DR. ACHILLE MARINO (Orcid ID : 0000-0002-3027-8009)

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Early joint replacement in juvenile idiopathic arthritis (JIA): trend over time and factors influencing implant survival

Achille Marino[1], MD, PhD
Irene Pontikaki[2], MD,
Marcello Truzzi[2], MD,
Alessandra Menon[3], PhD,
Carolina Artusi[2], MD,
Marco Di Marco[2], MD,
Pietro S. Randelli[2,4], MD, Prof,
Rolando Cimaz[2,5,#], MD, Prof
Roberto Viganò[2 #], MD.

1 Department of Pediatrics, Desio Hospital, ASST Monza, Desio, MB, Italy
2 ASST G.Pini-CTO, Milan, Italy
3 Laboratory of Applied Biomechanics, Department of Biomedical Sciences for Health, University of Milan, Milan, Italy
4 Department of Biomedical Sciences for Health, University of Milan, Milan, Italy
5 Department of Clinical Sciences and Community Health, and Research Center for Adult and Pediatric Rheumatic Diseases, University of Milan, Milan, Italy
# These authors contributed equally to the manuscript.
Corresponding Author:
Achille Marino
Department of Pediatrics,

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Desio Hospital,
Desio, Via Mazzini 1,
MB, Italy, 20832
Phone +39 0362 383 204
Fax +39 0362 383 028
achillemarino6@gmail.com

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Abstract

Objective

To describe early prostheses implantation in a cohort of patients with juvenile idiopathic arthritis (JIA) followed in a tertiary referral hospital and to analyze possible factors influencing implant survival.

Methods

This is a retrospective cohort study. Charts of all JIA patients who underwent total joint replacement at G. Pini Hospital, Milan, Italy from January 1992 to June 2019 were retrieved, and relevant data were analyzed.

Results

Eighty-five patients met the inclusion criteria for this study, with a median follow-up of 17.2 years. The median age at first prosthesis was 22.7 years. The total number of replaced joints was 198 over a period of 27 years. The hip was the most replaced joint accounting for almost two thirds of the total number of implants; the other third refers mostly to knee implants. Polyarticular (polyJIA) and systemic (sJIA) were the most represented JIA categories in the study cohort. A significant upward trend of the age at arthroplasty and of disease duration before arthroplasty over

decades was found. The rates of implant survival at 5, 10 and 15 years were comparable (from 84% to 89%); 50% of implants lasted 20 years or more.

Conclusions

We reported retrospective data on early joint replacement in a cohort of patients with JIA. We observed a progressive and significant upward trend of both age at arthroplasty and disease duration before the first arthroplasty over time. JIA category, year of implants and the presence of complications significantly affected implant survivorship.

Significance and Innovations.

- One of the largest study on total joint replacement in juvenile idiopathic arthritis (JIA) patients
- The long follow-up allowed us to detect changes over time in the age at first arthroplasty and disease duration before the surgical procedure
- We observed a significant upward trend over decades of the age at arthroplasty and of disease duration before arthroplasty
- JIA category, year of surgery and presence of complications significantly affected implant survival

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic condition in childhood with a prevalence ranging between 16 and 150 per 100,000. JIA is not a single disease, but includes all arthritides starting before 16 years, lasting for more than 6 weeks and of unknown etiology [1]. JIA has been always considered an important cause of short- and long-term disability, especially in the past when many patients failed to respond to medical treatment and required surgical management, up to joint replacement.

The ideal goal of therapy is to achieve the status of inactive disease and to prevent joint damage. However, it is not easy to reach and maintain this goal, especially for certain JIA categories such as polyarticular and systemic JIA, which are at high risk of joint damage [2].

Over the last decades, progress in knowledge of disease pathogenesis and the opportunity of new therapies acting on specific targets have led to a significant improvement in the management of JIA. Even if the rate of arthroplasty among JIA patients is decreasing [3], some patients may still show persistent disease activity leading to joint deformity, with the need to replace their damaged joints. When medical therapy fails, total joint replacement represents the standard treatment to obtain pain relief associated with a better functional outcome. Indeed, joint arthroplasty is considered the only solution for those JIA patients with severely damaged joints into adulthood, when full growth has been reached.

Surgery in JIA patients is challenging for multiple reasons. Due to the young age at arthroplasty, patients' compliance is not always easy to obtain. This influences both the preoperative management and the recovery phase, and patients' education is crucial for a good outcome. The inflammatory nature of the disease may compromise bone quality and therefore condition the surgical approach, with negative consequences on implant survival in short- and long-term [4]. Furthermore, particular attention should be reserved to the perioperative management of the immunosuppressive therapy, according to current recommendations [5].

Herein we describe a cohort of JIA patients followed in a tertiary referral hospital who underwent total joint replacement over a period of 27 years. We analyzed possible factors influencing implant survival, including medical therapy and surgical technique improvements over time .

Patients and Methods

This is a retrospective cohort study; patients were enrolled at Gaetano Pini Hospital, Milan, Italy from January 1992 to June 2019.

Inclusion criteria. All JIA patients who underwent total joint replacement followed in our institute. Patients had to be diagnosed with JIA according to the International League of Association for Rheumatology (ILAR) criteria [6] and to be followed for at least 1 year after the first surgical procedure.

Exclusion criteria. Presence of another chronic disease that may alter implants' outcome (e.g. chronic renal insufficiency and metabolic disease impacting bone quality); patients without sufficient data were also excluded.

Initially 94 patients were identified, nine of them were than excluded: 6 had a diagnosis of rheumatoid arthritis, 2 were diagnosed with adult onset Still's disease, and one JIA patient did not have sufficient data to be analyzed.

Data extracted from medical charts were collected in a customized database; these included demographic information, JIA category, age at disease onset, biologic treatment before implant and duration, corticosteroid therapy ("ever" and "at the time of surgery"), use of disease modifying anti-rheumatic drugs (DMARDs) ("ever" and "at the time of surgery"), number of implants for each patients, date of arthroplasty, age and disease activity at time of surgery (abstracted from last rheumatology evaluation within 3 months before surgery), replaced joint. Implant information included type, i.e. whether regular (first implant prosthesis), customized (individually tailored) or hybrid (a combination of regular implant and revision of one component), revision date if available, prosthesis complications if any and date of last orthopedic follow-up.

A multidisciplinary team including rheumatologists and orthopedic surgeons expert in inflammatory arthritis had assessed the eligibility for total joint replacement, the best timing for surgical procedure and the perioperative management of medical therapy.

Primary aim of the study was to describe our cohort including patients' demographic and clinical features along with the number and type of implants. Secondary objectives included outcome measures such as rate of complications and implant survival, along with the identification of possible differences over 27 years in terms of age at arthroplasty, disease duration before implant, number of complications and number of revisions.

Complications were defined as follows: intraoperative fracture, periprosthetic local or systemic infections, wound dehiscence, and prosthesis aseptic mobilization. The latter refers to the wear of

implant components that may cause the loosening of the connection between bone and prosthesis and the consequent mobilization of the prosthesis itself. Implant survival was defined as the time interval between the date of prosthesis and revision if any, or of the last orthopedic evaluation in the presence of a functionally efficient prosthesis.

Statistical analysis

Statistical analysis was performed using GraphPad Prism v 6.0 software (GraphPad Software Inc.) and SAS software, version 9.4 (SAS Institute, Inc., Cary, NC). Continuous variables were expressed as the mean ± standard deviation (SD) or medians and first and third quartiles [Q1 - Q3], as appropriate. The Shapiro-Wilk normality test was used to evaluate the normal distribution of the sample. The differences among groups of implants according to the year of surgery were evaluated with one-way ANOVA or Kruskal-Wallis t-test, according to the characteristics of the data distribution. When significant interaction effects were found, Dunn's multiple comparisons test was applied as a post hoc test for multiple comparisons of groups. Categorical variables are expressed in numbers of cases and frequencies.

Implant survival was represented by a Kaplan-Meier curve; factors predicting survival were identified fitting Cox regression models. For all analyses, the significance level was set at p-value lower than 0.05.

Results

Patients' features and prostheses data

Eighty-five patients met the inclusion criteria for this study with a median follow-up of 17.2 years (mean = 18.1 y ± SD 8.22). The majority of patients were female (65%).

The median age at first prosthesis was 22.7 years (mean= 25.1 y ± SD 6.9): 30 patients had the first arthroplasty at age < 20 years, 41 patients between the age of 20 and 30 years and 14 patients at age > 30 years; only 3 patients had the first arthroplasty at age > 40 years, with the oldest aged 46.5 years; the youngest patient had the first implant at 14.3 years of age.

The total number of replaced joints was 198 over 27 years (Figure 1); 78% of patients received more than one implant, with the majority receiving 2 arthroplasties (2 arthroplasties for 38 patients, 3 arthroplasties for 9 patients, 4 arthroplasties for 19 patients). Clinical features and implant data are reported in Table 1.

Polyarticular (polyJIA) and systemic (sJIA) categories were the most represented in the study cohort, followed by oligoarticular JIA (oligoJIA); very few patients had psoriatic JIA (psoJIA) and enthesitis-related arthritis (ERA) (4 and 3 patients, respectively), and just one patient was diagnosed with undifferentiated arthritis. As expected, polyJIA and sJIa patients accounted for the higher number of implants (88 and 62, respectively) (Table 1).

There were no significant differences among the JIA categories in terms of age at arthroplasty, disease duration before surgical procedure, number of implants and rate of complications.

In the whole cohort, median disease duration before the first implant was 17.4 years; patients with sJIA had shorter disease duration at first implant, in particular when compared to polyJIA (15 y vs 19.0 y). The overall rate of complications was 13% (25 arthroplasties in 20 patients). Patients with sJIA accounted for about half of those having complications; of note, all surgery-related infections occurred among patients belonging to this category. Thirteen implants of 11 patients were revised; all implants had a complication before undergoing revision.

The hip was the most frequently replaced joint, accounting for almost two thirds of the total number of implants in the study cohort; the other third refers mostly to knee implants. Eight patients underwent total ankle replacement (3 patients with oligoJIA, 3 with polyJIA, and 2 with sJIA) usually after having undergone other arthroplasty procedures. Three of them had both ankles replaced (2 patients with sJIA and 1 with polyJIA). No implants complications were recorded.

The hip was also the first replaced joint in 70 (83%) patients. The rate of custom and hybrid implants was low, and regular prostheses were preferred in almost 80% of arthroplasties.

Furthermore, we investigated the medication history of each patient. We collected data on steroid treatment in terms of "ever use of steroids" before first prosthesis and "use of steroids at the time of surgery" with relative dosage (mg of prednisone/day). The majority of patients received steroids over their disease course: 52 out of 70 patients who had this information available. The rate of steroid use was higher in sJIA group than in polyJIA group (82% and 69%, respectively). Steroids were used at the time of surgery in 53 cases from 39 patients for which there were available data. The average dose of prednisone was higher in polyJIA patients rather than in sJIA (7.5 mg ± 6.0 vs 5.1 mg ± 3.2). Eighty percent of patients in our cohort received DMARDs, which were used at the time of surgery in 84 cases from 39 patients.

With regard to biological therapy, 30 patients had received at least one biologic drug before the first arthroplasty, with a median disease duration before the introduction of the drug of 11.33 years

(range 0.3 – 34.3 years). The median biologic duration until the first arthroplasty was 4 years. Of the remaining patients, 27 did not receive any biologic and for 28 subjects data regarding biologic drug history were not available.

Arthroplasty trend over time

We sought to investigate differences among implant features over 27 years. In order to do so, we grouped all arthroplasties by the year of surgical procedure: 28 implants were performed before 2000 (group A), 94 implants between 2000 and 2010 (group B) and 76 implants after 2010 (group C). Then, we compared the groups in terms of age at arthroplasty, disease duration before the implant, number of complications and number of revisions (Figure 2).

A significant difference of the age at arthroplasty was found between group A and group B (21.93 y vs 26.82; p = 0.02) and between group A and group C (21.93 y vs 27.81 y; p = 0.00).

The same upward trend was found with regard to disease duration before arthroplasty, with a significant difference between group A and group B (16.98 y vs 21.66 y; p = 0.02) and between group A and group C (16.98 y vs 22.93 y; p= 0.00). There were no significant differences between group B and group C. Furthermore, no significant differences were found among groups in term of number of complications or revisions.

Implant survival

The rates of implant survival at 5, 10 and 15 years were comparable, ranging between 84% to 89%, whereas about half of eligible implants lasted 20 years or more (Figure 3). Survival rates are shown in Table 2.

Hip and knee implants had similar survival rates over time. sJIA patients showed lower survival rates at 10, 15 and 20 years compared to polyJIA patients. Furthermore, we investigated the presence of any factor influencing implant survival. Gender, JIA category, age at disease onset and at arthroplasty, number of prostheses for each patient, year of surgery, ordinal number of the implant (first, second, etc), disease duration before arthroplasty, replaced joint, type of implant, presence of complications, and disease activity before surgery were analyzed. In multivariate analysis, the year of surgery was found to be significantly related to implant survival [Hazard Ratio (HR) 1.001, confidence interval (CI) 1.0001-1.0006; p< 0.001], as well as the presence of complications (HR 3.69, CI 1.82-7.48; p < 0.001). Furthermore, JIA categories influenced implants survival, since prostheses of polyJIA RF negative patients had a higher possibility to last

longer than those of sJIA patients (HR 0.23, CI 0.09-0.53; p= 0.00), as well as implants of all polyJIA (RF positive and negative together) compared to sJIA ($p < 0.001$).

Factors related to medical treatment were not included in the multivariate analysis due to the high number of missing data; univariate analysis was then performed. The results of this analysis showed that the duration of biologic therapy before implant and the use of steroids at the time of surgery had an impact on implant survival. In fact, longer treatment duration with biologic therapy before arthroplasty was found to be a predictor of poor implant survival (HR 1.17, CI 1.02-1.36; p=0.02), whereas steroid treatment at the time of surgical procedure was found to be a favorable predictor for implant outcome (HR 0.32, CI 0.14-0.72; p=0.00).

Discussion

JIA patients may need complete replacement of severely damaged joints, and considering the inflammatory nature of the disease they need to be treated by orthopedic surgeons specialized in dealing with these particular type of patients.

We reported retrospective data on early joint prosthesis in a JIA cohort of 85 patients over a time period of 27 years. Almost all patients had the first arthroplasty before 40 years of age, with a median age of 22.7 years. The hip was the most replaced joint, highlighting both the frequency of its involvement in JIA and its fragility.

Three quarters of patients included in this study belonged to polyarticular and systemic JIA subsets. Systemic JIA patients showed shorter disease duration before surgery when compared to polyJIA (15 y vs 19 y), highlighting the severity of this JIA category. The overall rate of complications was low (13%): aseptic mobilization was the most frequent one, followed by intraoperative fractures. Interestingly, patients in the sJIA category accounted for almost half of those with complications, although there was no significant difference among JIA subsets. A very low number of prosthesis revisions was observed; sJIA, once again, accounted for about half of them.

We observed a progressive and significant increase of both age at arthroplasty and disease duration before the first arthroplasty over time (Figure 2). Indeed, those treated before 2000 were younger (up to 6 years) at the time of surgery and had a shorter disease duration (up to 6 years) than those treated after 2000. No significant differences were detected between the two groups of

patients after 2000. Interestingly, the first anti TNF-α drug, etanercept, was licensed by the European Medicines Agency (EMA) in 2000 as well.

Our data are in agreement with those reported in a recent U.S. population-based study performed in patients with inflammatory arthritis, where the rate of arthroplasty decreased by nearly 50% from 1991 to 2005 (0.22 per 100,000 versus 0.13 per 100,000) with a concomitant increase of the age at the time of arthroplasty (30.9 years versus 36.7 years) [3].

The overall outcome of patients included in this study was good in terms of low rate of complications and implant survival.

Recently, Swarup et al. reported survival data of 97 hip implants from 56 JIA patients with a median follow-up of 12 years and an average age at arthroplasty of 22 years. The retrospective analysis was conducted between 1982 and 2011. The survival rates of implants at 5, 10 and 20 years (96%, 84% and 50%, respectively) were very similar to our findings. Of note, we reported a higher survival at 15 years (86% versus 62%)[4].

In 2014 Heyse et al. investigated the outcome of 349 knee implants of 219 JIA patients recruited in 5 hospitals between 1979 and 2011 with a median follow-up of 12 years. The average age at surgery was 29 years. The survival rates at 10 years was comparable to ours (95%), whereas 82% of implants reached 20 years of survival compared to our 50% [7]. A monocentric retrospective study involving 34 knee implants of 20 JIA patients reported a 20 year survival of 58% [8].

Although very few patients received total ankle replacement, the outcome of these implants (50% reached the target survival) reflected data reported in literature [9].

Patients who underwent total joint replacement more recently showed an improved implant survival; this may be due to several reasons. The improvements in medical therapy likely allowed a better bone quality at the time of surgery. Moreover, surgical advancements over almost three decades are not negligible. First, surgical instruments upgrading allowed to reduce the procedure lengths and invasiveness, with positive consequences on patient recovery. Also, the improvement of implants' design (bone interface architecture) and materials (availability of titanium components) contributed to implant survival (Figure 4). Lastly, the improvement over time of surgical skills of the same team, despite not quantifiable, is indisputable.

Among JIA categories in this cohort, sJIA patients showed worse implant survival when compared to polyJIA patients. This may reflect not only the overall burden of joint inflammation in sJIA but also its challenging treatment that often, given the use of corticosteroids, alters the bone quality

impacting implants' outcome. In our cohort, indeed, sJIA patients received more frequently steroids than polyJIA patients, even if this difference was not statically significant.

As expected, the presence of complications was found to negatively affect implant survival: in our experience, aseptic mobilization was the most frequent problem, followed by intraoperative fracture. This highlights the importance of bone quality for the stability of the prosthesis over time.

We tried to understand the possible impact of treatment on the prosthesis outcome. We found that longer biologic treatment was associated with shorter implant duration. This might be explained by the assumption that patients who need prolonged treatments, often switching several biologics, are the most difficult to treat and therefore this might impact the long-term results of total joint replacement. Interestingly, steroid treatment at the time of surgery was found to be a protective factor for implant survival.

So far, studies on arthroplasty in JIA mostly expressed the orthopedic point of view, without considering the possibility of different medical therapeutic strategies impacting the implant outcome. Multicentric retrospective studies, although benefitting of large numbers and, therefore having more generalizable results, carry intrinsic limitations: different medical treatment strategies and, most importantly, different surgical approaches. Indeed, Heyse et al. reported a large number of knee arthroplasties (219 patients and 349 knee implants) among JIA patients recruited from 5 hospitals (4 from the U.S. and one from Belgium) with different surgical teams and approaches [7]. On the contrary, monocentric studies have lower numbers, therefore, abstracting any conclusion might be risky. Examples are the study by Swarup et al. on total hip replacement (56 patients and 97 implants) [4] and the experience of Malviya et al with knee arthroplasty (20 patients and 34 implants) [8].

Moreover, looking at implant survival the follow-up time of the studies is crucial, indeed the average follow-up of both Heyse et al. [7] and Swarup et al. [4] studies is lower than ours (12 y vs 18 y), while our median follow-up is comparable to the one reported by Malviya et al. (16 y vs 17 y) [8].

Herein we reported the experience with total joint replacement of JIA patients in a third level center where both rheumatologic and orthopedic competencies are combined for comprehensive care. Before undergoing surgery, the majority of JIA patients included in this study were followed by the rheumatology unit, with a comparable medical treatment approach among all patients. Looking at the orthopedic side, besides the large surgical experience for rheumatic patients,

another advantage in our study is that patients have been treated by the same orthopedic team over the years, with a uniform learning curve and comparable surgical approach. This led us to avoid possible biases such as different surgical procedures and different quality of surgical teams.
Furthermore, in this highly specialized setting the indication of total joint replacement is driven by both an orthopedic with proven expertise with rheumatic patients and the treating rheumatologist.
Another study peculiarity is that we did not only look at implant survival, but with a prolonged follow-up we could investigate and detect trends over time in terms of implant survival, disease duration before first arthroplasty and age at first arthroplasty.
Limitations of the study are intrinsic in its retrospective nature, that may lead to the possible selection and data collection biases. As for other monocentric experiences, although numbers of this study are not low, abstracting firm conclusions might be risky. Another limitation of this study is the lack of data on functional assessments of implants and the quality of life of these patients.
In conclusion, we reported retrospective data on early prostheses in a JIA cohort. We observed a progressive and significant upward trend of both age at arthroplasty and disease duration before the first arthroplasty over time. JIA category, year of implant and presence of complications significantly affected implant survivorship.
The progressive improvement of medical treatment will lower the need for total joint replacement. Future researches should assess functional outcome and survival of implants in relation to medical therapy and different surgical approaches.

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Figure 1. Arthroplasties performed per year.

Figure 2. Differences among three groups according to the year of surgery.

Figure 3. Kaplan-Meier survival curve of implants:

a) all implants

b) blue line: hip implants; red line: knee implants

Figure 4. Evolution of cementless total knee arthroplasty over time:

a) ’90s: polyethylene tibial component and metal alloy femoral part

b) ’00s and c) ’10s: titanium tibial component and metal alloy femoral part with a different design of bone-implant interface.

Table 1. Patients' clinical features and implant data.

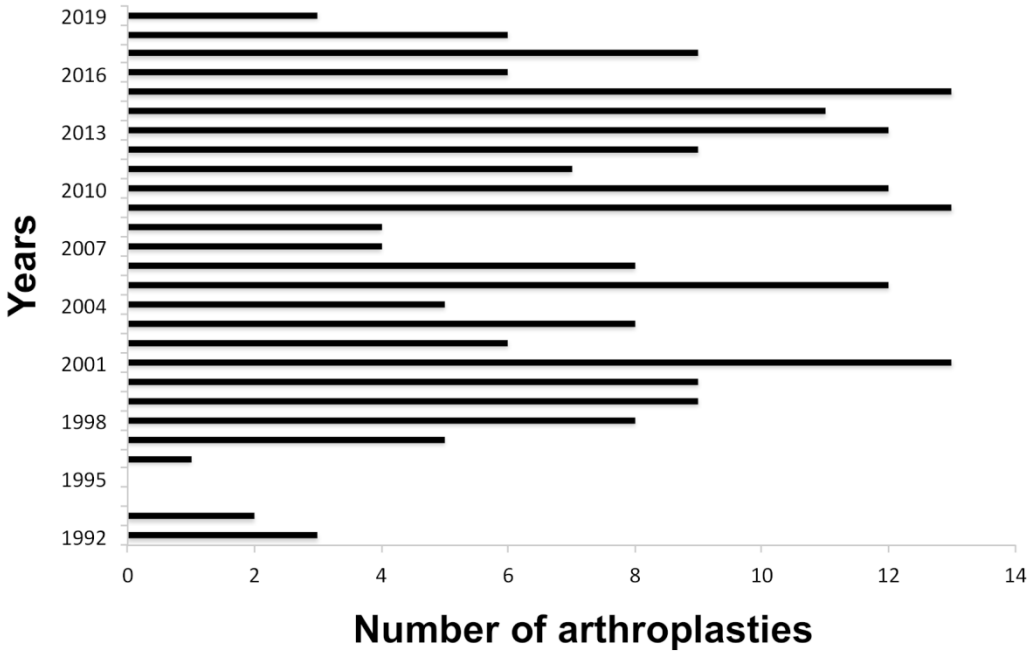
JIA: juvenile idiopathic arthritis; RF: rheumatoid factor; SD: standard deviation; y: years.

Total number of patients (F/M)	85 (5/30)
JIA categories	16 Oligoarticular 37 Polyarticular (7 RF-positive) 24 Systemic 8 other
Age at first arthroplasty, median (mean±SD; range)	22.7 y (25.1±6.9;14.3-46.5)
Disease duration at first arthroplasty, median (mean±SD; range)	17.4 y (18.6±8.1;1.88-43.7)
Follow-up, median (mean±SD; range)	17.2 y (18.1±8.2;2.0-42.5)
Number of arthroplasties	198
Patients with > 1 arthroplasty	66
Location of arthroplasty	121 Hips 66 Knees 11 Ankles
Type of arthroplasty	156 Regular 6 Custom 31 Hybrid 5 Unknown
Arthroplasty complications	8 Intraoperative fracture 3 Peri-prosthetic joint or systemic infections 0 Wound related issues 14 Aseptic mobilization
Revisions	13 (9 hips, 4 knees)
Whole cohort implant survival (mean±SD; range)	9.5 y (10.0±6.6;0.1-25.6)

Table 2. Implant survival raw rates sorted for replaced joint and JIA category

	Survival at 5y	**Survival at 10 y**	**Survival at 15 y**	**Survival at 20 y**
Hips	91/99 (92%)	62 /71 (87%)	44/51 (86%)	10/19 (53%)
Knees	47/54 (87%)	30/35 (86%)	13/17 (76%)	3/6 (50%)
Ankles	2/4 (50%)	NA	NA	NA
PolyJIA	68/72(94%)	43/44(98%)	25/27(93%)	8/9(89%)
SJIA	45/53 (91%)	30/41 (72%)	18/23 (78%)	4/12 (33%)
All cohort	140/157 (89%)	92/106 (87%)	57/68 (84%)	13/25 (52%)

Poly= Polyarticular juvenile idiopathic arthritis (JIA); SJIA= Systemic JIA; y: years; NA: not applicable.



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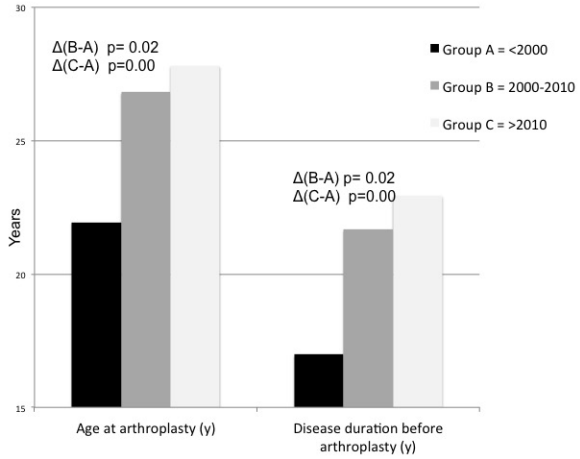

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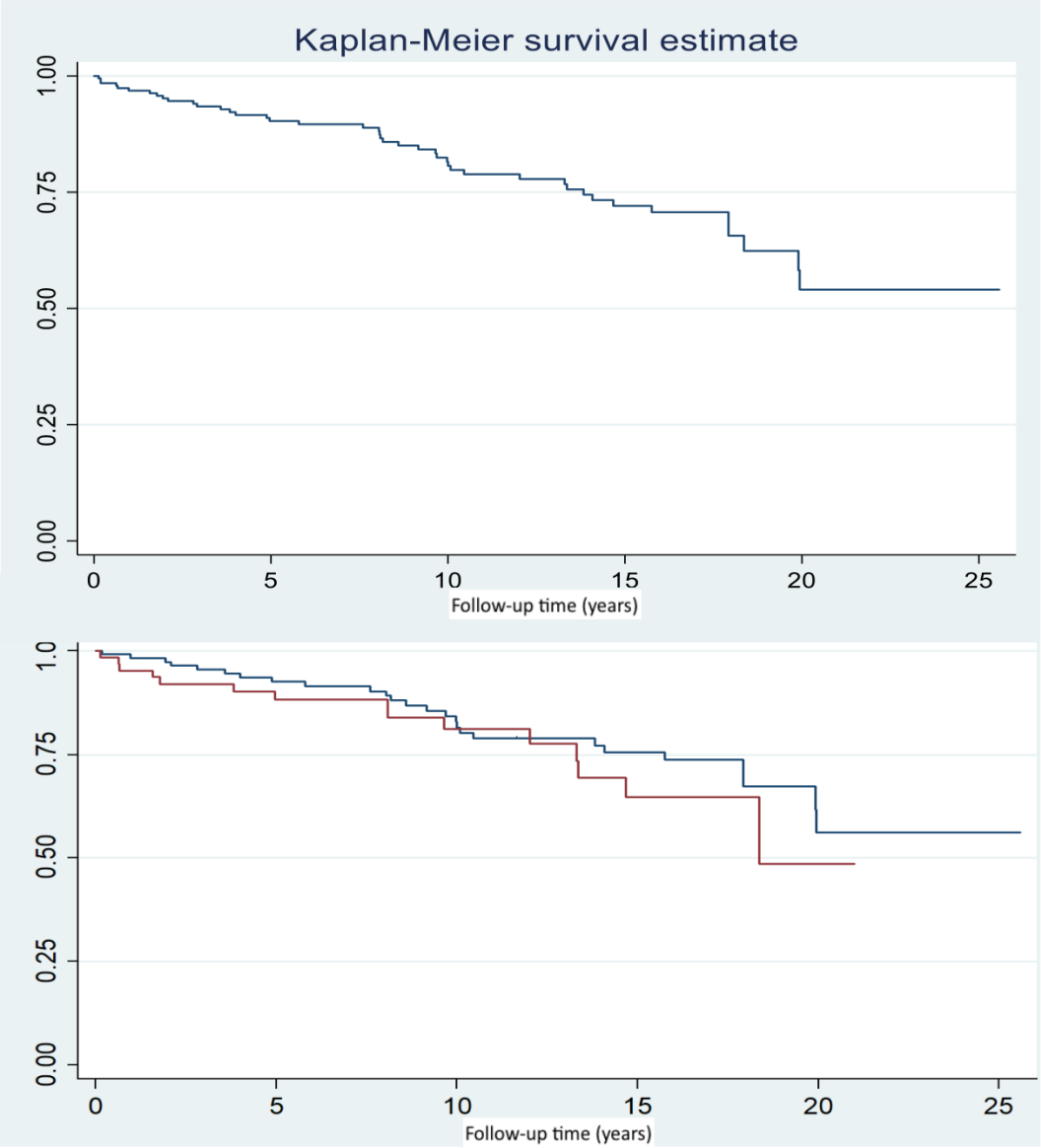

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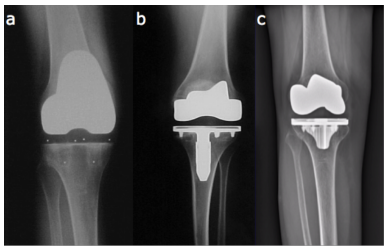

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