used as synonyms, sex and gender are two specific terms defining different aspects: sex refers to the biological and physiological characteristics that define women and men, while *gender* refers to the socially constructed roles, behaviours, activities and attributes that a given society considers appropriate for

women and men [18]. However, results were limited to a mid-term follow-up. Cartilage surgery is mainly performed in young patients, who expect to recover an active lifestyle and maintain it for a long-time. Since a progressive worsening over time was documented for cartilage procedures [35, 46, 47], possibly due to a deterioration of the tissue quality of the regenerated cartilage [48, 49], a long-term evaluation is paramount.

In the present study, 235 patients were prospectively followed up for a mean of 14 years after MACT for the treatment of knee chondral lesions. At this long-term follow-up, the analysis was performed at different levels. In the general population, the overall post-operative improvement of clinical scores observed in the previous mid-term study was maintained at 14 years' follow-up in both sexes, with long-term results in line with current literature findings [6, 7, 10–13, 15, 20, 33]. Further analysis underlined that women had worse results than men for all the clinical scores analysed. In particular, the raw IKDC subjective scores were significantly higher in males than in women, with a difference of almost 15 points and the cumulative survival analysis at 14 years confirmed a significant higher failure rate in women, as reported by previous studies [6, 24, 42, 43, 45]. The reason for these different results between men and women may be attributed to several factors. In fact, a sexual dimorphism has been reported by a substantial body of research for several physiological and pathological

aspects, ranging from response to sexual hormones, to anatomical and biomechanical characteristics. More in detail, specific receptors for sex hormones were found in human foetal cartilaginous tissue [5], and in human chondrocytes [50–52], where they can modify the turnover of matrix proteins in a dose- or age-dependent manner [53–55]. Moreover, adult males have 33%–42% higher knee cartilage volume than females at all sites, also after adjustment for physical characteristics and sport activity levels [56–58]. Cartilage composition and walking mechanics, including thinner cartilage, tendency to malalignments, joint instability and irregular loading make women more prone to lateral compartment cartilage loss and to the development degenerative conditions such as OA [59–62]. Even before the onset of clinical knee OA, gender-related differences represent a predisposition to cartilage lesions. Female sex has been associated with an increase in tibiofemoral cartilage defects and, at the patella, with a greater loss of cartilage volume [44, 59] becoming more marked from the age of 40 years [57]. Low quadriceps strength in women appears to contribute to the worsening of knee joint space narrowing, increasing the risk of cartilage damage in the tibiofemoral and patellofemoral joints [63, 64]. Finally, a study on healthy adolescents reported that female knee proprioception is less accurate compared to males, possibly contributing to the high incidence of knee injuries in females [65]. In this light, the data about failures appear to confirm a sex-related difference. Still, an in-depth analysis of the clinical outcomes showed a more complex scenario.

In this study, the analysis of the general population showed higher clinical scores in men compared to women. However, the measurement of the clinical outcomes is based on scales which present intrinsic biases. Indeed, it has been demonstrated that the evaluation of the normative data of the IKDC form in the healthy population varies according to different age and sex groups [31]. In detail, Anderson et al. demonstrated that an age-related decrease in scores may be observed both in patients with or without a history of knee problems, treatments and surgery. Moreover, women had lower scores than men when comparing the same age groups. Based on these findings, authors suggested that results from male and female patients should be referenced to the specific sex and age cohorts in clinical studies using the IKDC Subjective Knee Form. Thus, in the second level of analysis of the current study the IKDC subjective scores of the general population were compared between sexes after standardisation according to their sex and age category [31]. Having adjusted and thus more reliable values is even more important at such a long-term evaluation. In fact, some patients presented a switch of two age categories according to Anderson et al. [31], which could make raw data unrepresentative and not

comparable to those at baseline or shorter follow-ups, or to those of other patients. Nevertheless, after standardisation, women still presented significantly lower scores also at 14 years. This could be explained by considering that the males and females of this cohort significantly differed for defect localisation.

A higher percentage of women presented patellar lesions as well as a higher percentage, as well as many degenerative cartilage defects. Patellar lesions are known to be more common in females [28], reasonably due to their lesser retropatellar cartilage volume and lower quadriceps strength [56, 64]. Moreover, it has been demonstrated that the clinical results after cartilage treatment of a lesion located on the patella are lower compared to other locations [66]. In the female sex, this may be related to an insufficient proprioception and imbalances in muscle forces typical of women [67]. Furthermore, altered biomechanical characteristics have been found in women, like patellar orientation and tracking as well as tibiofemoral rotation at low flexion angles, that might alter contact pressures in the patellofemoral compartment, contributing to the worse outcome when subjected to cartilage repair restoration [68, 69]. Given also the lower activity level, which is confirmed in the current study, women are less subjected to traumatic lesions that are known to have a better clinical outcome [70], experimenting instead the more challenging degenerative conditions [71].

To remove the influence of these factors, two match-paired groups were blindly selected among the general population. The resulting two subgroups of males and females were homogenous for all characteristics except for Tegner activity level that remained significantly higher in men. While the analysis of raw scores showed significantly lower long-term IKDC values, after standardisation of the scores in the match-paired groups, no significant differences were confirmed at any follow-up, including the final long-term follow-up. Accordingly, women present more often unfavourable conditions but, when considered on equal terms, men and women have the same chance of success at long-term follow-up after cartilage surgery.

This study presents some limitations. First of all, there is not a complete homogeneity between the match-paired groups. In detail, the activity level was higher in men compared to women, and this may entail a more traumatic nature of the lesions (even though the aetiology was corrected in the match-paired analysis) and a higher compliance to rehabilitation protocols. It has been suggested that male athletes may minimise their symptoms in an effort to return to sport sooner and present lower disability, pain and depression compared to females, which are typically more concerned about long-term implications of the athletic injury and their future health [14, 72, 73]. Moreover, this is a survey-based analysis based on predefined clinical scores that might neglect some other important social or

psychological aspects or possible surgeon's different approaches during operations and results are far from being conclusive. Even the influence of biological and biomechanical factors could not be taken into account, and future studies should specifically analyse these aspects. Nonetheless, the high number of patients evaluated at such long-term follow-up and the robust methodology applied with a three-level analysis to specifically investigate results in men and women allowed to shed some light on the long-term influence of sex on the outcome of cartilage surgery. These results may be useful in designing and analysing studies on cartilage regeneration and may be of clinical relevance as well in clinical practice by providing patients undergoing regenerative cartilage treatments with more realistic expectations.

CONCLUSIONS

This long-term study on a large cohort of men and women treated for cartilage lesions demonstrated that MACT results are stable over time and sex per se does not imply a lower success potential. When both sexes are considered on equal terms, they have similar good results over time. However, the final scores and failures differ in the general population since women present more often unfavourable lesion patterns, which proved more challenging in terms of long-term outcome after MACT.

AUTHOR CONTRIBUTIONS

Giuseppe Filardo: Conceptualisation. **Luca Andriolo, Manuela Salerno, and Lucia Angelelli:** Methodology. **Manuela Salerno and Lucia Angelelli:** Data curation. **Manuela Salerno:** Writing—original draft preparation. **Luca Andriolo and Giuseppe Filardo:** Writing—review and editing. **Giuseppe Filardo, Cesare Faldini, and Stefano Zaffagnini:** Supervision. **Lucia Angelelli, Roberto Buda, Alberto Ferruzzi, and Francesca Vannini:** Patients' evaluation. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

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BIOMET, and Kensey Nash, outside the submitted work. The remaining authors declare no conflict of interest.

ETHICS STATEMENT

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Ethics Committee of IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy (Prot. n. 0001748, 01/02/2023). Informed consent was obtained from all subjects involved in the study.

ORCID

Manuela Salerno  <http://orcid.org/0000-0003-4830-0988>

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