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Ten-year hip and knee arthroplasty implant survival in patients with inflammatory arthritis receiving methotrexate monotherapy compared with osteoarthritis: a registry-based data linkage study

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The aim of this study was to evaluate the 10-year risk of revision surgery following total hip (THA) and knee (TKA) arthroplasty in patients with inflammatory arthritis (IA) receiving perioperative methotrexate (MTX) monotherapy and to compare their outcomes with those of propensity score–matched patients undergoing arthroplasty for osteoarthritis. We conducted a retrospective study using data from the Emilia-Romagna Orthopedic Arthroplasty Implants Register. The primary cohort included patients with rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis residing in Emilia-Romagna (Italy) who underwent primary THA or TKA and received at least one prescription of MTX within 90 days before or after surgery. The control cohort consisted of propensity score-matched patients who underwent THA/TKA for osteoarthritis. The perioperative MTX-treated IA group included 225 patients who underwent THA and 215 patients who underwent TKA. The control group consisted of 449 patients with osteoarthritis who received THA and 428 patients who received TKA. Implant survival rates at 10 years were not significantly different when comparing IA patients perioperatively treated with MTX monotherapy and matched osteoarthritis patients, in either those who underwent THA or TKA. This remained consistent when accounting for competing risk of death. These findings suggest that patients with IA receiving perioperative MTX monotherapy have 10-year revision outcomes comparable to those of propensity score–matched patients with osteoarthritis.

Keywords Methotrexate, Surgery, Arthritis, Arthroplasty, Survival, Safety

Inflammatory arthritis (IA) encompasses immune-mediated joint conditions that exhibit common clinical characteristics, including synovitis, tenosynovitis, enthesitis, and potentially extra-articular manifestations. Rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS) represent the most common forms of chronic IA, affecting an overall estimate of nearly 1% of the general population[1–3].

Even with the introduction of new therapies such as biologic (bDMARDs) or targeted-synthetic disease-modifying antirheumatic drugs (tsDMARDs), a considerable number of patients continue to experience uncontrolled inflammation, resulting in joint damage and eventual destruction[4], with a profound impact on quality of life[5] and on the risk of permanent disability[6]. Indeed, despite a clear decreasing trend, IA patients have a four-times higher probability of receiving joint replacement surgery[7,8]; the lifetime probability of total

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hip arthroplasty (THA) and total knee arthroplasty (TKA) in RA is estimated to be 22% and 17%, respectively, with higher risk observed when the disease arises in younger ages[9]. Furthermore, patients with IA are considered at higher risk of complications following arthroplasty[8,10], including prosthetic joint infection (PJI), which is amongst the leading causes of revision surgery in this patients' population[11,12].

Methotrexate (MTX) is a folic acid antagonist originally synthesized in the 1940s[13] for the treatment of cancer and designed to inhibit dihydrofolate reductase (DHFR), an essential enzyme for purine and pyrimidine synthesis. Over 70 years since its debut in treating RA[14,15], it continues to serve as the anchor therapy for most patients with IA due to its effectiveness and favorable safety profile at low weekly doses[16]. A meta-analysis of randomized controlled trials (RCTs) in adult patients with chronic inflammatory diseases confirmed that MTX monotherapy is not associated with an increased risk of total and serious infections compared to placebo[17]; similarly, use of MTX in combination with bDMARDs does not cause an excess of serious infections compared with bDMARDs monotherapy[18].

Despite the extensive real-world experience, limited information is available about the perioperative safety of MTX. To date, only one study has specifically examined the effect of perioperative discontinuation of MTX in RA patients undergoing orthopedic surgery[19]. This study suggested that continuing MTX treatment does not increase the risk of PJI or other surgical complications within one year of elective orthopedic surgery, with risk similar to or even lower than that observed in patients not exposed to MTX. A subsequent follow-up investigation, involving 75 patients from the original cohort, reported no occurrence of new PJI over the long term[20].

Building upon this, American College of Rheumatology (ACR) guidelines[21] conditionally recommend continuing the usual dosing of MTX throughout the perioperative period. However, given the broad utilization of MTX in patients with chronic inflammatory diseases, additional data on arthroplasty outcomes in patients receiving perioperative MTX would be valuable. Thus, the objective of this study was to evaluate long-term THA/TKA implant survival in patients with IA receiving perioperative MTX monotherapy and to compare their outcomes with those of propensity score-matched patients undergoing arthroplasty for osteoarthritis (OA), using data from a large arthroplasty registry.

Methods

Primary data source

The current study relies primarily on the data from the Emilia-Romagna Orthopedic Arthroplasty Implants Register (RIPO), a regional registry-based retrospective cohort[22]. Established in 1990, RIPO systematically gathers information from hip, knee, and shoulder arthroplasty procedures performed in 62 public or private orthopedic departments across the Emilia-Romagna region, which has a population of approximately 4.5 million inhabitants. The capture rate for data in RIPO is approximately 95%[22]. RIPO is a member of the International Society of Arthroplasty Registries (ISAR)[23].

For each patient, the registry records demographic information such as age at surgery, sex, and body mass index (BMI) category, the diagnosis leading to joint replacement, implant characteristics, surgeon and hospital identifiers, and information on revision procedures. The registry does not collect data on postoperative care, rehabilitation, or clinical outcome scores.

Data extraction from the RIPO database was performed in December 2024. The initial inclusion criteria were primary THA or TKA performed between 1 January 2002 and 31 December 2020. During this period, a total of 127,408 primary THA and 101,495 TKA procedures were recorded in Emilia-Romagna. For the present analysis, only the first surgery for each patient was considered.

Study cohorts

The primary cohort (IA patients receiving perioperative MTX monotherapy) included all patients with RA *or* PsA *or* AS resident in Emilia-Romagna who underwent primary THA or TKA and received *at least* one prescription of MTX (ATC code: L01BA01) in the 90 days preceding *or* in the 90 days following surgery. The control cohort consisted of propensity score-matched patients undergoing THA/TKA for primary OA (i.e. those who were included in the RIPO with OA as the primary diagnosis for THA/TKA).

Exclusion criteria for both cohorts were:

a) Patients residing outside Emilia-Romagna region.
b) Treatment with other conventional synthetic DMARDs (csDMARDs) in the 90 days preceding *and* 90 days following surgery: sulfasalazine (A07EC01); leflunomide (L04AK01); ciclosporin (L04AD01); azathioprine (L04AX01); hydroxychloroquine (P01BA02); mycophenolic acid (L04AA06); cyclophosphamide (L01AA01).
c) *Ever treated* with one of the following bDMARDs or tsDMARDs: adalimumab (L04AB04); certolizumab pegol (L04AB05); etanercept (L04AB01); golimumab (L04AB06); infliximab (L04AB02); bimekizumab (L04AC21); ixekizumab (L04AC13); secukinumab (L04AC10); guselkumab (L04AC16); ustekinumab (L04AC05); sarilumab (L04AC14); tocilizumab (L04AC07); abatacept (L04AA24); rituximab (L01XC02); anakinra (L04AA14); canakinumab (L04AC08); apremilast (L04AA32); baricitinib (L04AA37); filgotinib (L04AA45); tofacitinib (L04AA29); upadacitinib (L04AA44).

The process of patients' selection is graphically summarized in Fig. 1.

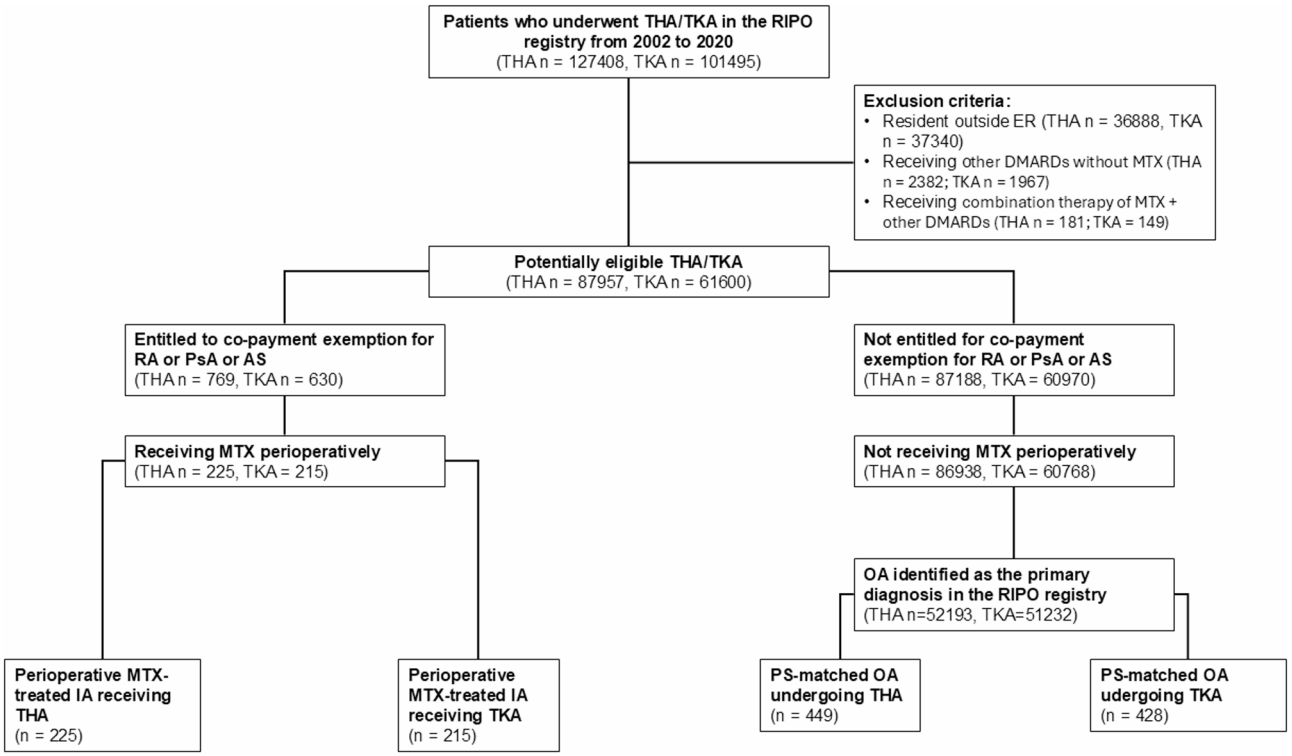

Fig. 1. Selection process and causes of exclusion according to prespecified inclusion and exclusion criteria. AS, ankylosing spondylitis; DMARDs, disease modifying antirheumatic drugs; ER, Emilia Romagna Region; IA, inflammatory arthritis; MTX, methotrexate; OA, osteoarthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RIPO, Registro Implantologia Protesica Ortopedica; THA, total hip arthroplasty; TKA, total knee arthroplasty.

Treatment identification

Record linkage between the RIPO registry and regional administrative databases was enabled through a unique anonymous patient identifier (PROG_PAZ) assigned by the regional Information System for Health Policies and Social Policies (SISEPS). This identifier allows secure cross-database linkage while preserving patient anonymity.

Identification of patients receiving the medications specified in the inclusion and exclusion criteria was performed by cross-matching RIPO records with the pharmaceutical territorial assistance (PTA) database, which systematically records all prescriptions dispensed through the Italian National Health System, including those used in patients with IA. After excluding patients fulfilling exclusion criteria b) and c), patients receiving MTX (ATC code L01BA01) and glucocorticoids (ATC code H02AB) were identified using the same database linkage approach.

Arthritis cases identification

Patients with RA, PsA, and AS were identified by cross-matching the RIPO registry with the regional co-payment exemption database. In Italy, co-payment exemptions for chronic diseases are granted after diagnosis confirmation by a consultant rheumatologist working in a public referral center of the Italian National Health System.

Patients entitled to disease-specific exemption codes for RA (006.714.X), PsA (045.696.0), and AS (054.720.0) were included in the perioperative MTX-treated IA cohort. The control cohort consisted of patients undergoing THA or TKA for primary OA, defined as those recorded in the RIPO registry with OA as the primary indication for surgery and without co-payment exemption codes for RA, PsA, or AS.

Ethical approval

This study was conducted using data from the RIPO registry, a regional registry coordinated by the IRCCS Istituto Ortopedico Rizzoli and officially established under Article 6, paragraph 1, letter c of the Regional Law of Emilia-Romagna no. 9/2017. The registry was created as part of the institutional mandate to support post-marketing surveillance, quality monitoring, and epidemiological research in orthopedic surgery across the Emilia-Romagna region. Its operation is authorized and co-funded by the Emilia-Romagna Regional Health Authority and governed within the ethical and regulatory framework of the Regional Health Service.

All patients signed an informed consent at the time of surgery, explicitly authorizing inclusion in the RIPO registry and the use of their clinical data for research purposes. Data are collected prospectively and analyzed in a pseudo-anonymized format, with no access to identifiable patient information. All experimental protocols related to the registry and its use for research purposes are overseen and approved by the relevant institutional

and regional health authorities, including the Emilia-Romagna Regional Health Department and the Comitato Etico Area Vasta Emilia Centro (CE-AVEC). All research activities were conducted in accordance with the principles of the Declaration of Helsinki and its most recent amendments[24].

Statistical analysis

Registry-based studies encompass a substantial amount of pre-existing data, which facilitates the analysis of all available cases rather than limiting the study to specific subsets, rendering a formal sample size calculation less essential[25]. On the other hand, several articles suggest that post-hoc power calculations may be inappropriate, as it is already known with certainty whether or not a statistically significant finding has occurred[26–28]. Consequently, due to the design of our study, we did not conduct a priori power calculation, as we included the entire population from the RIPO registry without sampling. Data are expressed as mean ± standard deviation, median [25th – 75th percentile] or number (percentage) as appropriate. For comparison, we generated a 1:2 matched group of patients with primary OA enrolled in the RIPO registry, using the propensity score, as previously described[29]. The covariates entered in the propensity score were gender, age class at THA/TKA, BMI and follow-up duration.

Continuous variables were compared between groups using Student's t-test; Fisher's exact test was used to detect differences in dichotomic variables. The survival rates of implants were calculated and plotted according to the Kaplan-Meier method. The main outcome was surgical revision, defined as the removal or change of any component of the implant. The log-rank test was employed to detect differences between survival curves. Further, as death changes the probability of a patient's prosthesis being revised, we performed a cumulative incidence competing risk analysis, treating death-from-any-cause as the competing event of interest. Revision rates were then compared between two or more groups using the Gray's test.

Additionally, to explore whether the timing of MTX exposure relative to surgery influenced revision risk, an exploratory Cox proportional hazards model was performed stratifying IA patients according to the timing of MTX prescriptions with respect to the index procedure (≥ 1 prescription within 90 days before surgery, ≥ 1 prescription within 90 days after surgery, or both), using propensity score–matched OA patients as the reference group. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated.

Two additional sensitivity analyses were also performed. First, a subgroup analysis restricted to patients with RA was conducted to minimize potential bias related to diagnostic heterogeneity within the IA cohort. Second, a sensitivity analysis was performed restricting the cohort to patients receiving MTX prescriptions both before and after surgery, in order to evaluate outcomes in patients with the most consistent perioperative exposure.

Prosthesis time incidence rates (PTIR) were used to describe the incidence (the rate of new events) of specific causes of arthroplasty failure/revision and express the number of revisions in each category divided by the total of the individual prosthesis-years at risk (per 1,000 years at risk).

Statistical analyses were performed using JMP®, Version 12.0.1. (SAS Institute Inc., Cary, NC, 1989–2007) and R version 3.4.2. (Comprehensive R Archive Network)[30].

Results

General characteristics of the study cohorts

The general characteristics of the study cohorts are reported in Table 1. The MTX monotherapy-treated IA group included 225 patients (72.4% female) who underwent THA and 215 patients (73.5% female) who underwent TKA. The control group consisted of 449 propensity score-matched patients with OA (72.4% female) who received THA and 428 (73.4% female) who received TKA. A large number of patients were excluded due to treatment with DMARDs other than MTX, as illustrated in the flowchart (Fig. 1). Among these excluded cases, a subgroup of patients receiving MTX in combination with other DMARDs was identified. The baseline characteristics of these patients, compared with those receiving MTX monotherapy in the analytic cohort, are reported in Supplementary Tables S1 and S2 for THA and TKA, respectively.

Among THA patients receiving MTX, 140 (62.2%) had it prescribed both before and after surgery, while 57 (25.3%) had a prescription only before surgery, and 28 (12.4%) had a prescription only after surgery. Similarly, among TKA patients receiving MTX, 111 (51.6%) had it prescribed both before and after surgery, 75 (34.9%) had a prescription only before surgery, and 29 (13.5%) had a prescription only after surgery.

Of note, a significantly higher proportion of IA patients perioperatively treated with MTX received steroids in the 90 days preceding surgery compared with OA controls (THA: 43.1% vs. 6.9%, $p < 0.001$; TKA: 40.9% vs. 6.1%, $p < 0.001$).

Arthroplasty survival

Implant survival rates at 10 years were not significantly different when comparing IA patients perioperatively treated with MTX monotherapy and propensity score-matched OA patients, in either those who underwent THA [10-year survival 93.9% (95%CI 89.7–98.2) vs. 96.1% (95%CI 93.8–98.5), $p = 0.302$; Fig. 2, panel A] or TKA [10-year survival 93.7% (95%CI 89.8–97.8) vs. 93.9% (95%CI 91.3–96.5), $p = 0.827$); Fig. 2, panel B].

To further substantiate this finding, as a significant proportion of patients died during follow-up [Deceased, n°: THA cohort – OA group 68 (16%), IA-MTX 39 (18%); TKA cohort – OA group 83 (20%), IA-MTX 51 (25%)], we performed a competing risk analysis using death as a competing event, as shown in Fig. 3, which confirmed no significant differences in THA/TKA survival between IA patients treated with MTX monotherapy and OA controls.

Additionally, we performed two further sub-analyses. First, a subgroup analysis restricted to RA patients (Supplementary Figure S1). Secondly, a sensitivity analysis restricted to patients receiving MTX both before and after surgery (Supplementary Figure S2). Results remained consistent with the primary analysis. In both cases, there was no significant difference in THA/TKA survival between RA patients treated with MTX monotherapy and OA controls.

	THA			TKA		
	OA *N* = 449	MTX-treated IA *N* = 225	*p*-value	OA *N* = 428	MTX-treated IA *N* = 215	*p*-value
Age, years	68.7 ± 8.4	68.1 ± 8.4	0.380	69.2 ± 8.1	68.5 ± 8.5	0.312
Age class, n (%)						0.943
<40 years	3 (0.7)	3 (1.3)	0.665	2 (0.5)	1 (0.5)	0.542
40–49 years	6 (1.3)	4 (1.8)	0.913	7 (1.6)	5 (2.3)	0.763
50–59 years	50 (11.1)	20 (8.9)	0.443	40 (9.3)	24 (11.2)	0.557
60–69 years	155 (34.5)	85 (37.8)	0.455	154 (36.0)	77 (35.8)	0.964
70–79 years	206 (45.9)	104 (46.2)	0.998	195 (45.6)	95 (44.2)	0.805
≥80 years	29 (6.5)	9 (4.0)	0.259	30 (7.0)	13 (6.0)	0.769
Female sex, n (%)	325 (72.4)	163 (72.4)	0.987	314 (73.4)	158 (73.5)	0.973
BMI category						> 0.999
Underweight, n (%)	6 (1.5)	3 (1.5)	0.724	0 (0.0)	0 (0.0)	N/A
Normal weight, n (%)	132 (33.9)	66 (33.8)	0.943	78 (21.3)	39 (21.2)	0.937
Overweight, n (%)	176 (45.2)	88 (45.1)	0.951	167 (45.6)	84 (45.7)	0.932
Obese, n (%)	75 (19.3)	38 (19.5)	0.959	121 (33.1)	61 (33.2)	0.941
Missing, n (%)	60 (13.4)	30 (13.3)	0.999	62 (14.4)	31 (14.4)	0.999
IA diagnosis						
RA, n (%)	–	186 (82.7)	N/A	–	171 (79.5)	N/A
PsA, n (%)	–	36 (16.0)	N/A	–	43 (20.0)	N/A
AS, n (%)	–	3 (1.3)	N/A	–	1 (0.5)	N/A
MTX timing						
Before surgery, n (%)	–	57 (25.3)	N/A	–	75 (34.9)	N/A
After surgery, n (%)	–	28 (12.4)	N/A	–	29 (13.5)	N/A
Before and after surgery, n (%)	–	140 (62.2)	N/A	–	111 (51.6)	N/A
Glucocorticoids before surgery, n (%)	31 (6.9)	97 (43.1)	< 0.001	26 (6.1)	88 (40.9)	< 0.001

Table 1. General characteristics of the study cohorts. IA: inflammatory arthritis; MTX: methotrexate; OA: osteoarthritis; THA: total hip arthroplasty; TKA: total knee arthroplasty, N/A: Not Applicable.

Finally, we explored whether the timing of MTX prescriptions relative to surgery influenced revision risk. In an exploratory Cox proportional hazards analysis stratifying patients according to MTX exposure (preoperative only, postoperative only, or both pre- and postoperative) and using matched OA patients as the reference group, no significant differences in revision risk were observed in either THA (overall $p = 0.678$) or TKA (overall $p = 0.981$).

Overall, 9 (PTIR 6.2/1000 PY 95% CI 2.84–11.78) THA patients in the perioperative MTX monotherapy cohort underwent revision surgery as compared to 12 (PTIR 3.94/1000 PY 95% CI 2.04–6.89) in OA controls; similarly, 10 (PTIR 6.86/1000 PY 95%CI 3.29–12.61) patients of the TKA perioperatively exposed to MTX monotherapy vs. 22 (PTIR 7.31/1000 PY 95%CI 4.58–11.07). Individual causes of revision surgery are reported in Table 2.

Discussion

While the clinical benefit of arthroplasty appear close to that observed in OA[31], concerns remain regarding the safety of surgery in patients with IA. A recent meta-analysis[32] confirmed a higher risk of postoperative complications in individuals with RA, including infection, thromboembolism, and periprosthetic fracture. The underlying mechanisms are likely multifactorial, involving disease-driven disturbances in osteometabolic response to the implant, as well as immune dysregulation attributable to both the disease process and its treatment.

Among these factors, the iatrogenic component may significantly contribute to the overall risk, while also offering greater potential for modulation. Although commonly used DMARDs demonstrated an overall favorable risk-benefit profile, the impact of prolonged immune-modulating therapy on orthopedic surgery outcomes remains underexplored, with the available evidence being somewhat contradictory. For example, studies on TNF inhibitors suggest an increased risk of PJI in exposed patients[33], while other key outcomes, such as the need for revision surgery, appear unaffected[34,35].

Despite being a cornerstone treatment for most patients with IA, data on surgical outcomes in patients receiving perioperative MTX remain limited. In a single-center retrospective analysis published in 1991, Perhala et al.[36] examined 121 RA patients undergoing THA or TKA, finding no increased risk of PJI or impaired wound healing in those receiving MTX in the perioperative period (n = 60). Following this, a randomized study evaluated the usefulness of perioperative MTX discontinuation in RA patients undergoing elective orthopedic surgery[19]. Patients were randomly assigned to either continue MTX (group A, n = 88) or discontinue it for two weeks before and after surgery (group B, n = 72). The study demonstrated a lower complication rate within one

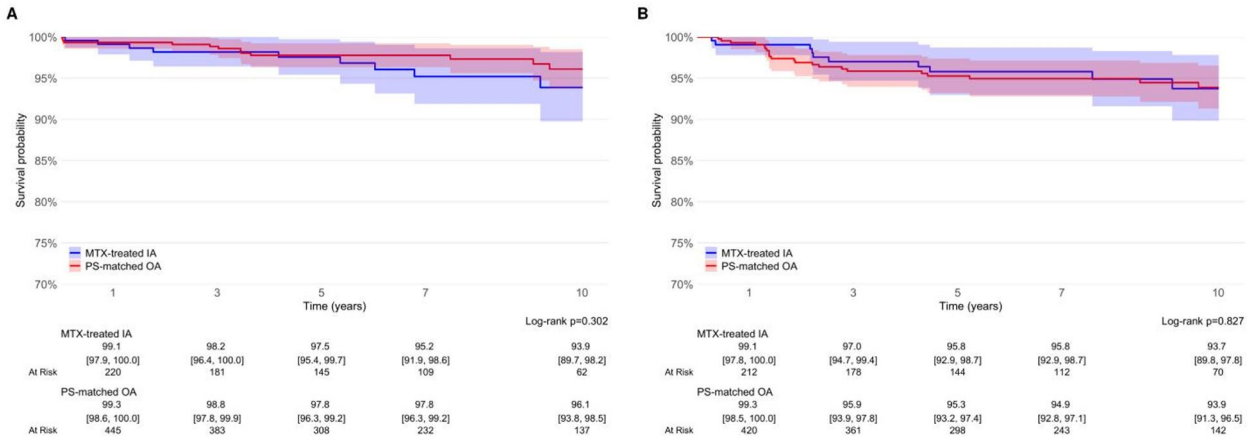

Fig. 2. Survival of total hip arthroplasty (THA, panel **A**) and total knee arthroplasty (TKA, panel **B**) in patients with inflammatory arthritis (IA) receiving perioperative methotrexate (MTX) monotherapy and propensity score-matched patients with osteoarthritis (OA).

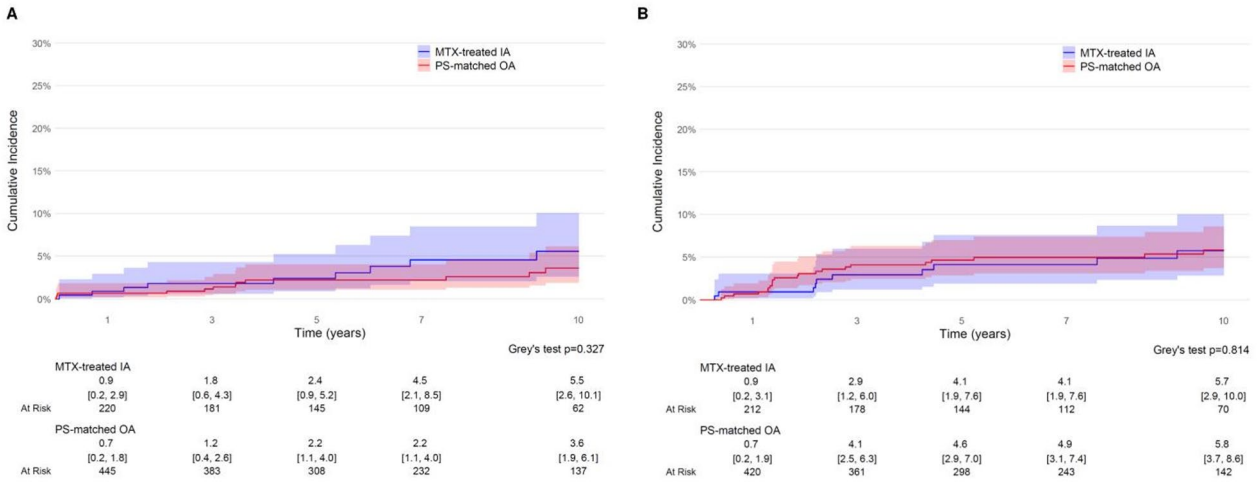

Fig. 3. Cause-specific cumulative incidence of total hip arthroplasty (THA, panel **A**) and total knee arthroplasty (TKA, panel **B**) revision accounting for competing risk of death in patients with inflammatory arthritis (IA) receiving perioperative methotrexate (MTX) monotherapy and propensity score-matched patients with osteoarthritis (OA).

	THA							
	MTX-treated IA ($n=225$)				OA ($n=449$)			
Event type	Events	PTIR/1000 PY	lower (95%)	upper (95%)	Events	PTIR/1000 PY	lower (95%)	upper (95%)
Septic loosening	1	0.69	0.02	3.84	0	0.00	0.00	1.21
Aseptic loosening	3	2.07	0.43	6.04	5	1.64	0.53	3.83
Periprosthetic fracture	2	1.38	0.17	4.98	3	0.99	0.20	2.88
Primary instability	0	0.00	0.00	2.54	0	0.00	0.00	1.21
Dislocation	2	1.38	0.17	4.98	0	0.00	0.00	1.21
Pain without loosening	0	0.00	0.00	2.54	1	0.33	0.01	1.83
Implant fracture	0	0.00	0.00	2.54	2	0.66	0.08	2.37
Other	0	0.00	0.00	2.54	0	0.00	0.00	1.21
Unknown	1	0.69	0.02	3.84	1	0.33	0.01	1.83
Total	9	6.20	2.84	11.78	12	3.94	2.04	6.89
	TKA							
	MTX-treated IA ($n=215$)				OA ($n=428$)			
Event type	Events	PTIR/1000 PY	lower (95%)	upper (95%)	Events	PTIR/1000 PY	lower (95%)	upper (95%)
Septic loosening	4	2.74	0.75	7.02	7	2.33	0.94	4.80
Aseptic loosening	2	1.37	0.17	4.95	6	2.00	0.73	4.34
Periprosthetic fracture	1	0.69	0.02	3.82	0	0.00	0.00	1.23
Primary instability	1	0.69	0.02	3.82	0	0.00	0.00	1.23
Dislocation	0	0.00	0.00	2.53	1	0.33	0.01	1.85
Pain without loosening	1	0.69	0.02	3.82	1	0.33	0.01	1.85
Implant fracture	0	0.00	0.00	2.53	1	0.33	0.01	1.85
Other	0	0.00	0.00	2.53	3	1.00	0.21	2.92
Unknown	1	0.69	0.02	3.82	3	1.00	0.21	2.92
Total	10	6.86	3.29	12.61	22	7.31	4.58	11.07

Table 2. Specific causes of revision. AS: ankylosing spondylitis; BMI: body mass index; IA: inflammatory arthritis; MTX: methotrexate; OA: osteoarthritis; PS: propensity score; PsA: psoriatic arthritis; PTIR: prosthesis time incidence rate; RA: rheumatoid arthritis; THA: total hip arthroplasty; TKA: total knee arthroplasty.

year in group A compared to group B and even compared to a third group of patients who had never received MTX. A subsequent 10-year follow-up of the same cohort confirmed the absence of new deep bone infections[20].

Evidence suggests that suspending MTX for more than two weeks significantly increases the risk of disease flares[37], which, in turn, may negatively impact surgical outcomes, as disease activity is a key prognostic factor for the success of arthroplasty in patients with IA[38]. Thus, the routine, preemptive discontinuation of MTX in all patients undergoing surgery may not be a one-size-fits-all approach. On this basis, the recent ACR guidelines[39] conditionally recommend continuing the standard dosing of MTX throughout the perioperative period.

Leveraging a large arthroplasty registry, we aimed to contribute to characterize long-term THA/TKA survival in patients with IA receiving perioperative MTX monotherapy and to compare revision outcomes with those of propensity score-matched patients with OA. According to our data, the overall implant survival rates at 10 years were excellent in IA patients receiving perioperative MTX monotherapy (~ 94% for both THA and TKA), with revision outcomes comparable to those of a propensity score-matched cohort of patients undergoing arthroplasty for primary OA. These results remained robust even after accounting for the competing risk of death. Additionally, in an exploratory Cox analysis stratifying patients according to the timing of MTX prescriptions relative to surgery, we did not observe any significant differences in revision risk. This finding further supports the robustness of the primary results and suggests that the timing of MTX prescriptions around the surgical procedure did not meaningfully influence long-term implant survival.

The significance of these data is further underscored by the fact that IA patients perioperatively exposed to MTX monotherapy were more likely than OA patients to have received glucocorticoids in the 90 days prior to surgery (> 40% vs. < 7%). Notably, perioperative steroid use is a significant negative prognostic factor, increasing the risk of PJI and all-cause revision[40]. Despite this potential risk factor being substantially more frequent in the IA cohort, implant survival remained comparable between groups. This observation may further support the overall safety of perioperative MTX monotherapy in this setting, suggesting that MTX exposure did not translate into an excess risk of revision even in a population with a higher burden of treatment-related risk factors.

While our study offers new insights into long-term THA/TKA outcomes in patients with IA receiving perioperative MTX monotherapy, it is important to acknowledge some limitations. Firstly, our methodology relied on interrogation of administrative databases to identify MTX-exposed patients. While this approach is generally assumed to have high sensitivity, it led to the absence of key clinical data, such as disease activity scores, C-reactive protein levels, and autoantibody status.

Secondly, our cohort was significantly imbalanced in favor of RA, which accounted for ~ 80% of patients in both the THA and TKA groups. While our data do not allow us to pinpoint the exact cause of this deviation from the global epidemiology of these conditions, it is likely that there is a substantial indication bias, as MTX monotherapy may negatively select patients with PsA or AS[41]. However, to address this issue, we conducted a subanalysis restricted to RA patients only, which showed revision outcomes comparable to those of the matched OA cohort, consistent with the results of the primary analysis. In addition, by design, we excluded patients receiving MTX in combination with other DMARDs. While this approach allowed us to isolate the effect of MTX monotherapy, it may limit the generalizability of our findings, as combination DMARD therapy is commonly used in clinical practice for the management of IA.

Third, only 62% of patients in the THA group and 52% in the TKA group were prescribed MTX both before and after surgery. While the original study protocol aimed to maximize the sample size by including patients with prescriptions only before surgery or only after surgery, we acknowledged that patients who received prescriptions both preoperatively and postoperatively may represent the subgroup with the most consistent perioperative MTX exposure. Consequently, we performed a subgroup analysis on this cohort, which revealed no deviations from the primary analysis.

Unfortunately, we were unable to determine the exact dose of MTX or the rate and duration of its perioperative discontinuation. While our clinic generally recommends stopping MTX one week before surgery and resuming it immediately after surgical healing, it is important to note that not all IA patients in the RIPO registry are directly managed by our rheumatology clinic. Different rheumatologists may adopt varying strategies for the perioperative management of antirheumatic therapy, particularly in the absence of national or European guidelines on the management of DMARDs during the perioperative period. This variability limits our ability to fully characterize how individualized perioperative MTX management may relate to surgical outcomes.

Further, our method of identifying treatment relied on actual medication prescriptions and pick-ups, but this approach may not fully account for non-adherence to prescribed treatment. Indeed, poor adherence has been reported in patients with IA[42,43].

Lastly, power calculation was not conducted since the entire population of the RIPO registry was included in the study. Numerous articles argue that post-hoc power calculations are inappropriate, as the occurrence of a statistically significant finding is already definitively known[26–28]. In relation to our study, particularly, it has been shown that if a *nonsignificant* finding is obtained (as in our specific case), the power to detect the observed effect size will always be low. This is because observed power is directly linked to the obtained p-value, offering no additional information beyond what the p-value already provides[26–28].

In conclusion, despite the aforementioned limitations, our data suggest that patients with IA receiving perioperative MTX monotherapy have long-term revision outcomes comparable to those of propensity score-matched patients undergoing arthroplasty for OA. These findings are consistent with the 2022 ACR guidelines, which conditionally recommend the continuation of MTX throughout the perioperative period, although causal inference regarding MTX continuation cannot be drawn from the present study design.

Data availability

The data underlying this study are not publicly available as they are derived from administrative sources subject to data use agreements. However, they may be made available from the corresponding author upon reasonable request and with appropriate institutional approvals, subject to applicable restrictions.

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Author contributions

CF, ADM, and FU conceived the study; BB performed the statistical analyses; FU wrote the first draft of the manuscript; JC, US, FR, and RC contributed to data interpretation and critically revised the manuscript for important intellectual content. All authors reviewed and approved the final version of the manuscript.

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Declarations

Competing interests
The authors declare no competing interests.

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