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Review Article

Incidence and risk factors for surgical site infection following total knee arthroplasty: a systematic review and meta-analysis

Lingde Kong, Junming Cao, Fei Meng, Yong Shen

Department of Orthopaedic Surgery, The Third Hospital of Hebei Medical University, Shijiazhuang, P. R. China

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Abstract: To identify the risk factors for postoperative surgical site infection (SSI) following total knee arthroplasty (TKA), a systematic search was performed in three databases: Pubmed, Embase, and Cochrane library databases until February 2016. Pooled odds ratios (ORs) or standardized mean differences (SMDs) with 95% confidence intervals (CIs) were calculated using random- or fixed-effects model. Patient-related factors, surgical-related factors and comorbidity were investigated. Fourteen studies were selected for the current meta-analysis. The pooled infection rate was 0.90% (95% CI, 0.30% to 1.50%). Factors associated with infection after TKA were male gender (OR, 2.23; 95% CI, 1.71 to 2.91), age (SMD, -0.11; 95% CI, -0.19 to -0.02), obesity (OR, 1.25; 95% CI, 1.06 to 1.48), smoking (OR, 2.57; 95% CI, 1.50 to 4.39), American society of anesthesiologists scale (ASA) > 2 (OR, 1.79; 95% CI, 1.50 to 2.15), operative time (SMD, 0.44; 95% CI, 0.26 to 0.63), transfusion (OR, 1.54; 95% CI, 1.18 to 2.02), and diabetes mellitus (OR, 1.51; 95% CI, 1.17 to 1.95). No sufficient evidences reveal that steroid use, bilateral surgery, drain usage, bone graft, urinary tract infection, hypertension, and rheumatoid arthritis lead to infection after TKA. This information could be used to prevent the onset of infection after TKA.

Keywords: Surgical site infection, total knee arthroplasty, review, meta-analysis, risk factors

Introduction

Total knee arthroplasty (TKA) is one of the most common procedures that is used to treat end stage knee disease. In spite of the success of TKA in terms of alleviating pain and improving function, serious complications like postoperative infection can occur, which not only limit function of the joint, increase mortality of the patients, but also rise health care expenditures of the society [1, 2]. Thus, it is important to identify variables that may increase the risk of surgical site infection (SSI) following TKA, so that we can find solutions to decrease its incidence.

Some studies have investigated and assessed potential factors that were associated with TKA infection, such as obesity [3], diabetes mellitus [4, 5], malignancy [6], rheumatoid arthritis (RA) [7], longer hospitalization [8], smoking [5] and injection of intra-articular steroid [9]. However, these studies were limited by inclusion of incomprehensive risk factors or small number of participants. Additionally, some of their results were controversial. For example, Minnema *et al.* considered that the use of suction drainage was associated with a higher risk of postoperative infection [10], whereas a study conducted by Dowsey *et al*. reported that the presence of a drain tube could reduce the risk [11]. We assumed that a single study may be unable to detect a true association due to the relatively small sample size. Nevertheless, meta-analysis, by pooling the results of several studies, can increase the statistical power of the association analysis and obtain more precise estimates of effect. In recently years, several authors have conducted meta-analysis and reported risk factors for infection after total joint arthroplasty [12, 13], but their studies did included some important data currently available. To get a better understanding of the incidence and risk factors for infection after TKA, we conducted this systematic review and meta-

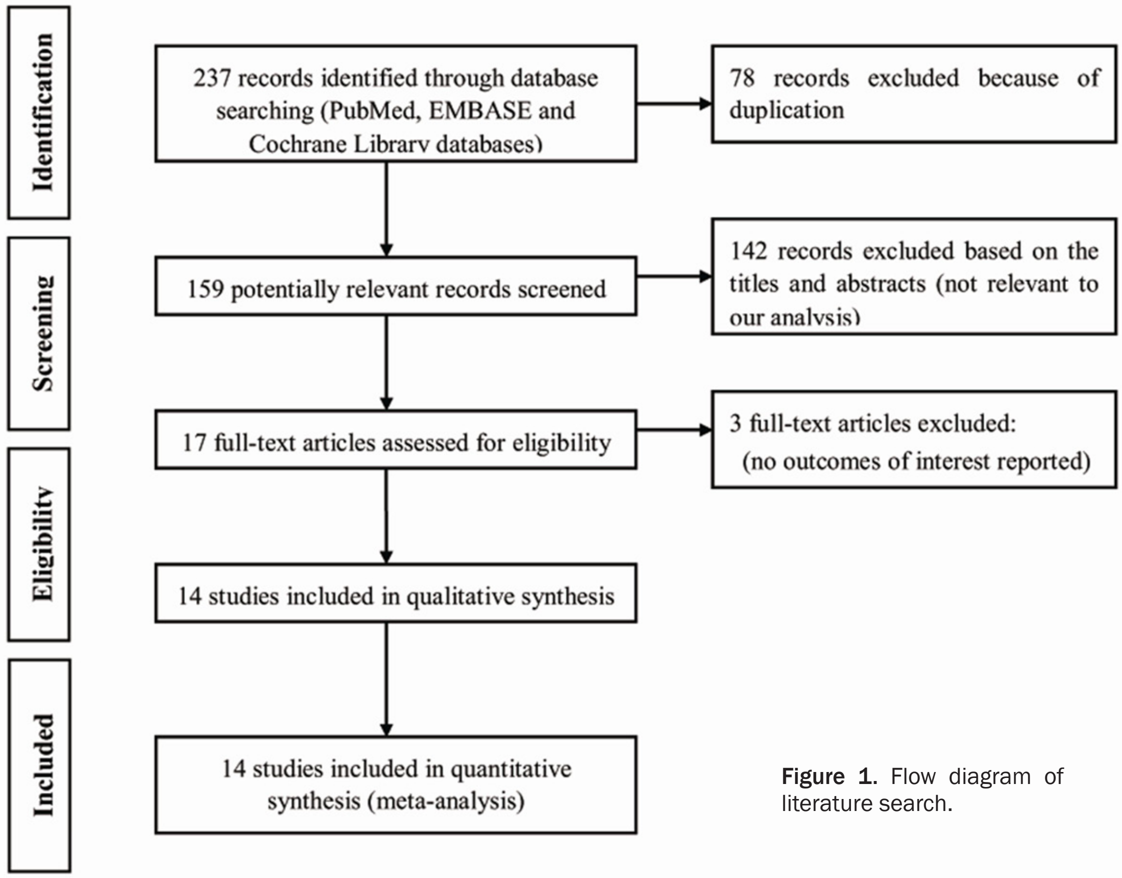

Figure 1. Flow diagram of literature search.

analysis. The current study may be useful for arriving at clinical recommendations.

Materials and methods

Literature search and inclusion criteria

The authors searched Pubmed, Embase, and Cochrane library databases to retrieve relevant studies that were published before February 2016. We used the following search terms and boolean operators: (“knee” OR “joint” OR “TKA” OR “TKR”) AND (“infection” OR “SSI”) AND (“risk” OR “predictor” OR “factor”). The “related articles” function in electronic database was used to broaden the search, and a manual search of the reference of the eligible publications was also performed to identify additional studies. The subjects were restricted to human beings, and languages were restricted to English.

Two reviewers independently reviewed the titles, abstracts and full-texts of identified papers. We used the following inclusion criteria: (1) the study design was observational study, including both cohort and case-control studies; (2) patients underwent primary TKA surgery; (3) postoperative infection was investigated; (4) possible risk factors for infection were explored; (5) sufficient data were present or can be calculated to estimate the odds ratios (ORs) or standardized mean differences (SMDs) with 95% confidence intervals (CIs). Studies had repeated data, or did not report the outcomes of interest were excluded.

Data extraction and outcome measures

The following variables were extracted from each study: the name of first author, publication year, country, duration of investigation, type of infection, and number of patients in both case and control groups. If the same population was reported in several publications, we retained only the most informative one to avoid duplication of information. Two authors extracted data independently, and if there were any disagreements concerning paper eligibility, they resolved them by discussion and consensus.

Table 1. The basic characteristics of the 14 included studies

First author	Publication year	Country	Period	Types of infection	Case	Control	Infection risk (%)	Quality score
Wilson [7]	1990	Boston	1973-1987	Deep	61	122	1.61	7
Minnema [10]	2004	Canada	1999-2001	Superficial, deep	22	66	--	6
Babkin [16]	2007	Israel	1999-2000	Superficial, deep	10	170	5.56	7
Dowsey [11]	2009	Australia	1998-2005	Deep	18	1196	1.48	8
Jamsen [17]	2009	Finland	1997-2004	Deep	298	39837	0.74	8
Asensio [18]	2010	Spain	2005-2006	Deep	36	106	0.91	7
Basora [19]	2010	Spain	2004-2005	Deep	61	849	6.70	6
Peel [20]	2011	Australia	2000-2007	Deep	27	54	--	7
Suzuki [21]	2011	Japan	1995-2006	Deep	17	2005	0.84	7
Bozic [4]	2012	United States	1998-2007	Deep	--	--	--	7
Song [22]	2012	Korea	2006-2009	Superficial, deep	83	3343	2.42	8
Namba [23]	2013	United States	2001-2009	Deep	404	55812	0.72	8
Gomez-Lesmes [24]	2014	Spain	2007-2009	Deep	32	1299	2.40	7
Crowe [25]	2015	United States	2009-2011	Deep	26	3393	0.76	8

Briefly, we investigated a total of fifteen risk factors involving three aspects: patient-related factors, surgical-related factors and comorbidity, including gender, age, obesity, smoking, steroid use, American society of anesthesiologists (ASA) scale, operative time, bilateral surgery, transfusion, drain usage, bone graft, diabetes mellitus, urinary tract infection, hypertension, and rheumatoid arthritis (RA).

The body mass index ≥ 30 kg/m^2 was considered as obesity; any form of systemic corticosteroid therapy for more than one week in the year of prosthesis implantation was defined as steroid use; and any autologous or homologous blood transfusion during surgery or within 48 hours after surgery was defined as transfusion. The Centers for Disease Control and Prevention criteria is commonly used to diagnose and classify SSI [14]. After TKA surgery, organ/space infection is difficult to distinguish from deep infection, and thus is deemed as deep infection.

Methodological quality

The Newcastle-Ottawa Scale (NOS) [15] was used to evaluate the quality of the included studies. The three main items and corresponding points were listed as follows: the selection of the study groups (0-4 points), the comparability of the groups (0-2 points), and the determination of either the exposure or outcome of interest (0-3 points). The total score is 9, and a study with NOS score ≥ 6 was deemed as high quality.

Statistical analysis

From each included study, we extracted ORs with 95% CIs for dichotomous outcomes and SMDs with 95% CIs for continuous outcomes. Adjusted OR was commonly used and crude OR was chosen only when adjusted OR was unavailable. We assessed the association between every potential factor and the risk of infection with $P < 0.05$ indicating a significant difference. The heterogeneity among the studies was qualitatively tested by Q-test statistics with the significance set at $P < 0.10$, and quantitatively tested by I^2 statistics with $I^2 > 50\%$ indicating large inconsistency. The fixed-effects model was used to calculate pooled ORs or SMDs if there was no significant heterogeneity ($P > 0.10$ or $I^2 < 50\%$); otherwise, the random-effects model was used.

If the number of analyzed studies ≥ 10, publication bias was assessed by the funnel plot and Begg test, and $P < 0.10$ was judged as statistically significant. All analyses were performed in this study using the software Stata 11.0 (Stata Corporation, College Station, TX).

Results

Literature search results

The literature search identified 237 potentially relevant articles, but 78 records were excluded because of duplication. After review of titles and abstracts, 142 records were excluded.

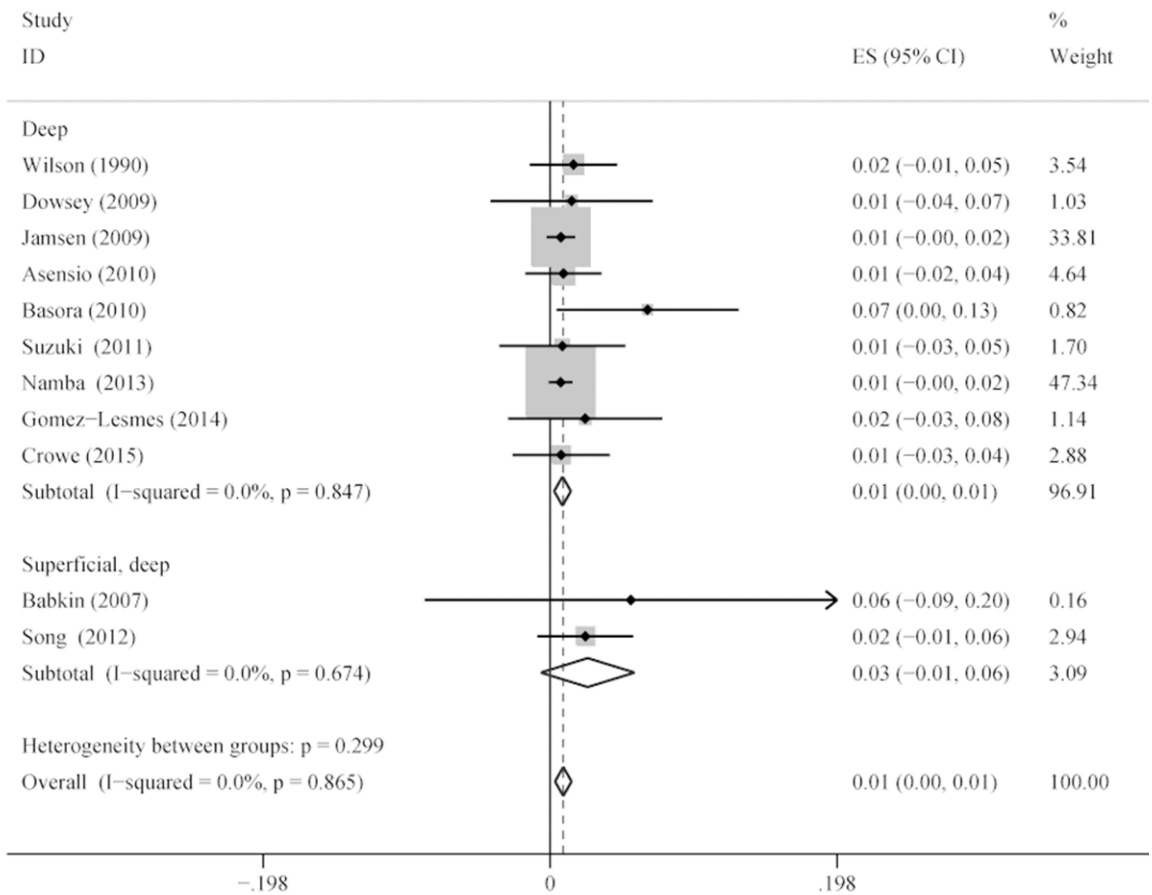

Figure 2. Forest plots showing the incidence of infection after TKA.

Then we retrieved 17 full-texts for further assessment, and 3 articles were excluded for insufficient data. Finally, 14 unique studies were available for data analysis [4, 7, 10, 11, 16-25] (**Figure 1**).

Study characteristics

The publication year of the 14 studies ranged from 1990 to 2015. Types of infection included superficial infection and deep infection. Based on the NOS score, 5 studies scored 8 [11, 17, 22, 23, 25], 7 studies scored 7 [4, 7, 16, 18, 20, 21, 24], and 2 studies scored 6 [10, 19]. All included studies were of high quality, and the basic characteristics of these studies are summarized in **Table 1**.

Pooled analysis of infection rate

Of the 14 studies, 11 reported the incidence of infection [7, 11, 16-19, 21-25]. Based on the results of 11 studies, the infection rate ranged from 0.72% to 6.70%, and the pooled rate was 0.90% (95% CI, 0.30% to 1.50%). Nine studies reported the incidence of deep infection [7, 11, 17-19, 21, 23-25], and the cumulated infection rate was 0.85% (95% CI, 0.30% to 1.40%); while the rate of superficial and deep infection was reported in two studies [16, 22], and the cumulated infection rate was 2.58% (95% CI, 0.60% to 5.80%, **Figure 2**).

Pooled analysis of risk factors

There was significant heterogeneity among the studies when evaluating the following potential risk factors: gender, steroid use, bilateral surgery, drain usage, diabetes mellitus, urinary tract infection, and RA. Based on the combined ORs or SMDs, we identified the following risk factors: male gender (OR, 2.23; 95% CI, 1.71 to 2.91), age (SMD, -0.11; 95% CI, -0.19 to -0.02), obesity (OR, 1.25; 95% CI, 1.06 to 1.48), smoking (OR, 2.57; 95% CI, 1.50 to 4.39), ASA score > 2 (OR, 1.79; 95% CI, 1.50 to 2.15), operative

Table 2. Detailed data on 15 potential risk factors for the surgical site infection and the outcome of meta-analysis

Risk factors	No. of studies	OR or SMD	LL 95% CI	UL 95% CI	*P* value	Q-test (*P*)	I^2 (%)
Patient-related factors							
Male gender	10	2.23[a]	1.71	2.91	< 0.01[d]	0.02	56.2
Age	5	-0.11[b]	-0.19	-0.02	0.01[c]	0.94	0.0
Obesity (BMI ≥ 30)	3	1.25[a]	1.06	1.48	0.01[c]	0.37	0.0
Smoking	4	2.57[a]	1.50	4.39	< 0.01[c]	0.68	0.0
Steroid use	3	1.85[a]	0.23	15.05	0.57[d]	0.12	58.4
ASA score > 2	5	1.79[a]	1.50	2.15	< 0.01[c]	0.33	14
Surgery-related factors							
Operative time	2	0.44[b]	0.26	0.63	< 0.01[c]	0.56	0.0
Bilateral surgery	2	0.79[a]	0.33	1.88	0.59[d]	0.02	81.5
Transfusion	6	1.54[a]	1.18	2.02	< 0.01[c]	0.10	45.7
Drain usage	3	0.58[a]	0.04	8.64	0.70[d]	< 0.01	89
Bone graft	2	0.86[a]	0.41	1.83	0.70[c]	0.81	0.0
Comorbidity							
Diabetes mellitus	10	1.51[a]	1.17	1.95	< 0.01[d]	0.05	47.4
Urinary tract infection	2	1.32[a]	0.72	2.42	0.38[d]	0.15	52.8
Hypertension	2	1.01[a]	0.92	1.11	0.83[c]	0.93	0.0
RA	5	1.60[a]	0.73	3.53	0.24[d]	0.03	62.7

OR, odds ratios; SMD, standardized mean differences; LL, lower limit; UL, upper limit; ASA, American society of anesthesiologists; BMI: body mass index; RA, rheumatoid arthritis. [a]OR; [b]SMD; [c]Fixed-effects model was performed; [d]Random-effects model was performed.

time (SMD, 0.44; 95% CI, 0.26 to 0.63), transfusion (OR, 1.54; 95% CI, 1.18 to 2.02), and diabetes mellitus (OR, 1.51; 95% CI, 1.17 to 1.95). The outcomes are listed in **Table 2**, and analysis for gender, age, ASA score > 2 and transfusion, as significant risk factors, are presented by forest plots in **Figure 3**. Steroid use, bilateral surgery, drain usage, bone graft, urinary tract infection, hypertension, and RA were not identified as significant risk factors for infection following TKA ($P > 0.05$).

Publication bias

Funnel plot and Begg test showed that no significant publication bias was found among the studies regarding the risk of male gender (P = 0.21, **Figure 4A**) or diabetes mellitus (P = 0.86, **Figure 4B**).

Discussion

As we know, the development of infection is complicated. According to the most accepted view, postoperative infection is considered to be a multifactorial complication [26-28]. Among the included studies, the infection rate ranged from 0.72% to 6.7%, and the accumulated incidence of postoperative infection is 0.90%. After meta-analysis of risk factors, statistically significant associations were identified for male gender, age, obesity, smoking, higher ASA score, operative time, transfusion, and diabetes mellitus. Other factors, such as steroid use, bilateral surgery, drain usage, bone graft, urinary tract infection, hypertension and RA, were not identified as significant risk factors for infection following TKA.

Five patient-related factors were shown to be associated with SSI in our meta-analysis. Significant associations of younger age and male gender with SSI were demonstrated, and this result was consistent with a previous study conducted by Malinzak *et al* [29]. Younger and male patients are generally more active than older and female patients and thus may potentially cycle their implant in greater numbers leading to wear and potential revision surgery. ASA score represents the severity of preexisting illness, and it is reasonable to consider that patients with higher ASA score had a higher incidence of infection. Smoking was an important factor associated with infection [5]. It may

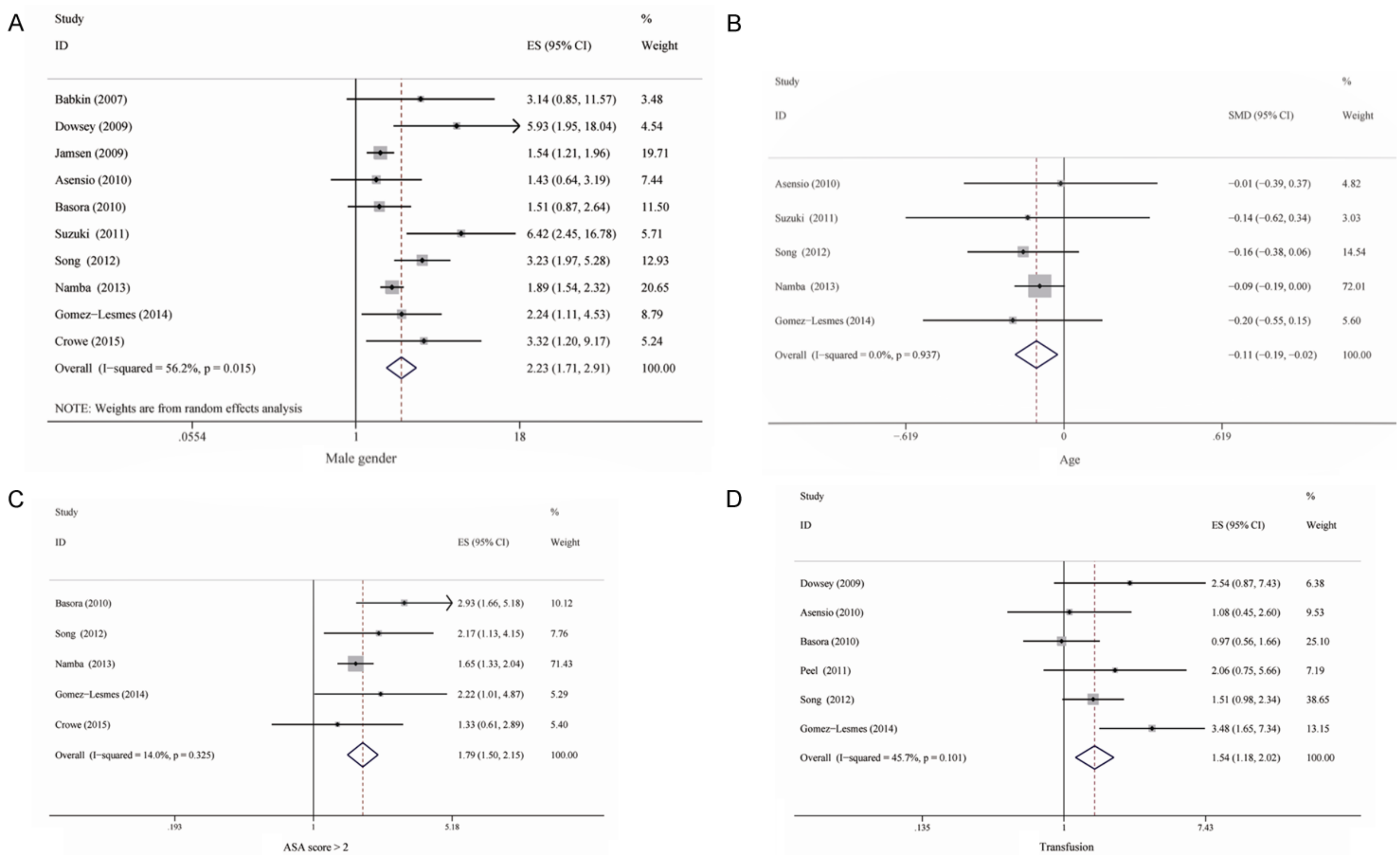

Figure 3. Forest plots of the meta-analysis of (A) male gender, (B) age, (C) ASA score > 2, and (D) transfusion as significant factors for postoperative infection after TKA. OR, odds ratio; CI, confidence interval.

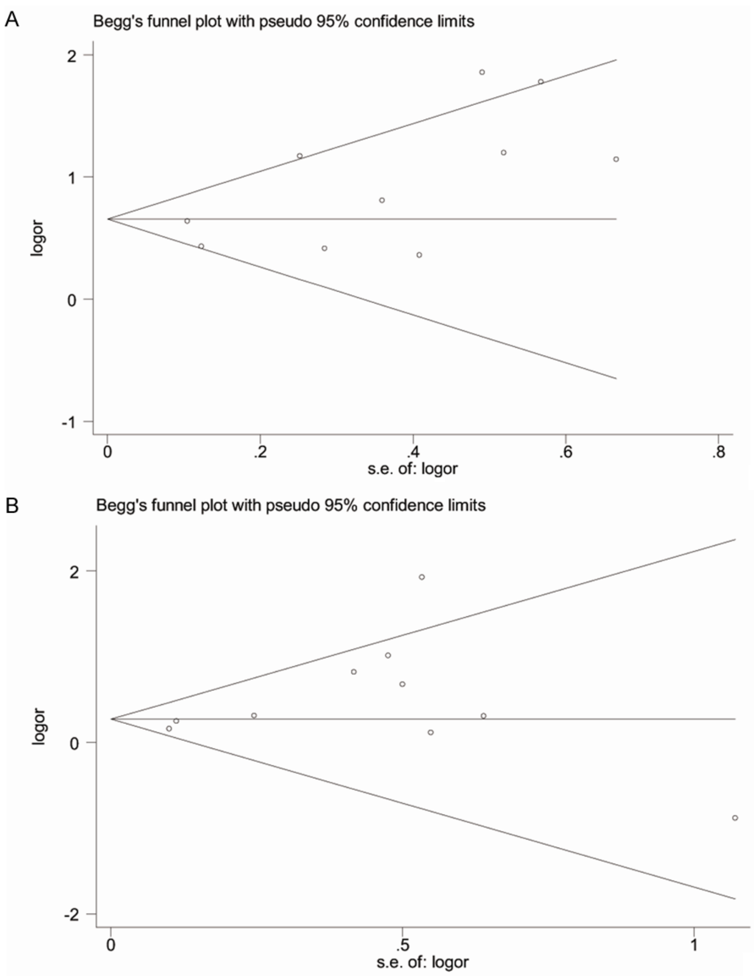

Figure 4. Begg's funnel plot for publication bias (with 95% pseudoconfidence limits) of the studies that investigated (A) male gender (Pr > |z| = 0.21) and (B) diabetes mellitus (Pr > |z| = 0.86) as potential risk factors for infection.

influence wound healing by causing microvascular contraction and leading to tissue ischaemia. Patients to be operated on may benefit from preoperative smoking cessation and nicotine replacement therapy. We used a BMI value of 30 kg/m^2 as the threshold for obesity. The results showed that obesity was associated with a higher risk of SSI. Obese patients tended to have thick adipose layers that could be easily damaged during the surgical procedure. Besides, a larger layer of subcutaneous tissue can lead to potential dead space after closure, and increase the risk of infection. Based on these results, we assumed that patients with these risk factors should be informed of the infection risk preoperatively.

Among the surgical-related factors, operative time and transfusion were demonstrated to be associated with infection. In accordance with our findings, the study conducted by Namba et al. observed an increased risk of infection per every additional fifteen minutes of operative time [23]. In the study conducted by Kurtz et al., the authors found that a TKA operative time of longer than 210 minutes, compared with less than 120 minutes, was significantly associated with an increased risk of infection [30]. There is a chance that patients with increased operative time underwent a complex surgical procedure, which added the risk of infection. Blood transfusion is another well-known risk factor for SSI [31, 32], as our findings suggest. Transfusion is likely a proxy for the larger blood loss, which could result in the immune suppression in the recipient and infection of the incision. These procedure-related factors mentioned above could be controlled by surgeons, and they can decrease the possibility of infection to some extent by improving the surgical proficiency.

Comorbid diabetes mellitus also act as a risk factor for infection in patients undergoing TKA. Diabetic patients are known to be susceptible to SSI due to their immuno-compromised state, poor micro-vascularization, and reduced wound healing potential. Besides, diabetes mellitus could impair wound healing because microangiopathic changes usually lead to local tissue ischaemia and reduce the tissue concentrations of antibiotics [33]. Thus, we think diabetes management may reduce patients' infection risk. Though urinary tract infection, hypertension, or RA is not deemed to be risk factors in this study, there are numerous other comorbid conditions that may be associated with SSI following TKA [34].

This meta-analysis had some limitations that should be noticed. First, the original diseases, types of SSI, and duration of follow-up were varied amongst these studies, which might result in considerable heterogeneity and affect our final results. Second, though both superficial infection and deep infection were investigated by these citations, we did not clearly distinguish them and make further subgroup analyses because of the relatively small numbers of studies in both subgroups. Third, because of the limited numbers of studies, it was impossible for us to estimate the effects of every possible risk factor. Further studies should also pay attention to other factors. Finally, most of the included studies were observational and retrospective, and this can result in considerable bias and had potential impacts on the final results. Consequently, these quantitative results should be interpreted with caution.

In spite of the limitations mentioned above, this study is clinically valuable to some extent. In summary, the present analysis demonstrates that male gender, age, obesity, smoking, higher ASA score, operative time, transfusion, and diabetes mellitus are significant risk factors for postoperative infection after TKA surgery. Awareness of these risk factors will help surgeons optimize the patient's preoperative condition and surgical procedure, and help decrease the incidence of postoperative infection.

Disclosure of conflict of interest

None.

Address correspondence to: Yong Shen, Department of Orthopaedic Surgery, The Third Hospital of Hebei Medical University, 139 Ziqiang Road, Shijiazhuang 050051, P. R. China. Tel: 86-311-88602316; Fax: 86-311-88602016; E-mail: shenyongspine@126.com

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