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Infection and revision rates following primary total knee arthroplasty in patients with rheumatoid arthritis versus osteoarthritis: a meta-analysis

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Abstract

Purpose This meta-analysis compared infection and revision rates in patients with rheumatoid arthritis (RA) and osteoarthritis (OA) who underwent total knee arthroplasty (TKA). Rates of superficial wound and deep periprosthetic infections were compared in the groups, as were whether revision rates associated with infectious and noninfectious causes differed in the RA and OA groups.

Methods Studies were included in the meta-analysis if they (1) compared infection and revision rates after primary TKA in RA and OA patients; (2) directly compared superficial wound and deep periprosthetic infection rates in RA and OA patients who underwent primary TKA; and (3) reported the actual numbers of RA and OA patients who underwent TKA and developed postoperative infection and/or required revision.

Results The rate of superficial wound infections after primary TKA was similar in the RA and OA groups (15/258 [5.8 %] vs. 77/1609 [4.7 %]; odds ratio [OR] 1.12, 95 % confidence interval [CI] 0.36–3.46; P = n.n.), but the deep infection rate was significantly higher in RA than in OA patients (229/7651 [3.0 %] vs. 642/68628 [0.9 %]; OR 2.04, 95 % CI 1.37–3.05; $P < 0.001$). The proportion of subjects who required revision resulting from infection after TKA was significantly higher in the RA than in the OA group (86/8201 [1.0 %] vs. 555/118755 [0.5 %]; OR 1.89, 95 % CI 1,34–2.66; $P < 0.001$), whereas the proportion of subjects requiring revision due to noninfectious causes did not differ significantly (46/594 [7.7 %] vs. 52/904 [5.7 %]; OR 1.22, 95 % CI 0.74–2.00; P = n.n.)

Conclusion Following primary TKA, RA patients had a significantly higher rate of deep periprosthetic infections than OA patients, but their superficial infection rates were similar. The revision rate due to infectious causes was significantly higher in RA than in OA patients, but their revision rates due to noninfectious causes did not differ. Therefore, the surgeon should fully explain to RA patients scheduled to undergo primary TKA that, compared to OA patients, they are more likely to experience a deep infection postsurgery.

Level of evidence Meta-analysis Level III.

Keywords Rheumatoid arthritis · Osteoarthritis · Infection · Revision · Total knee arthroplasty · Meta-analysis

Introduction

The long-term prognosis of patients with rheumatoid arthritis (RA) has improved due to the development of new medications, such as disease-modifying anti-rheumatic drugs (DMARDs) and biologic agents [10, 14]. Nevertheless, approximately 18–24 % of RA patients still progress to end-stage arthritis and require arthroplasty [8, 13], with the knee joint being the most frequent site of arthroplasty

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in RA patients [31]. The number of RA patients undergoing total knee arthroplasty (TKA) has increased [18], although the vast majority of patients who undergo TKA do so for advanced knee osteoarthritis (OA) [6, 16]. Surgical results of TKA have been regarded as poorer in RA than in OA patients, due to the high infection and revision rates resulting from the characteristics of RA, such as chronic inflammation [3, 24, 25, 27]. To date, however, few studies have directly compared infection and/or revision rates in patients with RA and OA, with some of these comparative studies showing contradictory results [17]. Comparisons have also been hampered by unclear definitions of infection, by whether superficial wounds or deep periprosthetic infections were being compared, and by whether revisions are or are not infection related.

This meta-analysis was therefore designed to better compare the surgical outcomes of TKA for RA and OA, including infection and revision rates. Subgroup analyses were used to compare the rates of superficial wound and deep periprosthetic infections in the two groups, and to determine whether the revision rates due to infectious and noninfectious causes differed between the RA and OA groups.

Materials and methods

Data and literature sources

This study was based on Cochrane review methods. Multiple comprehensive databases, including MEDLINE, EMBASE, Web of Science, SCOPUS, and the Cochrane Library (January 1, 1987– June 30, 2015), were searched for studies that compared superficial and/or deep infection rates and revision rates resulting from infectious and/or noninfectious causes following primary TKA in RA and OA patients. There were no restrictions on language or year of publication. Search terms used in the title, abstract, MeSH, and keywords fields included "arthroplasty" [tiab] OR "replacements" [tiab] OR "knee" [tiab], and "rheumatoid arthritis" [MeSH] OR "osteoarthritis" [MeSH] OR "infection" [tiab] OR "revision" [tiab]. After the initial electronic search, relevant articles and their bibliographies were searched manually. The identified articles were individually assessed for inclusion.

Study selection

From the title and abstract, two reviewers independently selected the relevant studies for full review. The full text of an article was reviewed if the abstract did not provide sufficient data to make a decision. Studies were included in the meta-analysis if they (1) compared infection and revision rates after primary TKA in RA and OA patients; (2) directly compared superficial wound and deep periprosthetic infection rates and their associated revision rates in RA and OA patients who underwent primary TKA; and (3) reported the actual numbers of total RA and OA patients who underwent TKA and the actual numbers who developed postoperative infection and/or required revision. Studies were excluded if they did not clearly distinguish between superficial and deep infections or did not clearly determine the cause of revision, whether infectious or noninfectious.

Data extraction

Two reviewers independently recorded data from each study using a predefined data extraction form. Disagreements between the reviewers were resolved by consensus or by discussion with a third investigator when a consensus could not be reached. Variables recorded included those associated with assessing infection and revision rates: (1) the numbers of patients with RA or OA who developed superficial wound and/or deep periprosthetic infections following primary TKA; (2) the number of revisions due to infectious and noninfectious causes after primary TKA in the RA and OA groups; and (3) the sample size of each group. If these variables were not mentioned in the articles, the study authors were contacted to retrieve further information. Superficial and deep infections were defined based mainly on Center for Disease Control (CDC) Criteria as follows: superficial infection does not require reoperation and is cured by antibiotics alone, whereas deep infection requires additional surgery such as open or arthroscopic debridement, or two-stage revision [7].

Assessment of methodological quality

Two reviewers independently assessed the methodological qualities of each study using the Newcastle-Ottawa Scale, as recommended by the Cochrane Non-Randomized Studies Methods Working Group. For the purposes of the current meta-analysis, the adjusted Newcastle-Ottawa Scale star system was used. The Newcastle-Ottawa Scale had three criteria: the selection of the study groups; the comparability of the groups; and, for case–control and cohort studies, the determination of exposure or outcome of interest. Studies of high quality were defined as those having scores >5 points. Disagreements in scores were resolved by discussion and consensus between the two reviewers.

Data synthesis and statistical analysis

The main outcomes of the meta-analysis were the proportions of patients in the RA and OA groups who underwent

TKA and experienced superficial and deep infections and the proportions of patients requiring revision due to infectious and noninfectious causes. The odds ratios (ORs) and 95 % confidence intervals (CI) of binary outcomes were calculated for all comparisons. These values were analysed with a random effects model. Interrater reliability in assessing methodological quality was evaluated by kappa (κ), with values of ≤0.40, 0.41–0.60, 0.61–0.80, and 0.81–1.00 indicating no, moderate, substantial, and almost perfect agreement, respectively. Heterogeneity was determined by estimating the proportion of between-study inconsistencies due to actual differences between studies, rather than differences due to random error or chance, using I^2 statistics, with 25, 50, and 75 % defined as low, moderate, and high heterogeneity, respectively. All statistical analyses were performed with RevMan version 5.2 statistics software.

Results

Identification of studies

Figure 1 shows details of study identification, inclusion, and exclusion. An electronic search yielded 2990 studies in PubMed (MEDLINE), 3328 in EMBASE, 692 in Web of Science, 4598 in SCOPUS, and 248 in the Cochrane Library. Two additional publications were identified through manual searching. After 4905 duplicates were removed, 6953 studies remained. Of these, 6894 were excluded as it was clear from their abstracts and titles that they did not fulfil the selection criteria. An additional 46 studies were excluded because they did not provide usable information, did not differentiate between superficial and deep infection, or did not clearly describe cause of revision. Thus, 13 studies [1, 5, 7, 9, 11, 12, 17, 19–21, 25, 28, 30] were included in this meta-analysis.

Study characteristics and quality of the included studies

Of the 13 included studies, five compared infection rate, including superficial and/or deep infection rate, between RA and OA groups; six compared revision rate due to infectious and noninfectious causes, and two compared both infection and revision rates between RA and OA groups (Table 1).

All 13 studies were at low risk of selection bias. All provided detailed demographic data of each RA and OA group. None assessed possible confounding factors. Of these 13 studies, eight were considered high quality, with >5 points on the Newcastle-Ottawa Scale. Interrater reliabilities (κ values) for all items of NOS ranged from 0.71 to 0.89, indicating at least more than substantial agreement between two investigators.

Superficial versus deep infection

Of the 13 studies, three reported rates of superficial infection; six reported rates of deep prosthetic infection; and three reported total infection rates, including both superficial and deep infection rates, after in RA and OA patients who underwent primary TKA. The rate of superficial wound infections after primary TKA was similar in the RA and OA groups (15/258 [5.8 %] vs. 77/1609 [4.7 %]; OR 1.12, 95 % CI 0.36–3.46; P = n.n.). In contrast, the rate of deep prosthetic infection was significantly higher in RA than in OA patients (229/7651 [3.0 %] vs. 642/68628 [0.9 %]; OR 2.04, 95 % CI 1.37–3.05; $P < 0.001$, Fig. 2).

Infectious versus noninfectious causes of revision

Of the 13 studies, seven and five reported rates of revision due to infectious and noninfectious causes, respectively, in RA and OA patients who underwent primary TKA. The rate of revision due to infectious causes was significantly higher in the RA than in the OA group (86/8201 [1.0 %] vs. 555/118755 [0.5 %]; OR 1.89, 95 % CI 1, 34–2.66; $P < 0.001$), whereas the rate of revision due to noninfectious causes was similar in these two groups (46/594 [7.7 %] vs. 52/904 [5.7 %]; OR 1.22, 95 % CI 0.74–2.00; P = n.n., Fig. 3).

Meta-regression analyses

The results of meta-regression analyses are reported in Table 2. Age and gender were not significantly associated with differences in infection and revision rates after primary TKA in the RA and OA groups. This finding indicated that the results of the current meta-analysis were not biased by the demographic characteristics of the patients in the included studies. Another meta-regression analysis was performed to evaluate the confounding effect of follow-up period on differences in superficial or deep infection rates between RA and OA patients. The results showed no significant association between follow-up duration and differences in superficial or deep infection rates, indicating that follow-up duration did not influence the differences in superficial or deep infection rates between RA and OA patients.

Discussion

The most important findings of this meta-analysis were that the rates of deep, but not superficial, infections and the

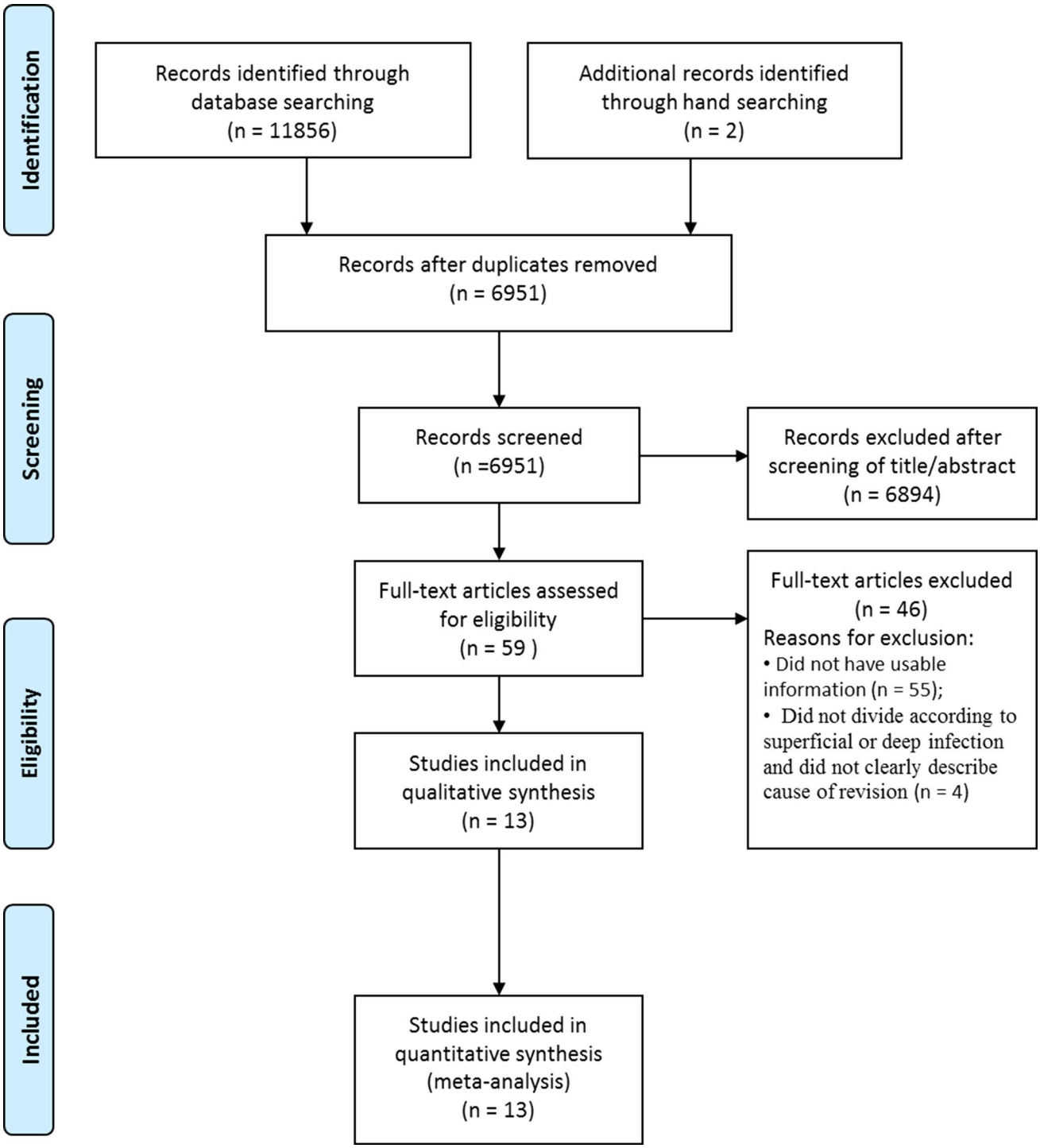

Fig. 1 PRISMA (preferred reporting items for systematic reviews and meta-analyses) flow diagram of the identification and selection of the studies included in this meta-analysis

rates of revision due to infectious, but not noninfectious, causes were significantly higher in patients who underwent primary TKA for RA than for OA.

Infections after TKA can be classified as superficial wound and deep periprosthetic infections. Distinguishing between these two categories is important because their treatment strategies differ. Superficial infections can usually be controlled by antibiotic therapy, whereas deep infections usually require prosthesis removal followed by second stage revision. Despite the importance of knowing

Table 1 Characteristics of the included studies

References	Year	Study type	Sample size		Quality score	Measured parameters
			RA	OA		
Bengtson.et al. [1]	1991	RCS	4534	7534	6	DI
Chesney et al. [5]	2008	PCS	71	1235	8	SI, DI
da Cunha et al. [7]	2015	RCS	28	56	6	SI, DI
Elke et al. [9]	1995	PCS	61	415	6	RDTIC, RDTNIC
Goldberg et al. [11]	1998	PCS	43	66	7	RDTNIC
Jamsen et al. [12]	2009	PCS	3040	35,298	8	RDTIC
LoVerde et al. [17]	2015	RCT	159	318	5	SI, DI
Nafei et al. [19]	1996	PCS	164	184	7	RDTIC, RDTNIC
Partio et al. [20]	1994	PCS	193	167	6	DI, RDTIC, RDTNIC
Ravi et al. [21]	2014	PCS	2692	59,564	5	DI
Scharama et al. [25]	2010	PCS	2462	21,832	4	RDTIC
Tayton et al. [28]	2015	RCS	2148	60,787	6	RDTIC
Weir et al. [30]	1996	PCS	133	72	5	DI, RDTIC, RDTNIC

RCT randomized controlled trial; *RCS* retrospective comparative study; *PCS* prospective comparative study; *DI* deep infection; *SI* superficial infection; *RDTIC* revision due to infectious cause; *RDTNIC* revision due to noninfectious cause

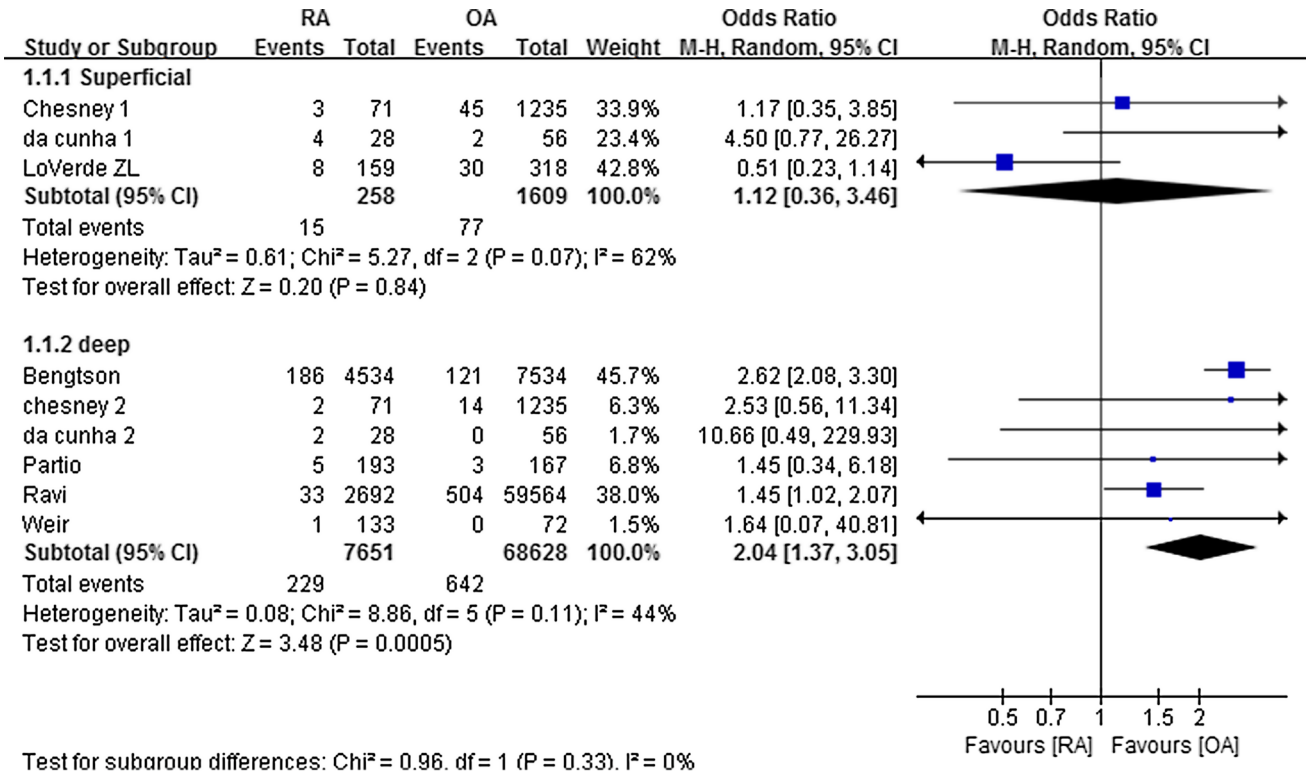

Fig. 2 Forest plot showing infection rates in patients with rheumatoid arthritis (RA) and osteoarthritis (OA). The rates of superficial wound infections after primary TKA were similar in the RA and OA groups (15/258 [5.8 %] vs. 77/1609 [4.7 %]; OR 1.12, 95 % CI 0.36–3.46; P = n.s.). In contrast, the rate of deep periprosthetic infections was significantly higher in RA than in OA patients (229/7651 [3.0 %] vs. 642/68628 [0.9 %]; OR 2.04, 95 % CI 1.37–3.05; $P < 0.001$)

the rates of superficial and deep infections, several previous studies [24, 27] comparing infection rates after TKA for RA and OA did not distinguish between superficial and deep infections. This meta-analysis may therefore be meaningful in that it included subgroup analysis of superficial and deep infection rates after TKA for RA and OA.

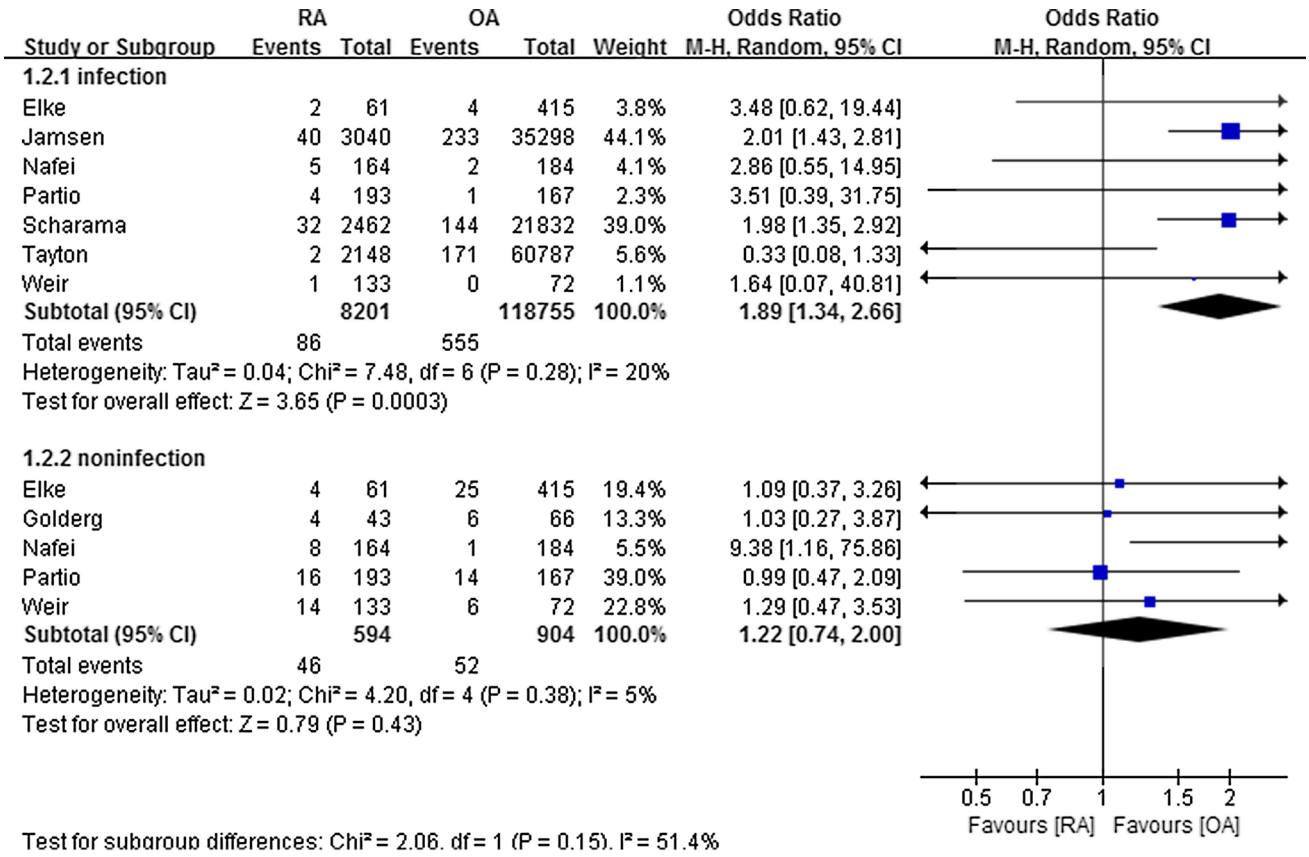

Fig. 3 Forest plot showing revision rates in patients with rheumatoid arthritis (RA) and osteoarthritis (OA). The rate of revision due to infection was significantly higher in RA than in OA patients (86/8201 [1.0 %] vs. 555/118755 [0.5 %]; OR 1.89, 95 % CI 1, 34–2.66; $P < 0.001$). In contrast, the rates of revision due to noninfectious causes were similar in the two groups (46/594 [7.7 %] vs. 52/904 [5.7 %]; OR 1.22, 95 % CI 0.74–2.00; $P =$ n.n.)

Table 2 Meta-regression analyses between age, gender, follow-up duration, and differences in infection and revision rates after total knee arthroplasty in patients with rheumatoid arthritis and osteoarthritis

Variable	Coefficient	Standard error	*P* value	95 % confidence interval
Difference of infection rate after TKA between RA and OA				
Age	2.551	0.590	n.s.	–4.957 to 10.061
Gender	–2.865	0.950	n.s.	–14.946 to 9.214
Difference of revision rate after TKA between RA and OA				
Age	3.772	5.583	n.s.	–9.103 to 16.648
Gender	–1.289	4.908	n.s.	–12.608 to 10.029
Superficial infection rate after TKA between RA and OA				
Follow-up period	0.021	0.014	n.s.	−0.155 to 0.198
Deep infection rate after TKA between RA and OA				
Follow-up period	−0.001	0.002	n.s.	−0.026 to 0.024

Although the causes of the higher deep prosthesis infection rate in RA than in OA patients have not yet been determined, immunosuppressive treatment of RA patients with corticosteroids and/or immunomodulatory drugs may be associated with deep prosthesis infection [21, 24, 27]. Similarly, allogenic transfusion may increase the deep infection rate in these patients. Many patients with RA experience anaemia due to bone marrow suppression by chronic disease and medication [26]. These patients are more likely susceptible to postoperative anaemia,

increasing the need for allogenic blood transfusion, which can increase the risk of postoperative infection by inducing transfusion-related immunomodulation [2, 4, 23]. It is therefore unclear whether RA itself or its treatment, including immunomodulation and allogenic transfusion, increases the risk for deep prosthesis infection after surgery.

This meta-analysis, however, found no significant difference in rates of superficial infection between RA and OA patients. Although immunosuppressive factors such as RA medications and transfusion can affect both superficial and deep infections, it is unclear why deep, but not superficial, infection rates differed between the RA and OA groups. Perioperative antibiotics may prevent or cure superficial wound infections, even in immunosuppressed patients, such as those with RA. However, once a biofilm forms around a prosthesis (deep periprosthetic infection), it may be more difficult for antibiotics to eliminate the bacteria, even those with low virulence, in immunosuppressed RA than in OA patients [32]. These differences in the effectiveness of antibiotics for superficial and deep infections in RA, but not in OA, patients may contribute to their similar superficial infection rates, along with a higher deep infection rate in RA than in OA patients.

The current meta-analysis also showed that the revision rate due to infectious causes was higher in RA than in OA patients, but there were no significant between-group differences in revision rates due to noninfectious causes. This finding indicated that the main cause of revision in RA patients was infection, not complications due to chronic inflammation, such as soft tissue laxity or attenuation of the posterior cruciate ligament. These latter conditions were regarded as important concerns in RA patients undergoing primary TKA. Prosthesis instability was reported to be more common in cruciate retaining (CR) than in posterior substitution (PS)-type prostheses. This result has been attributed to joint laxity and PCL attenuation caused by chronic inflammation [15]. However, recent increases in the use of PS than of CR-type TKA may reduce revision rates due to noninfectious causes, including prosthesis instability [29]. The similar revision rates due to noninfectious causes may also be due to the relative lower activity level in RA than in OA patients [22, 26, 27].

This study had several limitations. The possibility of other confounding factors affecting the results could not be completely ruled out, especially as age distributions differed between the RA and OA groups. Different age distributions in the two groups may have influenced the superficial infection and revision rates by underestimating the real incidence of infection and revision in the RA group, because patients in that group were younger and tended to be healthier compared to the group of patients with OA. However, the meta-regression analysis performed in our study showed that age and gender were not significantly associated with differences in the rates of infection and revision in RA and OA patients, thereby excluding any confounding effect of age distribution on infection and revision rates after TKA in the two groups. The present study sought to analyse other confounding factors such as BMI, surgical time and techniques, and institutional perioperative care. Moreover, there may have been inconsistencies among the included studies in terms of the diagnosis criteria used for infection after TKA, for example whether the infection was diagnosed based on clinical decisions or culture results from aspiration or intraoperative tissue specimen; this may have affected the difference in infection rate. However, due to a lack of information for these confounding factors in each study, meta-regression with the above factors could not be performed.

Another limitation may have been potential bias stemming from unmeasured or unknown confounders, including medications and disease severity in patients with RA. Lastly, it would be ideal to perform a meta-analysis including only randomized control trials (RCTs). However, most studies in the orthopaedic field are not RCTs, because most deal with surgical results. Therefore, although the current meta-analysis included non-RCT studies comparing the infection and revision rate between RA and OA patients, we believe that it constitutes an examination of the best evidence currently available.

Conclusions

The deep periprosthetic infection rate after primary TKA was higher in RA than in OA patients, whereas the superficial wound infection rate was similar in the two groups. Revision rates caused by soft tissue laxity or PCL attenuation following primary TKA were also similar in RA and OA patients. In contrast, the revision rate due to periprosthetic infection was significantly higher in RA than in OA patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Funding No funds were received to do this research.

Ethical approval There were no ethical approval, because this study was a meta-analysis based on the data of previously published studies.

Informed consent Informed consent was not applicable since the study design was a meta-analysis.

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