



Initiating chemotherapy in joint arthroplasty patients increases the risk of periprosthetic joint infections

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Abstract

Background Total Joint Arthroplasties (TJAs) are becoming more popular, resulting in a growing economic burden due to potential postoperative complications, with periprosthetic joint infections (PJIs) playing a significant role. The effect of immunosuppression on PJI risk, particularly in cancer patients following chemotherapy, is unknown. The hypothesis of this study investigated whether chemotherapy increases PJI rates in patients who received post-arthroplasty chemotherapy within one year of surgery.

Methods Data from the M161Ortho dataset of PearlDiver patient records database were utilized using ICD-9, ICD-10, and CPT codes. The cohort includes Total Knee Arthroplasty (TKA), Total Hip Arthroplasty (THA), and Total Shoulder Arthroplasty (TSA) patients who underwent post-arthroplasty chemotherapy within one year after surgery between 2010 and 2022. Patients in the matched control group did not receive post-arthroplasty chemotherapy. Pre-arthroplasty chemotherapy recipients, PJI, and post-op first year revisions were excluded. Analyses including the linear logistic regression were performed via R statistical software.

Results Totally, 17,026 patients (8,558 TKAs, 6,707 THAs, and 1,761 TSAs) were included. At two (OR = 1.59, $p = 0.034$), three (OR = 1.57, $p = 0.009$), and four (OR = 1.40, $p = 0.032$) years for TKA, and two (OR = 2.27, $p = 0.008$), three (OR = 2.32, $p < 0.001$), and four (OR = 2.25, $p < 0.001$) years for THA, PJI rates were significantly higher in the chemotherapy group. TSA patients had a significant rise in PJI after four years (OR = 2.20, $p = 0.031$).

Conclusions This study reveals a possible relationship between postoperative chemotherapy and an increased incidence of PJI in patients with arthroplasty. Chemotherapy suppresses the immune system, rendering patients more vulnerable to infections. Additional research is required to confirm these findings.

Keywords Arthroplasty · Cancer · Chemotherapy · Periprosthetic joint infections

Introduction

Primary Total Joint Arthroplasties are becoming more common, with growing trends in utilization expected over the next few decades [25]. Increased utilization of healthcare resources for these procedures leads to an increase in economic burden, as postoperative problems are likely to rise correspondingly [5; 14; 25].

Periprosthetic joint infections (PJIs) is a post-operative complication that takes up a considerable portion of the cost burden [11]. The prevalence of PJIs varies according

to the joint involved, as well as ethnic and socioeconomic backgrounds associated with different countries [12; 24]. In the United States, PJI after Total Hip Arthroplasty (THA), Total Knee Arthroplasty (TKA), and Total Shoulder Arthroplasty is reported to be 0.5–1%, 0.25–2%, and less than 1%, respectively [23]. There are numerous recognized risk factors for the development of PJIs, each of which has varied degrees of influence on the development of post-operative complications [29]. Diabetes mellitus, smoking, solid organ failure such as kidney or liver failure, autoimmune diseases,

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and alcohol consumption are just a few of the known risk factors for PJIs after Total Joint Arthroplasty (TJA) [7].

The cornerstone of our humoral and cellular immunity response is defending against foreign materials and combating infections. Certain conditions such as diabetes mellitus, and rheumatoid arthritis are known comorbidities resulting in an increased risk for PJI's after TJA, as these conditions yield lower immunity and impaired ability of the body to fight off foreign invaders [13]. Immunosuppression in cancer is another example of lowered immunity giving rise to an increased risk of PJI after TJA. However, it has not received as much attention as the other more common risk factors for PJI. Previous research has found that cancer patients could have a reduced degree of immunity [28]. Furthermore, in many situations, cancer therapy necessitates the use of immunosuppressive medicines, which might include induction, maintenance, and rescue therapies. These various treatment modalities can act to reduce T-cell precursors, lower antigen presentation efficacy, inhibit cytokine transcription, or inhibit transduction of growth factor signals, all of which are required steps in the effective management of foreign elements, including bacteria that can cause infections [15]. As a result, the use of immunosuppressive medicine such as chemotherapy in the treatment of various tumors may be responsible for an increased prevalence of PJIs in TJA patients.

The aim of this study is to show the effect of cancer and chemotherapy in the development of PJI in patients undergoing TJA in the United States by assessing a national database record from 2010 to 2022.

Methods

Data source

We used the PearlDiver patient records database in this retrospective cohort study (available at www.pearldiverinc.com, located in Colorado Springs, CO, USA). This comprehensive database includes patient demographics, procedural data, diagnoses classified according to procedures identified by Current Procedural Terminology (CPT) codes, the International Classification of Diseases 9th Revision (ICD-9) and 10th Revision (ICD-10) from multiple insurers including the Centers for Medicare & Medicaid Services, Medicare, United Healthcare, and Humana.

Our research was done based on the M161Ortho dataset, which is a subset of approximately 100 million patients from the Mariner database. All patient data from these various sources has been de-identified in accordance with the Health Insurance Portability and Accountability Act

(HIPAA). It's worth noting that our study was exempt from the need for institutional review board approval.

Study population

The study's patient cohort included individuals who had chemotherapy after total knee, total hip, or total shoulder arthroplasty procedures between 2010 and 2022. To gather the necessary information, data was collected using the ICD-9, ICD-10, and CPT codes listed in Appendix (Table S1). Patients had to have documented records of chemotherapy administered within one year of their respective arthroplasty surgeries in order to meet the inclusion criteria. Patients who did not receive chemotherapy made up the control group. No limitations were planned based on cancer types. Individuals who had received chemotherapy prior to joint arthroplasty, or who had periprosthetic joint infection (PJI) or underwent revision within the first year after arthroplasty (the proposed timeframe for chemotherapy), were excluded from the study.

Outcomes of interest

The primary goal of this study was to compare the incidence of total joint revision arthroplasty and PJI at 2, 3, and 4 years after surgery in patients who received chemotherapy after total joint arthroplasty and those who did not receive chemotherapy after the same surgical procedures. Moreover, due to limited access to the individual data on PearlDiver, to compare chemotherapy interval between PJI and no PJI cases, number of chemotherapy records were assumed to represent chemotherapy interval.

Statistical analysis

All statistical analyses were carried out using the R statistical software (Version 4.1.0; R Project for Statistical Computing, Vienna, Austria), which was integrated into the PearlDiver software, with a significance level of $p < 0.05$ set for all statistical tests.

To account for potential confounding factors, matching was done in a one-to-one case-control ratio based on age, gender, Elixhauser comorbidity index (ECI) score, history of diabetes, tobacco use, obesity, and alcohol abuse. The Chi-squared test was used to compare categorical demographics (gender, history of diabetes, tobacco use, alcohol abuse, and obesity) between chemotherapy and non-chemotherapy cases. The mean age of the chemotherapy and non-chemotherapy groups, as well as the mean ECI scores within these two groups, were compared using an independent samples t-test. Moreover, we tried to compare mean record number of chemotherapy prescription within a year

following surgery between failed or revised TJA cases in the chemotherapy group utilizing this analytical method.

A generalized linear model (GLM) with logistic regression was applied to the matched groups to assess the relationship between chemotherapy treatment and the risk of PJI or revision arthroplasty. The outcomes are shown as odds ratios (OR) with a 95% confidence interval (CI).

Results

Patient selection and baseline characteristics

After applying inclusion and exclusion criteria, a number of 17,026 patients having chemotherapy within one year following the arthroplasty were included (8558 TKAs, 6707 THAs, 1761 TSAs) (Fig. 1). Mean age of the population was 66.6 years in THAs, 67.0 years in TKAs, and 69.4 years in TSAs (Table 1). Female predominance was observed in all groups. TSA cases seemed to have a higher average ECI score (6.09 versus 5.19 (THA) and 4.86 (TKA)) and tobacco use prevalence (53.8% versus 52.0% (THA) and 44.4% (TKA)) compared to others. Obesity (50.9% versus

46.2% (TSA) and 38.7% (THA)) and history of diabetes (49.1% versus 48.2% (TSA) and 42.3% (THA)) were more common in patients undergoing post-op chemotherapy after TKA compared to other joints. However, THA patients had a higher prevalence of alcohol abuse (8.0% versus 7.2% (TSA) and 5.6% (TKA)).

Post-op chemotherapy and PJI following TKA

PJI and all-cause revision incidence were evaluated within two, three, and four years after the index surgery (Table 2). Interestingly, patients having chemotherapy had a higher likelihood of PJI compared to the control during two (OR = 1.59 [1.04–2.47], $p=0.034$), three (OR = 1.57 [1.13–2.24], $p=0.009$), and four (OR = 1.40 [1.03–1.91], $p=0.032$) years following the index surgery. On the other hand, there was no significant association between post-op chemotherapy and 2-year (OR = 0.70 [0.49–1.00], $p=0.050$), 3-year (OR = 0.86 [0.64–1.16], $p=0.329$), and 4-year (OR = 0.88 [0.67–1.16], $p=0.364$) all-cause revision rate.

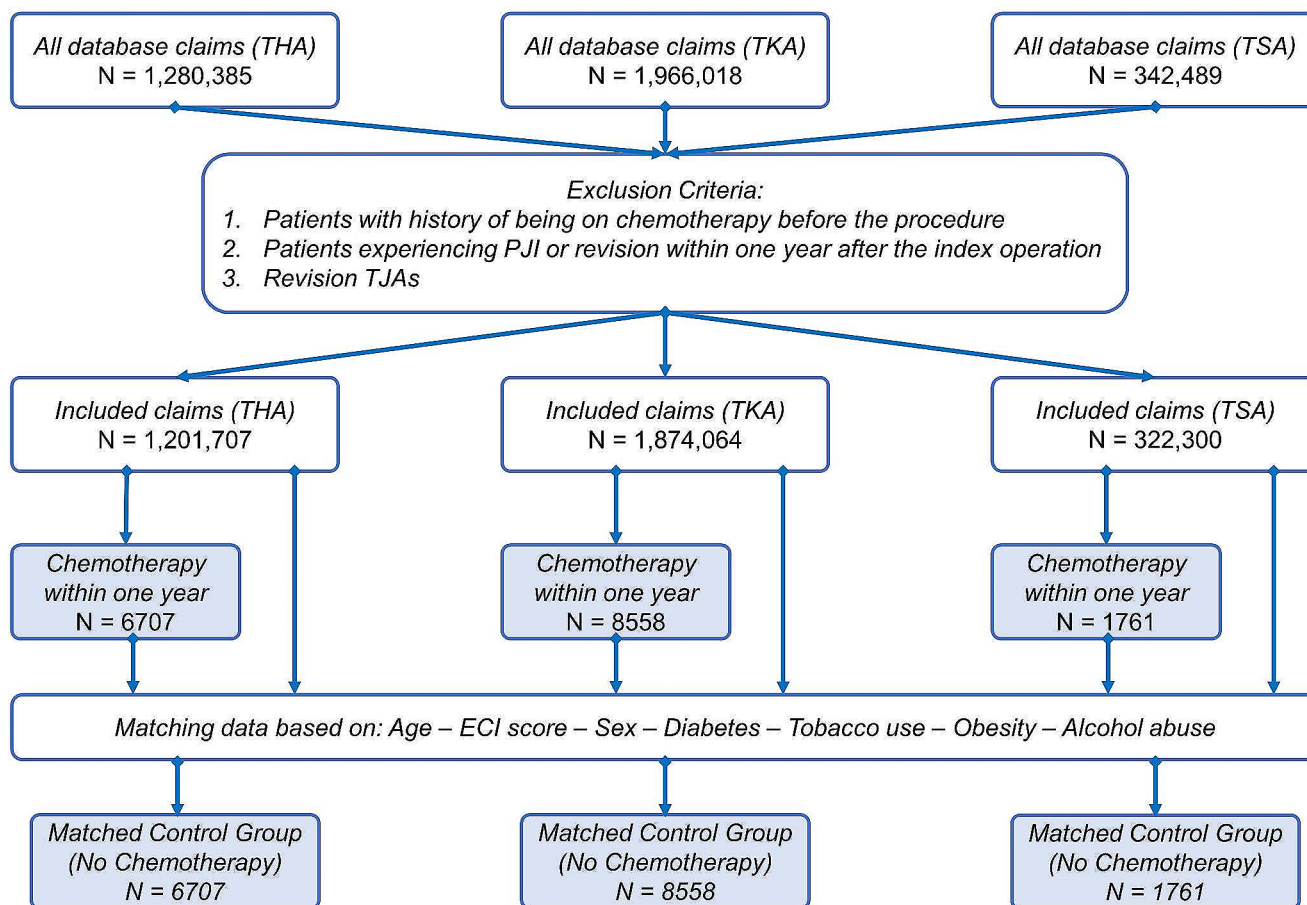


Fig. 1 Patient selection

Table 1 Demographic variables and comorbidities in patients getting chemotherapy within one year after total joint arthroplasty and their matched control population

Variables	Total hip arthroplasty			Total knee arthroplasty			Total shoulder arthroplasty		
	Chemotherapy (n = 6707)	No Chemotherapy (n = 6707)	P-value	Chemotherapy (n = 8558)	No Chemotherapy (n = 8558)	P-value	Chemotherapy (n = 1761)	No Chemotherapy (n = 1761)	P-value
Age, years (Mean ± SD)	66.61 ± 9.93	66.66 ± 9.93	0.788	67.02 ± 8.65	67.05 ± 8.65	0.826	69.42 ± 7.82	69.44 ± 7.82	0.946
Sex, n (%)									
Male	2996 (44.7%)	2996 (44.7%)	1.000	3338 (39.0%)	3338 (39.0%)	1.000	780 (44.3%)	780 (44.3%)	1.000
Female	3711 (55.3%)	3711 (55.3%)		5220 (61.0%)	5220 (61.0%)		981 (55.7%)	981 (55.7%)	
ECI score (Mean ± SD)	5.19 ± 3.43	5.19 ± 3.43	1.000	4.86 ± 3.31	4.86 ± 3.31	1.000	6.09 ± 3.67	6.09 ± 3.67	1.000
Obesity, n (%)									
Yes	2595 (38.7%)	2595 (38.7%)	1.000	4360 (50.9%)	4360 (50.9%)	1.000	814 (46.2%)	814 (46.2%)	1.000
No	4112 (61.3%)	4112 (61.3%)		4198 (49.1%)	4198 (49.1%)		947 (53.8%)	947 (53.8%)	
History of diabetes, n (%)									
Yes	2840 (42.3%)	2840 (42.3%)	1.000	4200 (49.1%)	4200 (49.1%)	1.000	848 (48.2%)	848 (48.2%)	1.000
No	3867 (57.7%)	3867 (57.7%)		4358 (50.9%)	4358 (50.9%)		913 (51.8%)	913 (51.8%)	
Tobacco use, n (%)									
Yes	3485 (52.0%)	3485 (52.0%)	1.000	3802 (44.4%)	3802 (44.4%)	1.000	948 (53.8%)	948 (53.8%)	1.000
No	3222 (48.0%)	3222 (48.0%)		4756 (55.6%)	4756 (55.6%)		813 (46.2%)	813 (46.2%)	
Alcohol abuse, n (%)									
Yes	496 (8.0%)	496 (8.0%)	1.000	483 (5.6%)	483 (5.6%)	1.000	126 (7.2%)	126 (7.2%)	1.000
No	6211 (92.0%)	6211 (92.0%)		8075 (94.4%)	8075 (94.4%)		1635 (92.8%)	1635 (92.8%)	

Abbreviations n, number; ECI, Elixhauser Comorbidity Index; SD, Standard Deviation

Post-op chemotherapy and PJI following THA

Same as TKA, post-op PJI seemed to be more common in the chemotherapy group within two (OR = 2.27[1.26–4.30], $p = 0.008$), three (OR = 2.32[1.43–3.92], $p < 0.001$), and four (OR = 2.25[1.47–3.55], $p < 0.001$) years subsequent to THA. Although a meaningful relationship between PJI and post-op chemotherapy was revealed, 2-year (OR = 0.80[0.44–1.44], $p = 0.456$), 3-year (OR = 0.91[0.56–1.49], $p = 0.709$), and 4-year (OR = 0.87[0.56–1.33], $p = 0.512$) all-cause revision were comparable between the groups.

Post-op chemotherapy and PJI following TSA

About TSA, 4-year PJI incidence was significantly higher in the chemotherapy group (OR = 2.20[1.10–4.68], $p = 0.031$). Nonetheless, 2-year (OR = 2.51[0.84–9.16], $p = 0.121$) and 3-year (OR = 2.26[1.01–5.52], $p = 0.055$) PJI seemed not to be different between cases and controls. This was also applied to all-cause revision rate within two (OR = 2.51[0.84–9.16], $p = 0.121$), three (OR = 1.76[0.75–4.41], $p = 0.205$), and four (OR = 1.81[0.83–3.93], $p = 0.135$) years following TSA.

PJI incidence and 1-year post-op chemotherapy course numbers

In this part, we wanted to observe if there was any noteworthy association between number of prescribed post-operative chemotherapy courses and PJI at last follow-up (Fig. 2). Final findings revealed that PJI cases had a higher mean number of chemotherapy database records within one year after THA (4.03 ± 2.84 vs. 2.03 ± 1.22 , $p < 0.001$), TKA (4.40 ± 2.65 vs. 2.01 ± 1.15 , $p < 0.001$), and TSA (4.75 ± 3.58 vs. 1.98 ± 1.16 , $p < 0.001$) when compared to the patients who did not get infection.

Discussion

The association of post-operative chemotherapy and rate of PJI in total joint arthroplasty has not been investigated although it is known that chemotherapy as an immunosuppressive factor can increase the risk of infection in certain situations and major surgery [8]. Total joint arthroplasties, as major procedures being performed in an elderly population, can aggravate this vulnerable state. The association of chemotherapy with postoperative PJI has been mooted

Table 2 All-cause revision and PJI incidence in patients being on chemotherapy within one year after total joint arthroplasty compared with matched control population

Outcome	Total hip arthroplasty			Total knee arthroplasty			Total shoulder arthroplasty					
	Chemotherapy (n = 6707)	No (n = 6707)	OR [CI 95%]	P-value	Chemotherapy (n = 8558)	No (n = 8558)	OR [CI 95%]	P-value	Chemotherapy (n = 1761)	No Chemo- therapy (n = 1761)	OR [CI 95%]	P-value
PJI, n (%)												
2-year	34 (0.51%)	15 (0.22%)	2.27 [1.26–4.30]	0.008	54 (0.63%)	34 (0.40%)	1.59 [1.04–2.47]	0.034	10 (0.57%)	4 (0.23%)	2.51 [0.84–9.16]	0.121
3-year	51 (0.76%)	22 (0.33%)	2.32 [1.43–3.92]	< 0.001	85 (0.99%)	54 (0.63%)	1.57 [1.13–2.24]	0.009	18 (1.02%)	8 (0.45%)	2.26 [1.01–5.52]	0.055
4-year	65 (0.97%)	29 (0.43%)	2.25 [1.47–3.55]	< 0.001	99 (1.16%)	71 (0.83%)	1.40 [1.03–1.91]	0.032	24 (1.36%)	11 (0.62%)	2.20 [1.10–4.68]	0.031
All-cause revision, n (%)												
2-year	20 (0.30%)	25 (0.37%)	0.80 [0.44–1.44]	0.456	52 (0.61%)	74 (0.86%)	0.70 [0.49–1.00]	0.050	10 (0.57%)	4 (0.23%)	2.51 [0.84–9.16]	0.121
3-year	31 (0.46%)	34 (0.51%)	0.91 [0.56–1.49]	0.709	83 (0.97%)	96 (1.12%)	0.86 [0.64–1.16]	0.329	14 (0.79%)	8 (0.45%)	1.76 [0.75–4.41]	0.205
4-year	39 (0.58%)	45 (0.67%)	0.87 [0.56–1.33]	0.512	97 (1.13%)	110 (1.29%)	0.88 [0.67–1.16]	0.364	18 (1.02%)	10 (0.57%)	1.81 [0.83–3.93]	0.135

Abbreviations PJI, Peri-prosthetic Joint Infection; n, number; OR, Odds Ratio; CI, Confidence Interval

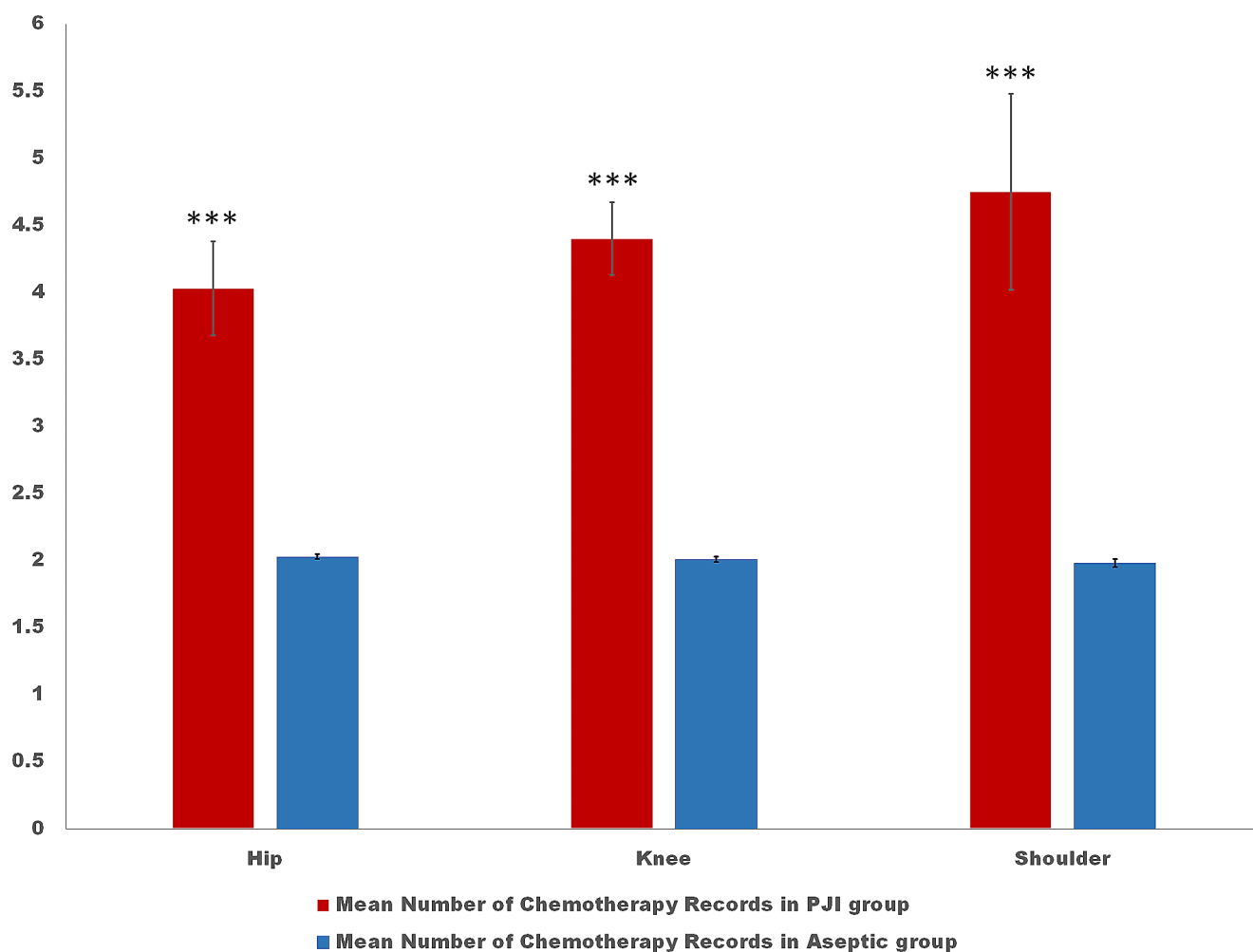


Fig. 2 Post-operative chemotherapy courses and PJI at last follow-up

because of the paucity of prospective studies investigating the risk of chemotherapy for PJI.

In our current study, an increase in the rate of PJI in the knee and hip was observed at the end of each 2, 3, and 4-year follow-up period, and it was significantly higher in the group of patients who underwent chemotherapy compared to matched individuals without chemotherapy. However, in the TSA category, the incidence rate of PJI in chemotherapy patients was significantly higher only after the 4-year follow-up period. There were no significant differences in all cause revision among the groups in any follow-up period.

Cancer has been considered to be a controversial risk factor of prosthetic infection, probably with the mechanism of immunosuppression [4; 22]. Moreover, Hardes et al. demonstrated that PJI was more likely in patients with bone sarcoma who received chemotherapy than those without chemotherapy [9]. Another study of 4 patients with hematological malignancies showed that an immunocompromised state following chemotherapy can result in PJI in these patients [3]. There have also been reported a case of

Waldenström macroglobulinemia who developed multiple PJIs in the shoulder and knee joints following a one-year course of ibrutinib [16]. Furthermore, it has previously shown that the rate of PJI can be 7–28% higher in oncologic joint arthroplasty compared to regular arthroplasty, which is hypothesized to be mainly due to immunosuppression caused by anticancer treatments [30].

In the light of the constant evolution of cancer treatments, despite the promising management and improved survivorship, the side effects of chemotherapy have been inevitable. Some chemotherapy mechanism in certain malignancies, induce the apoptosis of progenitor cells, cause febrile neutropenia, which in protracted form can last longer than 10 days, is considered high risk and exposes patients to more chemotherapy-related complications [11; 17]. On the other hand, patients with chemotherapy-induced immunosuppression may be at increased risk of direct infection through orthopedic hardware and are also hypothesized to be more susceptible to hematogenous dissemination of microbial species in the long term [21]. It is also the case

that chemotherapy can subsequently increase the risk of PJI by disrupting the wound healing process at all phases of inflammation, proliferation, and remodeling [2; 29].

Despite the satisfactory results of chemotherapy, the current study showed that the history of receiving chemotherapy after TKA or THA can contribute to the development of PJI, which highlights profound concerns about the side effects of this practice, most importantly resulting in poor immune response. Beyond the costs and burden that patients with PJI incur for hospitalization and surgery, prostheses, a relatively longer duration of inpatient recovery, antibiotic treatment and the potential possibility of revision, studies have shown that these patients have a mortality rate up to five times higher than the uninfected group [27]. Accordingly, post-operation interprofessional follow-up in short-term intervals aimed at early detection and referral can potentially mitigate the risk of PJI and other comorbidity in patients with chemotherapy-related immunosuppression.

The American Society of Clinical Oncology and the Infectious Diseases Society of America (ASCO/IDSA) has developed a practical guideline, with antifungal and antibacterial therapy with fluoroquinolone for patients who have experienced febrile neutropenia or protracted neutropenia that puts them at higher risk of infection [26]. Also, the American Association of Hip and Knee Surgeons (AAHKS) recommended that one preoperative dose of antibiotic prophylaxis be prescribed to the patients and be continued postoperatively for the first 24 h, and that this duration can increase in clinical practice and reach up to 5 days [6; 20].

Despite the heightened prevalence of periprosthetic joint infection (PJI), we did not find any correlation between cancer patients undergoing chemotherapy and an increased risk of revision arthroplasty. This may be due to the possibility that orthopedic surgeons may choose for non-surgical methods when treating PJI in immunocompromised patients. Surgical treatment for PJI in immunocompromised patients, such as those living with HIV, has not been shown to have a high success rate in the medical literature [1; 18].

To our knowledge, this was the first study to comprehensively investigate the potential risk of PJI in 17,026 patients who received chemotherapy within one year following TKA, THA, and TSA. However, there were several limitations that this study faced. First, we were not able to include the type of cancer because of the variety of codes appointed for various cancers in the literature (more than 500 ICD-9 and ICD-10 codes). To confine this, we therefore had to merely include those types of cancer which required chemotherapy within the first year (Higher stages mostly). Second, it should be kept in mind that there is a considerable possibility that the patients had other treatments in addition to chemotherapy in their disease approach, what were the type of medications, dosages, and duration of administration

course. In regard to the retrospective nature of this study, we did not have access to all of that data and were unable to include it in our analyses. This is a gap worthy of consideration in knowledge, since the side effects of drugs are mainly different depending on their mechanism of action. Further prospective studies, focusing on types of administered chemotherapy agents, doses and treatment courses, are needed in order to more certainly claim the contribution of chemotherapeutic agents in the development of PJI. We also encourage future studies to develop a comprehensive interprofessional guideline for chemotherapy-induced immunocompromised patients, including preoperative, preventive and prophylaxis considerations, as well as how to approach the patient in the event of PJI.

In conclusion, the current study identified that postoperative chemotherapy agents may potentiate the development of PJI in patients who have undergone knee, hip, or shoulder joint arthroplasty. Future prospective studies focusing on this potential correlation would be crucial, so that essential and preventive measures can be taken into account.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00402-024-05307-4>.

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