SYSTEMATIC REVIEW

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Risk factors for metachronous periprosthetic joint infection in patients with multiple prosthetic joints: a systematic review and meta-analysis



Yi Li^{1†}, Xiaolin Quan^{2†}, Cheng Zhou², Xin Duan¹, Mao Nie^{2*} and Haibo Si^{1*}

Abstract

Object Although periprosthetic joint infection (PJI) can affect multiple joints simultaneously, most individuals with multiple joint involvement exhibit PJI in only one joint. Data regarding the metachronous PJI management for these patients are limited. This study aimed to explore the risk factors for metachronous PJI in patients with multiple prosthetic joints, thereby guiding and optimizing clinical practice.

Methods The MEDLINE, Web of Science, Cochrane Library, and EMBASE were searched for all clinical studies of metachronous PJI from inception until May 2024. The clinical studies on risk factors for metachronous PJI in patients with multiple prosthetic joints after experiencing a periprosthetic infection were collected, with two authors independently screening the literatures. Newcastle Ottawa scale was used as a quality assessment tool for the included studies, and the meta-analysis was conducted to evaluate the potential risk factors of metachronous PJI.

Results A total of 1,544 patients with PJI after multiple joint arthroplasties were reported in 9 studies, including 189 with metachronous PJI. The meta-analysis showed that methicillin-resistant staphylococcus aureus (MRSA; OR, 3.43; 95%Cl, 1.71–6.88; p=0.0005), rheumatoid arthritis (RA; OR, 2.38; 95%Cl, 1.06–5.38; p=0.04), history of steroid use (OR, 2.93; 95%Cl, 1.58–5.43; p=0.0007), and previous or ongoing non-periprosthetic infection (OR, 4.47; 95%Cl, 1.45–13.82; p=0.009) were identified as significant risk factors for metachronous PJI in patients with multiple prosthetic joints. However, there was no significant difference between the metachronous PJI group and non-metachronous group in terms of revision, age, diabetes, and gender.

Conclusion Patients with MRSA, RA, history of steroid use, previous or ongoing non-periprosthetic infection are at significantly higher risk for metachronous PJI. Further research is needed to optimize management strategies for preventing metachronous PJI in patients with multiple prostheses after a single joint PJI.

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Highlights

• Patients with MRSA, RA, history of steroid use, previous or ongoing non-periprosthetic infection are at significantly higher risk for metachronous PJIs.

Keywords Risk factors, Metachronous periprosthetic joint infection, Multiple prosthetic joints, Arthroplasty

Introduction

Joint arthroplasty is an excellent solution for end-stage joint diseases, with its prevalence increasing annually [1]. The demands for primary total hip and knee arthroplasties are estimated to grow exponentially by 2030 [2]. The number of patients undergoing multiple joint arthroplasties is also increasing, with a 30–45% likelihood of a secondary arthroplasty in contralateral cognate joints and about 5% in non-cognate joints within 20 years of the initial arthroplasty [3]. Although joint arthroplasty boasts high success rates, it remains susceptible to serious complications, such as periprosthetic joint infection (PJI), periprosthetic fracture, and dislocation.

PJI is deemed "catastrophic" by surgeons and patients alike [4], and PJI in one artificial joint may heighten the infection risk for other prostheses in patients with multiple prosthetic joints [5]. PJI is one of the leading causes of arthroplasty failure and often puts patients in a dilemma of recurrent infections, long-term use of antibiotics, revision, and even amputation, resulting in increased disability and mortality rates [6, 7]. Meanwhile, the economic impact of PJI is also substantial. Premkumar et al. estimated that the annual cost for PJI will rise to \$1.82 billion by 2030 [8]. In addition, PJI involves different pathogens and infection types and is closely related to the primary joint disease, comorbidities, and physical condition, which increases the difficulty of prevention and treatment.

Considering that PJI may occur anytime during the lifetime of a patient, those with multiple prostheses in place would cumulatively be at a higher risk for PJI compared to those with a single arthroplasty, and the reported prevalence of PJI involving a second joint ranges from 6.3-20%.⁵ Currently, with the increasing number of patients with multiple prosthetic joints, the incidence of both synchronous and metachronous PJI cases is projected to rise [9]. Metachronous PJI is the infection in two or more joints with a disease-free interval, and evaluating the risk factors for metachronous PJI when a PJI occurs is crucial for developing effective preventive strategies in patients with a history of multiple joint arthroplasties. However, the potential risk factors of PJI in another "silent" joint are still controversial when one PJI occurs in patients with multiple prostheses. Abblitt et al. suggested that bacteremia at the time of PJI is an important factor for developing subsequent PJI [10], while Jafari et al. deemed that a compromised immune system and lower overall health contributed to multiple PJI [11].

Given the scarcity of reported studies on metachronous PJI and the scattered, controversial findings on its risk factors and clinical management strategies, it's challenging to grasp core issues from single studies accurately. Therefore, evidence-based methods are urgently needed to evaluate the risk factors for metachronous PJI, which has never been reported before. This study aims to comprehensively review prior literature on metachronous PJI risk factors in patients with multiple prosthetic joints and conduct a systematic evaluation and meta-analysis. As a result, by integrating existing results to enhance statistical power, the potential risk factors for metachronous PJI in patients with multiple prosthetic joints were identified. The findings are expected to guide future clinical practice, especially for the development and optimization of the preventive strategies.

Methods

This review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [12], and the checklist is reported in the supplemental document. The protocol for this study was registered on PROSPERO. Adaptations were made to the strategy for data synthesis and reported in the protocol. This study was registered in the International Prospective Register of Systematic Reviews. Each quality assessment was based on AMSTAR 2 (Supplemental document) [13].

Data sources and study selection

We searched the following databases (from inception until May 2024): MEDLINE, Web of Science, Cochrane Library, and EMBASE. Possible additional relevant records were hand-searched through the reference lists of eligible studies and relevant systematic reviews. After de-duplication, two reviewers independently screened titles and abstracts of the identified records for inclusion (inter-rater reliability of kappa=0.82). In case of unresolved disagreements, a third reviewer was consulted. Subsequently, the remaining records were independently screened by the same two reviewers on full text, and unresolved discrepancies were arbitrated by the third reviewer. The whole process is reported in the flow diagram. (Fig. 1).

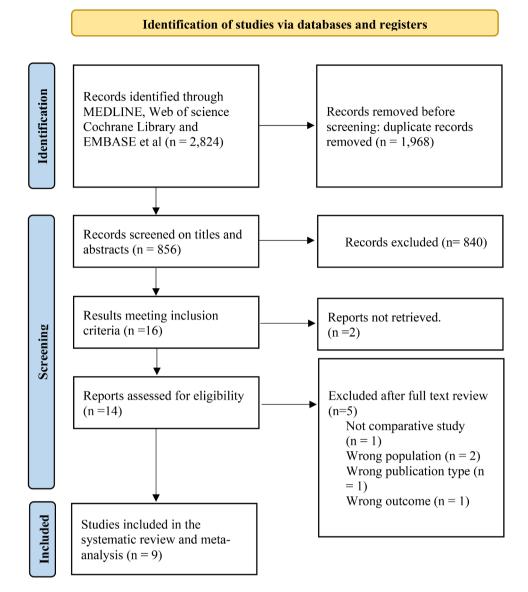


Fig. 1 The preferred reporting items for systematic reviews and meta-analysis (PRISMA) flow diagram to show study selection

Eligibility criteria

A PJI was defined according to the adapted diagnostic criteria of the Musculoskeletal Infection Society [14]. The studies were included if the following criteria were met: (1) original interventional, observational, cross-sectional, and cohort studies; (2) published in English; (3) the metachronous PJI was reported in patients with multiple prosthetic joints. The studies only reported synchronous multiple PJIs or metachronous PJI in the same joint were excluded.

Data extraction

Two reviewers independently extracted data from included studies, while a third reviewer resolved disagreements. The following information was obtained: (1) study design; (2) participants characteristics (age, gender); (3) sample size and comorbidities; (4) primary risk factors in each study; (5) follow-up time; (6) statistical analyses. Authors had been contacted in case of missing data.

Risk of bias

The risk of bias (RoB) assessment was performed by the same reviewers who independently evaluated the methodological quality of the included studies using the Newcastle Ottawa Quality Assessment Scale (NOS) [15]. The NOS includes 8 items related to 3 domains of bias (selection, comparability, and outcome), with a maximum score of 9 points. Differences in scoring were arbitrated by the third reviewer.

scores

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infection

RA、 immunosuppressive agents 、

Steroids,

ΣZ

Σ

ΣZ

Σ

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£ ^{*}≥ 10 27

Male/Female

Gender

Ages (Years) Mean (SD)^{*}

Patients

Country

Follow-up

time

period

publication

Year of

References

Table 1

Baseline characteristics, primary risk factors and NOS scores

Steroids, RA, infection

38/80

12/15

27/41

61.0 (14.6) 62.0 (12.9)

JSA JSA

6 years

975-1984 981-1993

1996

uessenhop et al.

991

Murray et al.

118 58

ω 00

Peripheral

Decreased general health(Charlson Index)*

21/23

2/6 2//6

53.0 (13.4)

4

= $\widetilde{\mathbb{C}}$

JSA

2000-2009 995-2011

> 2012 2016

Jafari et al.

Haverstock et al.

59 (10.7)

70.4 (11.0)

193

Canada

12months At least

Initial I&D^{*}、Initial 2 Stage^{*}、DVT^{*}、 Edema、 Peripheral Vascular Disease 00 Ś

Positive MRSA* carrier status. PJI of a total knee

Bacteremia at initial infection

26/40

2/4

68.0(0.0)

62.8 (0.0)

99

Q 4

USA

29/15

73.0 (10.9)

40

reland

2014-2017

2008 2008

Clesham et al.

Abblitt et al.

2003-2014

NOS*

Primary risk factor(s)

Data analysis

A meta-analysis was performed using Review Manager software to identify the primary risk factors for metachronous PJI in patients with multiple prosthetic joints (version 5.4; Cochrane Collaboration). An OR with a 95% confidence interval (CI) and P-value were calculated for the potential risk factors, and the forest plot was also constructed. Heterogeneity among studies was reported as the I square (I [2]) statistics. Guidelines for the I [2] test state: $0 \sim 25\%$ is low-level heterogeneity, $25 \sim 50\%$ is moderate heterogeneity, 50~75% is high-level heterogeneity, and more than 75% is considerable level heterogeneity [16]. When I [2] is greater than 50%, the M-H random model is selected for the forest map model. Otherwise, the M-H fixed model is selected. Publication bias was evaluated visually by creating funnel plots via Review Manager software and by conducting Egger's regression tests for outcomes with ten or more included studies. Due to the limited inclusion of studies, the funnel plot suggests a slight risk of publication bias (supplementary file). A p-value of less than 0.05 was considered statistically significant.

Results

Literature search

A total of 2,824 records were retrieved from the initial search strategy. After excluding 1,968 duplicate articles, 840 citations were excluded based on titles and abstracts. Consecutively, screening the full text of the 16 remaining records resulted in 9 records to be included. The flow diagram and reasons for exclusion are depicted in Fig. 1. Patient characteristics and primary risk factors reported in the included studies are shown in Table 1. This study included a total of 1,544 patients with PJI after multi joint arthroplasties, of which 189 were identified as metachronous PJI, with an incidence rate of approximately 12.2%.

Quality assessment of included studies

For non-randomized controlled studies, the NOS was used for quality evaluation. All included studies were scored according to the selection of subjects in different studies, the comparability between groups, and the outcome measurement. The total score is 9, and the final score of each study is presented in Table 2.

Results of meta-analysis

Impact of MRSA (methicillin-resistant staphylococcus aureus) on metachronous PJI

Three studies recorded MRSA (Fig. 2). In patients with multiple prosthetic joints, the total number of patients with PJI was 337, of which 49 metachronous PJI were identified. Sixteen out of 49 individuals in the metachronous PJI group and 36 out of 288 individuals in the non-metachronous PJI group were positive for

	sectored in the sector size that the sector se	ange; Initial 2 Stac	Ψ	rrigation and d	Index; Initial I&D, ii
d by Charlso	letachronous Second-site PJI with MPJ; NOS, Newcastle-Ottawa Scale; SD, Standard deviation, Charlson Index, Systemic health was measured by Charlso	chronous Second	Abbreviations: M, Metachronous Second-site PJI with MPJ; NM, Metac	Metachronous	Abbreviations: M,
	index, adjacent joint				
6	Germany 73 588 73.4 (17.0) 68.6(12.4) 10/63 290/298 Female Ciabetes patients with a polymicrobial	Germany	2010–2018 83.7months	2023	Sangaletti et al.
	stages of resection arthroplasty、 PJI caused by MRSA				

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PJI with systemic inflammatory response syndrome.

bacteremia

RA,

Females, MRSA,

92/79 40/37

6/20 12/7

64.5(11.5)

66.4 (10.5)

17

USA

Average 3.6 years At least 10 years

2000-2017

2020

Somnos et al.

2021

ee et al.

994-2020

67.4(8.7)

(8.9)

52.7

2

China

26 19

replacement

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MRSA-carrying status. The meta-analysis indicated that the positive MRSA-carrying status is associated with an increased risk of metachronous PJI (OR, 3.43; 95% CI, 1.71-6.88; p = 0.0005).

Impact of RA (rheumatoid arthritis) on metachronous PJI

Seven studies recorded RA (Fig. 3). In patients with multiple prosthetic joints, the total number of patients with PJI was 1,417. Thirty-eight out of 172 individuals in the metachronous PJIs group and 130 out of 1,245 individuals in the non-metachronous multiple PJI group suffered from RA. The meta-analysis revealed that RA is associated with an increased risk of metachronous PJI infection (OR, 2.38; 95% CI, 1.06–5.38; p = 0.04).

Impact of history of steroid use on metachronous PJI

Seven studies recorded history of steroid use (Fig. 4). In patients with multiple prosthetic joints, one thousand three hundred and three PJI individuals were reported. Twenty out of 159 individuals in the metachronous PJI group have had previously or were currently using steroids, while 61 out of 1,144 in the non-metachronous PJI group. The meta-analysis suggested that history of steroid use is associated with an increased risk of metachronous PJI (OR, 2.93; 95% CI, 1.58–5.43; p = 0.0007).

Impact of previous or ongoing non-periprosthetic infection on metachronous PJI

Six studies recorded previous or ongoing non-periprosthetic infection (Fig. 5). In patients with multiple prosthetic joints, seven hundred and thirty-two PJI individuals were reported. Thirty-one out of 86 individuals in the metachronous PJI group and 61 out of 646 individuals in the non-metachronous PJI group have previously or currently suffered non-periprosthetic infection. The meta-analysis indicated that the previous or ongoing non-periprosthetic infection is associated with an increased risk of metachronous PJI (OR, 4.47; 95% CI, 1.45–13.82; p = 0.009).

Impact of revisions, age, diabetes, and gender on metachronous PJI

There were four studies, including 1,160 individuals with PJI, reported revisions (Fig. 6). In the metachronous PJI group, thirty-five out of 131 individuals experienced revisions, and there is a trend that revisions reduced the risk of metachronous PJI in patients with multiple prosthetic joints, but the results did not reach statistical significance (OR, 0.80; 95% CI, 0.53–1.22; p = 0.31). Moreover, there were four studies (1,026 individuals with PJI), eight studies (1,476 individuals with PJI), and six studies (1,226 individuals with PJI) that reported the potential effect of age, diabetes, and gender on metachronous PJI respectively. However, no statistical differences in age (OR,

0.69; 95% CI, -4.76–6.14; p=0.80), diabetes (OR, 1.42; 95% CI, 0.69–2.96; p=0.34), and female (OR, 1.59; 95% CI, 0.61–4.10; p=0.34) between the metachronous PJI and non-metachronous PJI groups was observed (Fig. 6), which indicates these factors do not increase the risk of metachronous PJI in the patients with multiple prosthetic joints after undergoing PJI.

Systematic review

The preference for infection to spread from the primary site to other implants appears to result from altered or diminished host immune function, and the impairment of RA on the immune system reduces the patient's resistance to infection [17]. Murray and Luessenhop et al. pointed out that long-term use of immunosuppressive agents or steroids for controlling and treating RA increases the risk of infection recurrence or new infection after PJI [18, 19]. Surgical treatment of infection is at the discretion of the attending surgeon, the general protocol for early post-operative and acute hematogenous infections includes irrigation and debridement accompanied with intravenous antibiotics. Haverstock et al. supposed that patients who developed metachronous PJI were likelier to have undergone an initial irrigation and debridement and were less likely to have been treated with an initial two-stage revision [20]. In addition, Lee et al. observed that patients with three stages of resection arthroplasty might be likelier to develop metachronous PJI, and an extended course of antibiotic administration may contribute to irrigation and debridement and decrease failure rates [21, 22].

Meanwhile, irrigation and debridement, repeated twostage resection arthroplasty, permanent resection arthroplasty, or amputation were not indicated as significant risk factors in the studies. In recent years, researchers have found that a metachronous PJI is significantly more likely to occur in an adjacent joint within the same limb (e.g., ipsilateral hip and knee) as opposed to a joint in a different limb (i.e., contralateral or upper vs. lower limb). Metachronous PJI in the same limb also happen significantly earlier than PJIs in different limbs and are more likely to be caused by the same organism [23]. Moreover, the risk of ipsilateral metachronous PJI in patients with multiple joint arthroplasties is associated with shorter stature and stem-to-stem distance [24], and future studies might evaluate the risk of ipsilateral metachronous PJI owing to bone adjacency.

Publication bias

The inverted or asymmetric funnel plot suggests a slight risk of publication bias due to the limited number of studies included (supplementary file).

References	Selection (maximum 4 stars)	num 4 stars)			Comparability (maxi-	Outcomes (m	Outcomes (maximum 3 stars)		Total stars Over-	Over-
					mum 2 stars)				(Scores)	all
	Representative of the observa- tion cohort	Selection of control cohort	Representative Selection Ascertainment of the observa- of control of observation tion cohort cohort	Representative Selection Ascertainment Demonstration that of the observa- of control of observation outcome of interest tion cohort cohort was not present at start of study	Comparability of cohorts Assessment Adequacy of on the basis of the de- of outcomes follow-up of sign or analysis cohorts	Assessment of outcomes	Assessment Adequacy of of outcomes follow-up of cohorts	Completeness of the observation versus the control cohort		RoB*
Murray et al.	*	*	*	*	*	*	*	*	ø	т
Luessenhop et al.	*	*	*	*	*	*	ı	*	7	Т
Jafari et al.	*	*	*	*	**	*	I	*	80	Т
Haverstock et al.	*	*	*	*	*	*	*	*	80	Т
Abblitt et al.	*	*	*	*	**	*	ı	*	8	Т
Clesham et al.	*	*	*	*	*	I	I	*	9	Σ
Komnos et al.	*	*	*	*	**	*	*	*	6	Т
Lee et al.	*	*	*	*	**	*	*	*	6	т
Sangaletti et al.	*	*	*	*	**	*	*	*	6	Т

Discussion

PJI ranks among the prevalent causes of failure and subsequent revision following arthroplasty [25, 26]. It represents a highly destructive complication, characterized by intricate diagnostic and treatment procedures [27, 28]. Regarding the risk factors for metachronous PJI, a wide array of viewpoints exists. This study is the first to conduct a systematic review and meta-analysis of the risk factors for metachronous PJI in patients with multiple prosthetic joints. The results of this study show that MRSA, RA, history of steroid use, and previous or ongoing non-periprosthetic infections are important risk factors for metachronous PJI in patients with multiple prosthetic joints.

Staphylococcus aureus was the most common pathogenic microorganism for PJI, followed by streptococci and Gram-negative rods [29]. This study suggests that positive MRSA carrier status is associated with an increased risk of metachronous PJI. Patients with positive MRSA carrier status are prone to PJI due to the risk of hematogenous dissemination, prolonged hospital stay, and antibiotic treatment. MRSA demonstrates high virulence, prolonged latency, and formidable eradication challenges, possibly rendering patients more susceptible to subsequent PJI in other prosthetic joints [22, 30]. Volin et al. demonstrated that two-stage revision was equally effective against methicillin-resistant infections and methicillin-susceptible infections [31]. However, Lim et al. quoted a treatment failure rate of 22% for MRSAmediated PJI, and Leung et al. reported similar findings with a 21% treatment failure rate [32, 33]. Infection with MRSA has been proven to have a higher treatment failure rate than other susceptible organisms, indicating that the difficulty of curing PJI caused by this pathogen is very high [34].

Meanwhile, we also found that previous or ongoing non-periprosthetic infections are a significant risk factor for metachronous PJI, but there is a lack of reports on specific bacterial strains. A study showed that patients who received a clean primary total knee arthroplasty (TKA) with a history of total hip arthroplasty (THA) or TKA PJI in another joint had a three-fold higher risk of PJI compared with matched controls with a tenyear cumulative incidence rate of 6.1%. Meanwhile, in patients who use antibiotics for a long time, the risk of PJI increases by 15 times [35]. We suspected that bacteremia caused by infection may be involved in the pathogenesis, but further research into reasons for this and mitigation strategies is recommended.

Systemic diseases such as diabetes, RA, and atherosclerotic peripheral vascular disease are all related to poor wound healing, and RA has been proven to be a risk factor for early and late prosthesis deep infection [36, 37]. RA lesions often involve multiple joints, and patients

	Metachronous PJI group Non-metachro		Non-metachronous PJI	group		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
Clesham 2018	1	4	5	40	9.9%	2.33 [0.20, 27.03]	
Komnos 2020	7	26	24	171	66.9%	2.26 [0.86, 5.94]	+-∎
Lee 2021	8	19	7	77	23.2%	7.27 [2.20, 24.08]	
Total (95% CI)		49		288	100.0%	3.43 [1.71, 6.88]	◆
Total events	16		36				
Heterogeneity: Chi ² =	= 2.33, df = 2 (P = 0	.31); $I^2 = 1$	4%				0.002 0.1 1 10 500
Test for overall effect	Z = 3.47 (P = 0.00)	05)					Metachronous PJI group Non-metachronous PJI group

Fig. 2 Forest plot of MRSA on metachronous PJI

	Metachronous PJI group		ronous PJI group Non-metachronous PJI group			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
Clesham 2018	1	4	1	40	5.8%	13.00 [0.64, 263.82]	
Haverstock 2016	2	13	19	193	13.7%	1.67 [0.34, 8.08]	
Komnos 2020	7	26	11	171	19.0%	5.36 [1.86, 15.47]	_
Lee 2021	0	19	4	77	5.9%	0.42 [0.02, 8.12]	
Luessenhop 1996	19	27	32	118	20.7%	6.38 [2.54, 16.02]	
Murray 1991	5	10	27	58	15.9%	1.15 [0.30, 4.40]	
Sangaletti 2023	4	73	36	588	19.0%	0.89 [0.31, 2.57]	
Total (95% CI)		172		1245	100.0%	2.38 [1.06, 5.38]	◆
Total events	38		130				
Heterogeneity: Tau ² =	Heterogeneity: Tau ² = 0.61; Chi ² = 13.78, df = 6 (P = 0.03); I ² = 56%					t.	
Test for overall effect	t: $Z = 2.09 (P = 0.04)$)					0.001 0.1 1 10 1000 Metachronous PJI group Non-metachronous PJI group

Fig. 3 Forest plot of RA on metachronous PJI

	Metachronous PJI	group	Non-metachronous PJ	I group		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% Cl
Abblitt 2018	0	6	9	66	16.5%	0.47 [0.02, 8.96]	• • • • • • • • • • • • • • • • • • •
Haverstock 2016	0	13	10	193	13.5%	0.65 [0.04, 11.65]	· · · · · · · · · · · · · · · · · · ·
Jafari 2012	0	11	2	44	10.0%	0.74 [0.03, 16.50]	· · · · · · · · · · · · · · · · · · ·
Lee 2021	2	19	0	77	1.8%	22.14 [1.02, 481.96]	· · · · · · · · · · · · · · · · · · ·
Luessenhop 1996	9	27	14	118	34.4%	3.71 [1.40, 9.85]	
Murray 1991	7	10	25	58	21.8%	3.08 [0.72, 13.12]	↓
Sangaletti 2023	2	73	1	588	2.1%	16.54 [1.48, 184.67]	· · · · · · · · · · · · · · · · · · ·
Total (95% CI)		159		1144	100.0%	2.93 [1.58, 5.43]	▲
Total events	20		61				
Heterogeneity: Chi ² =	= 7.16, df = 6 (P = 0	.31); I ² =	16%				
Test for overall effect	z = 3.41 (P = 0.00)	07)					0.001 0.1 İ İO 1000 Metachronous PJI group Non-metachronous PJI group

Fig. 4 Forest plot of history of steroid use on metachronous PJI

	Metachronous PJI group Non-metachronous PJI group			Odds Ratio		Odds Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Rai	ndom, 95% CI	
Abblitt 2018	3	6	12	66	16.6%	4.50 [0.81, 25.09]				
Clesham 2018	1	4	5	40	11.9%	2.33 [0.20, 27.03]				
Haverstock 2016	0	13	7	193	9.6%	0.92 [0.05, 17.00]				
Komnos 2020	5	26	22	171	21.7%	1.61 [0.55, 4.72]		-	- -	
Luessenhop 1996	17	27	7	118	21.5%	26.96 [9.04, 80.38]				<u> </u>
Murray 1991	5	10	8	58	18.7%	6.25 [1.47, 26.56]				
Total (95% CI)		86		646	100.0%	4.47 [1.45, 13.82]				
Total events	31		61							
Heterogeneity: Tau ² =	= 1.23; Chi ² = 15.1	7, df = 5 ($P = 0.010$; $I^2 = 67\%$				-	01	1 10	
Test for overall effect	Z = 2.60 (P = 0.00)	09)					0.002 Meta	0.1 Ichronous PJI grou	1 10 Ip Non-metachrono	500 ous PJI group

Fig. 5 Forest plot of previous or ongoing non-periprosthetic infection on metachronous PJI

with RA may have more than one prosthetic implant, which may be more common compared to other types of joint diseases. We can assume that patients with RA have a higher risk of metachronous PJIs, as they have more prosthetic joints at risk after a PJI [38, 39]. Meanwhile, impairment of the immune system by RA decreases the patient's resistance to infection. Patients with RA often need to take long-term medications such as steroids, anti-rheumatic drugs, immunosuppressants, etc., to control and delay their condition. The above medicines may be due to a decrease in the host's immune system, increasing the risk of PJI. The risk associated with the use of steroids is comparable to that of RA, as it may potentially result in additional joint infections. Wilson et al. concluded that steroids may represent a comorbid variable and reflect the activity or aggressiveness of the underlying rheumatoid process [19, 23, 40]. However, recent studies have shown that compared to those who do not take steroids, RA patients who take glucocorticoids exceeding 10 milligrams per day have almost twice the risk of infection after joint replacement surgery compared to those who do not take steroids [41, 42]. We postulate that the presence of RA, along with the use of steroids and immunosuppressants, can disrupt and even undermine the host's immune function. The consequent impairment of the immune system and the deterioration of overall health then heighten the risk of metachronous PJI among patients with multiple joint prostheses.

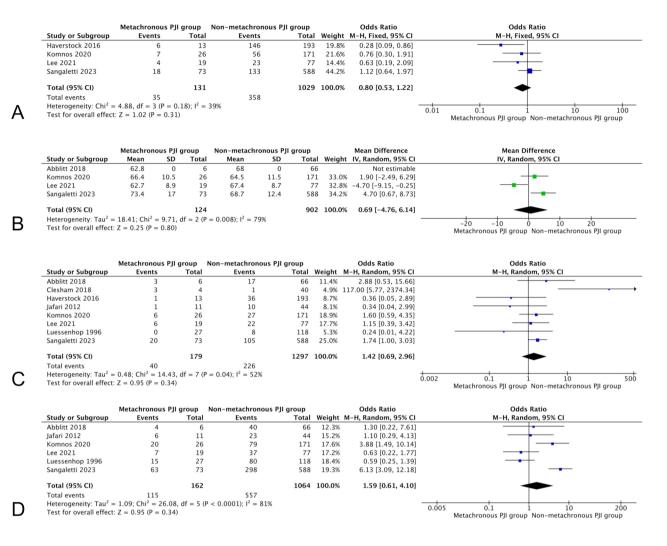


Fig. 6 Forest plot of revisions (A), age (B), diabetes (C), and gender (D) on metachronous PJI

Previously, Sangaletti et al. suggested that female patients, diabetic patients, as well as those with a polymicrobial index PJI, face a substantially elevated risk of developing a metachronous PJI [23]. However, this study found no significant correlation between revision, age, diabetes, gender, and metachronous PJI. The absence of a significant correlation between revision surgery, age, diabetes, and gender and metachronous PJI can be attributed to multiple factors [43]. Regarding revision surgery, the diverse procedures and variable pre- and post- operative conditions often confound the results [44]. Agerelated immune alterations are intricate and frequently overshadowed by comorbidities [45]. The influence of diabetes on PJI hinges on glycemic control and its interactions with other elements [46]. As for gender, there is a lack of robust biological evidence for differences, and social factors further confound this relationship [47]. Furthermore, there is also an urgent need for more large sample, high-quality prospective cohort studies to further demonstrate the significance of these factors and their potential clinical impact.

This study has several limitations. Firstly, this study incorporated cases of PJI involving the wrist, shoulder, ankle, and elbow joints. These particular joints are characterized by relatively scant soft-tissue coverage, which significantly amplifies the risk of postoperative infection during joint replacement procedures. This condition may exert a certain influence on the outcomes of our study. Given the limited number of relevant studies available at present, a subgroup analysis based on joint location has not been conducted. Secondly, given that this study is a retrospective observational one, it is subject to potential biases such as selection bias, information bias, and confounding bias. In addition, due to the limited number of eligible literature, with a total of 9 studies included in this meta-analysis, the meta-analysis exhibited deficiencies in aspects such as statistical power and heterogeneity assessment, which may have restricted

the generalizability of the research findings. Therefore, in future research, prospective multicenter cohort studies and microbial profile analyses can be further carried out, and in-depth exploration of the sources of heterogeneity can be conducted. These efforts aim to enhance the generalizability of research results and provide more optimized strategies for the clinical prevention, diagnosis, and treatment of metachronous PJI.

Conclusion

This meta-analysis identifies MRSA, RA, history of steroid use, and previous or ongoing non-periprosthetic infection as independent risk factors for metachronous PJI. These findings underscore the need for prospective multicenter and large-sample cohorts to validate biological mechanisms and identify additional modifiable predictors. Implementation of targeted surveillance protocols in high-risk populations and preemptive prophylactic measures could optimize clinical management while reducing the clinical and economic burden of recurrent prosthetic complications.

Supplementary Information

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Supplementary Material 1
Supplementary Material 2
Supplementary Material 3

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Author contributions

All authors have contributed significantly, and that all authors agree with the content of the manuscript. Conception and design (Mao Nie and Haibo Si). Acquisition, analysis, and interpretation of the data (Yi Li, Xiaolin Quan, Cheng Zhou and Xin Duan). Manuscript preparation and editing (all authors). Final approval of the article (all authors).

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was registered in the International Prospective Register of Systematic Reviews (PROSPERO number CRD42024562732).

Consent for publication

As corresponding author of this manuscript, we hereby explicitly agree to have this manuscript published by Journal of Orthopaedic Surgery and Research. We fully understand and acknowledge all the terms and regulations involved in the publishing process, including but not limited to copyright transfer, manuscript editing and modification, as well as arrangements regarding the publishing format and channels. We promise that the content of the manuscript is authentic, legal and free from any infringement upon the rights and interests of others, and we are willing to assume all legal responsibilities and consequences arising from the content of the manuscript.

Competing interests

The authors declare no competing interests.

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