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Review

Risk factors for periprosthetic joint infection after total joint arthroplasty: a systematic review and meta-analysis

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SUMMARY

Many of the mooted risk factors associated with periprosthetic joint infection (PJI) after total joint arthroplasty (TJA) remain controversial and are not well characterized. Online and manual searches were performed using Medline, Embase, Chinese National Knowledge Infrastructure and the Cochrane Central Database from January 1980 to March 2014). For inclusion, studies had to meet the quality assessment criteria of the CONSORT statement, and be concerned with evaluation of risk factors for PJI after TJA. Two reviewers extracted the relevant data independently and any disagreements were resolved by consensus. Fourteen studies were included in this meta-analysis. The following significant risk factors for PJI were identified: body mass index (both continuous and dichotomous variables); diabetes mellitus; corticosteroid therapy; hypoalbuminaemia; history of rheumatoid arthritis; blood transfusion; presence of a wound drain; wound dehiscence; superficial surgical site infection; coagulopathy; malignancy, immunodepression; National Nosocomial Infections Surveillance Score $\geq$2; other nosocomial infection; prolonged operative time; and previous surgery. Factors that were not significantly associated with PJI were: cirrhosis; hypothyroidism; urinary tract infection; illicit drug abuse; alcohol abuse; hypercholesterolaemia; hypertension, ischaemic heart disease; peptic ulcer disease; hemiplegia or paraplegia; dementia; and operation performed by a staff surgeon (vs a trainee). Strategies to prevent PJI after TJA should focus, in particular, on those patients at greatest risk of infection according to their individual risk factors.

Introduction

Although total joint arthroplasty (TJA) is one of the most common procedures used to treat severe joint disease and for the surgical management of traumatic fracture, it is compromised by periprostheic joint infection (PJI) which may result in severely limited joint function and increased mortality.[1–3] Management of PJI often requires multiple surgical procedures, which may further increase morbidity and even

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mortality, especially in elderly patients.[1,4,5] Bozic *et al.* reported that 14.7% of revision hip arthroplasties and 25.2% of failed total knee arthroplasties were due to PJI.[6,7] Given the growing number of TJAs being performed, the burden of PJI will also increase; therefore, it is vital to identify which factors place patients at greater risk of PJI in order to identify those individuals who could gain the greatest benefit from strategies designed to reduce the risk of PJI.

Numerous putative risk factors for PJI have been proposed, such as obesity,[2,8–10] diabetes mellitus,[8–12] corticosteroid therapy,[11,12] rheumatoid arthritis,[8,9,11] blood transfusion,[2,11] presence of wound drains[11–14] and coagulopathy.[8,9,11] However, the precise significance of these risk factors is difficult to determine as individual studies are often limited by issues such as small sample size and inclusion of a single criterion or very few risk criteria. As a result, conclusions that can be drawn from individual studies can be limited. Furthermore, results obtained from different studies examining the same risk factor may yield apparently conflicting results.[11–16]

Given the difficulties associated with characterizing the risk factors for PJI, a meta-analysis was performed using data from primary studies to identify which factors are most strongly associated with PJI in order to develop effective management strategies for prevention.

Methods

Literature search

Medline, Embase, Chinese National Knowledge Infrastructure and the Cochrane Central Database were searched from January 1980 to March 2014 to identify relevant studies for further analysis. The main key words were: 'factor' or 'predictor' or 'risk' AND 'infection' AND 'joint' or 'total joint' or 'periprosthetic'. A manual search of the reference lists of the selected publications was also performed to identify additional studies for potential inclusion.

Two reviewers (F. Zhang and W. Chen) independently evaluated the titles and abstracts of papers identified in the search. Full-text articles alone were included, with no language restriction. Inclusion criteria were: (1) observational, cohort or randomized controlled trials; (2) cases and controls defined according to the presence or absence of infections after TJA, respectively; and (3) sufficient data presented to allow estimates of odds ratios (ORs) or hazard ratios with 95% confidence intervals (CIs).

Quality of studies included

Study quality was evaluated independently by two reviewers (F. Zhang and W. Chen) using a standardized set of 17 predefined criteria derived from the CONSORT statement[17] and used in previous reviews.[18,19] One point was scored when each criterion was met; otherwise, no score was awarded. Total scores from each study were calculated, and conflicting scores were resolved by consensus.

Data extraction and definitions of risk factors

The following data were abstracted independently from each study by two reviewers (F. Zhang and Chen): publication year; country of origin; risk factors examined; case definitions; numbers of cases and controls; and total TJA examined. Any disagreement was settled by discussion, and consensus was reached for all data. Definitions of all risk factors studied in this meta-analysis were the same as those used in the primary studies.

Body mass index (BMI) was defined as the patient's body weight/height squared Diabetes mellitus was defined according to the criteria of the National Diabetes and Data Group or the Australia Diabetes Society, and rheumatoid arthritis was defined according to the criteria of the American Rheumatism Society. Steroid therapy was defined as any form of systemic corticosteroid therapy for more than one week in the year preceding TJA, and malignancy was defined as any malignancy diagnosed within the five years preceding TJA. Blood transfusion was defined as any autologous or homologous blood transfusion within 24 h of prosthesis implantation. Renal disease was defined as creatinine clearance $\leq$30 ml/min using the Cockcroft–Gault equation. Superficial incisional surgical site infection was defined as infection involving the skin or subcutaneous tissue surrounding the incision site within 30 days of TJA.

Statistical analyses

When possible, adjusted ORs (from multi-variate analysis models) and 95% CIs were extracted from the original studies for each risk factor. When adjusted ORs were not provided in the original studies, crude ORs were computed based on the given frequency. Abstracted ORs were pooled across studies to assess associations between different variables and the risk of PJI. $P < 0.05$ was considered to indicate significance. Heterogeneity between the studies was tested qualitatively using the Q-test, with significance set at $P < 0.10$.[20] I^2 was used as a quantitative measure of heterogeneity, with $I^2 > 50\%$ indicating significant inconsistency. A random effects model was used to calculate pooled ORs in the case of significant heterogeneity ($P < 0.10$ or $I^2 > 50\%$); otherwise, a fixed-effects model was used.[21] A meta-analysis of significant risk factors was summarized graphically using a Forest plot. Publication bias was assessed using Begg's test and presented as a funnel plot, with $P < 0.10$ considered to indicate significance. To explore sources of heterogeneity, sensitivity analysis was performed for certain risk factors with: lower methodological quality of an included study and larger CIs. All analyses were performed using Stata Version 11.0 (Stata Corp., College Station, TX, USA).

To better illustrate the associations between the identified risk factors and PJI, OR$\geq$2 was considered to be highly significant and 1<OR<2 was considered to be moderately significant, in accordance with previous studies.[19,22]

Results

In total, 236 full-text studies were retrieved; of these, 14 studies were eligible for inclusion in the meta-analysis (Figure 1). Eleven studies were published in English and three studies were published in Chinese. One study was published in 1998, and the remaining 13 studies were published between 2007 and 2014. Six studies were designed as matched case–control investigations, and two studies did not provide detailed data on the numbers of cases and controls. Therefore, six

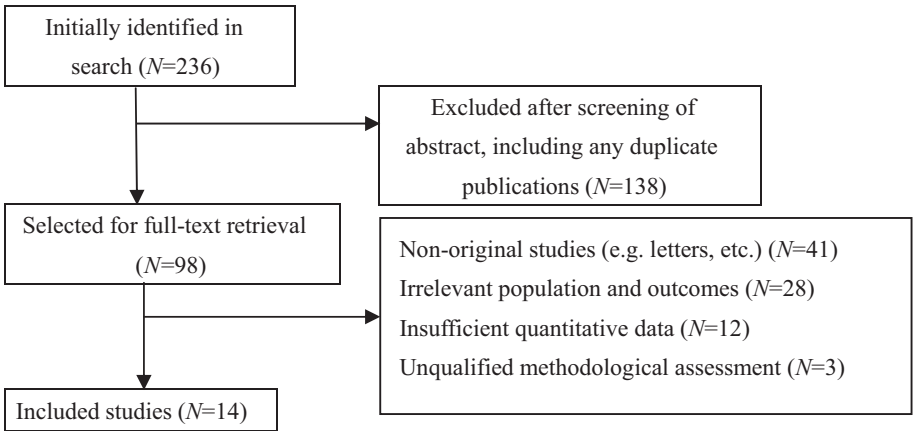


Figure 1. Flow diagram of literature search.

Table I
Characteristics of the 14 eligible studies

Author	Publication	Country	Controls	Cases	Total	Age (years)	Significant factors
Berbari *et al.*[11]	1998	USA	462	462	924	NA	NNIS score of 1 or 2, malignancy, history of arthroplasty
Jover-Saénz *et al.*[25]	2007	Spain	80	40	120	NA	High NNIS score, postoperative non-infectious complications
Pulido *et al.*[2]	2008	USA	9182	63	9245	64.3 (mean)	Higher ASA score, obesity, TKA, bilateral arthroplasty, allogenic transfusion, postoperative atrial fibrillation, myocardial infarction, urinary tract infection, longer hospitalization
Aslam *et al.*[26]	2010	USA	63	63	126	60.8 (mean)	Bacteraemia during the previous year, non-surgical trauma to the prosthetic joint, SSI
Peel *et al.*[15]	2011	Australia	126	63	189	69.0 (mean)	Systemic steroid use, increased SSI drain tube losses, wound discharge, superficial incisional SSIs
Suzuki *et al.*[23]	2011	Japan	2005	17	2022	70.6 (mean)	History of ORIF, male gender, remnants of previous internal fixation material, BMI
Jämsen *et al.*[10]	2012	USA	8723	52	8775	NA	Diabetes and morbid obesity
Kessler *et al.*[13]	2012	Switzerland	104	26	130	NA	History of surgery on the ankle, low pre-operative AOFAS hindfoot score, prolonged operative time, prolonged wound dehiscence or secondary wound healing
Renaud *et al.*[24]	2012	Canada	3517	106	3623	NA	Poor operative methods
Bozic *et al.*[9]	2012	USA	NA	NA	83,011	≥65	CHF, CPD, RA, anaemia, diabetes, depression, renal disease, pulmonary circulation disorders, obesity, psychoses, metastatic tumour, peripheral vascular disease, valvular disease
Bozic *et al.*[8]	2012	USA	NA	NA	40,919	≥65	Rheumatological disease, obesity, coagulopathy, pre-operative anaemia
Zhang and Zhu[12]	2013	China	82	4	86	58.4 (mean)	Age, operative time, postoperative drainage, use of steroids, diabetes mellitus, history of surgery, serum albumin
Shi *et al.*[14]	2013	China	294	24	318	≥60	Duration of surgery, bilateral hip arthroplasty, smoke abuse, prolonged postoperative drainage
Huang and Yuan[16]	2014	China	27	54	81	69	Drainage tube placement, purulent exudation, BMI, drainage amount, superficial infection

NA, not available; NNIS, National Nosocomial Infection Surveillance; ASA, American Society of Anesthesiologists; TKA, total knee arthroplasty; SSI, surgical site infection; ORIF, open reduction and internal fixation; BMI, body mass index; AOFAS, American Orthopaedic Foot and Ankle Society; CHF, chronic heart failure; CPD, chronic pulmonary disease; RA, rheumatoid arthritis.

studies that included 24,069 TJAs and 266 cases of PJI (overall incidence 1.1%) were available for further analysis. Detailed information about these six studies is provided in Table I.

The mean (± standard deviation) quality score was 14.67 ± 1.54 (range 12–17). Three studies scored 12,[9,15] two studies scored 13,[12,14] one study scored 14,[23] five studies scored 15,[8,16,24–26] three studies scored 16,[2,11,13] and one study scored 17.[10] Detailed information on the quality assessment is presented in Table A (see online supplementary material).

The main results of the meta-analysis conducted to analyse risk factors are summarized in Table II. Combined ORs ranged from 0.98 to 9.13. Significant heterogeneity was observed between studies in terms of BMI (continuous variables), renal disease, rheumatoid arthritis and presence of a wound drain. On the basis of the combined ORs and corresponding 95% CIs, the following risk factors were found to be significantly associated with PJI after TJA: BMI (both continuous and dichotomous variables); diabetes mellitus; corticosteroid therapy; serum albumin < 34 g/l; rheumatoid arthritis; blood transfusion; presence of a wound drain; wound dehiscence; surgical site infection; coagulopathy; malignancy; immunodepression; National Nosocomial Infection Surveillance (NNIS) score ≥2, superficial wound infection; other nosocomial infection; prolonged operative time; and previous surgery. The outcomes of some variables as significant risk factors have been presented using Forest plots (Figure 2). The following variables were not found to be significantly associated with risk of PJI after TJA ($P > 0.05$): cirrhosis; hypothyroidism; urinary tract infection; illicit drug abuse; alcohol abuse; hypercholesterolaemia; hypertension; ischaemic heart disease; peptic ulcer disease; hemiplegia or paraplegia; dementia; and operation performed by a staff surgeon (vs a trainee).

A sensitivity analysis was performed for risk factors with significant heterogeneity [BMI (continuous variables), renal disease, rheumatoid arthritis and presence of a wound drain] by excluding outlier studies of low quality or with larger CIs for some ORs. This indicated I^2 <50%, but meta-analysis results for these factors including BMI and wound drainage did not change the significance, indicating that the results were robust. However, when the study by Peel *et al.*[15] was excluded, I^2 for

Table II
Detailed data on 31 potential risk factors for periprosthetic joint infection and the outcomes of meta-analysis

Potential risk	No of studies	Pooled OR or SMD	LL 95% CI	UL 95% CI	*P*-value	Q-test (*P*)	I^2 (%)[c]
BMI (continuous)	3	1.08	1.02	1.15	0.009[b]	0.087	59.1
BMI (>40 kg/m^2)	2	3.74	2.01	6.96	<0.001[a]	0.376	0
Diabetes mellitus	8	1.26	1.15	1.38	<0.001[a]	0.376	7.0
Cirrhosis	3	1.07	0.87	1.32	0.524[a]	0.792	0
Steroid therapy	5	2.19	1.52	3.15	<0.001[a]	0.413	0
Hypothyroidism	2	0.98	0.89	1.08	0.732[a]	0.925	0
Urinary tract infection	3	1.08	0.99	1.19	0.886[a]	0.339	7.6
Renal disease	4	1.02	0.93	1.08	0.378[b]	0.028	67.1
Albumin level < 34 g/l	2	2.94	1.57	5.53	<0.001[a]	0.462	0
Hypercholesterolaemia	2	0.93	0.85	1.01	0.097	0.659	0
Rheumatoid arthritis	7	1.41	1.26	1.57	<0.001[b]	0.019	60.4
Blood transfusion	5	1.60	1.22	2.10	<0.001[a]	0.682	0
Wound drainage	6	2.00	1.15	3.48	0.015[b]	0.007	68.9
Wound dehiscence	3	8.08	3.96	16.46	<0.001[a]	0.345	6.0
Surgical site infection	3	9.13	4.14	20.11	<0.001[a]	0.179	41.8
Drug abuse	2	1.07	0.56	2.05	0.836[a]	0.822	0
Alcohol abuse	2	1.39	0.93	2.07	0.109[a]	0.283	13.2
Coagulopathy	3	1.31	1.13	1.52	<0.001[a]	0.146	48.1
Hypertension	2	1.05	0.97	1.14	0.241[a]	0.173	46.1
IHD	2	1.07	0.98	1.17	0.115[a]	0.230	30.1
Peptic ulcer disease	2	1.19	0.89	1.59	0.252	0.714	0
Hemiplegia or paraplegia	2	1.10	0.69	1.74	0.693	0.200	39.2
Malignancy	5	1.17	1.02	1.22	0.017[a]	0.103	48.1
Immunodepression	2	1.32	1.15	1.50	<0.001[a]	0.593	0
Dementia	2	1.03	0.75	1.41	0.878[a]	0.976	0
Nosocomial infection	2	2.48	1.07	5.73	0.034[a]	0.643	0
NNIS score≥2	2	4.93	2.88	8.43	<0.001[a]	0.716	0
Superficial infection	2	4.52	1.53	13.35	0.006[a]	0.708	0
Operation performed by trainee (vs staff surgeon)	2	1.24	0.50	3.10	0.641	0.138	54.5
Operative time	2	2.18	1.39	3.42	0.001[a]	0.710	0
Previous surgery	2	3.15	1.49	6.63	0.003[a]	0.324	0

BMI, body mass index; SMD, standardized mean difference; OR, odds ratio; LL, lower limit; UL, upper limit; IHD, ischaemic heart disease.
[a] Fixed-effects model was performed.
[b] Random-effects model was performed.
[c] I^2 was defined as the proportion of heterogeneity that was not due to chance or random error.

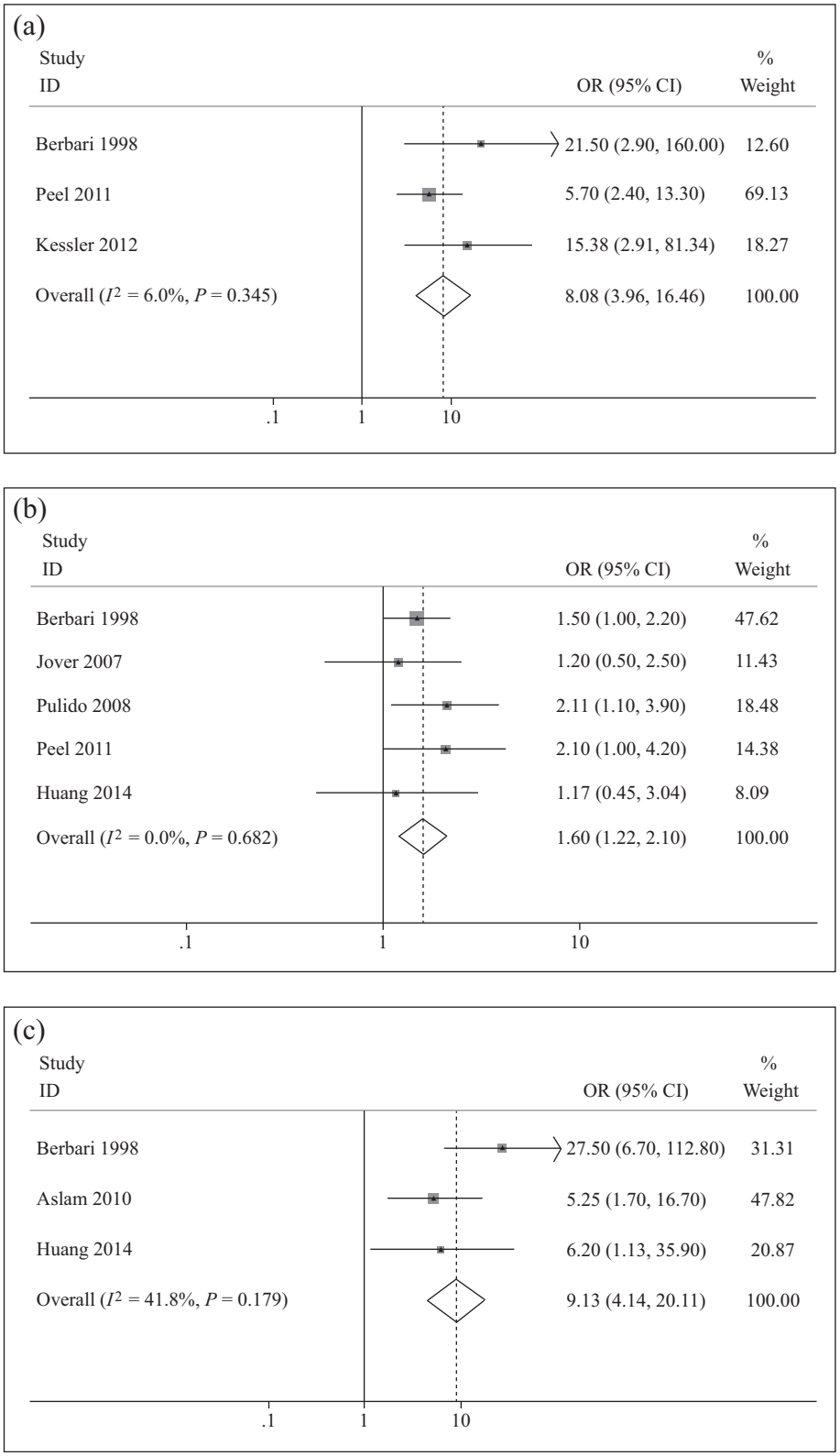
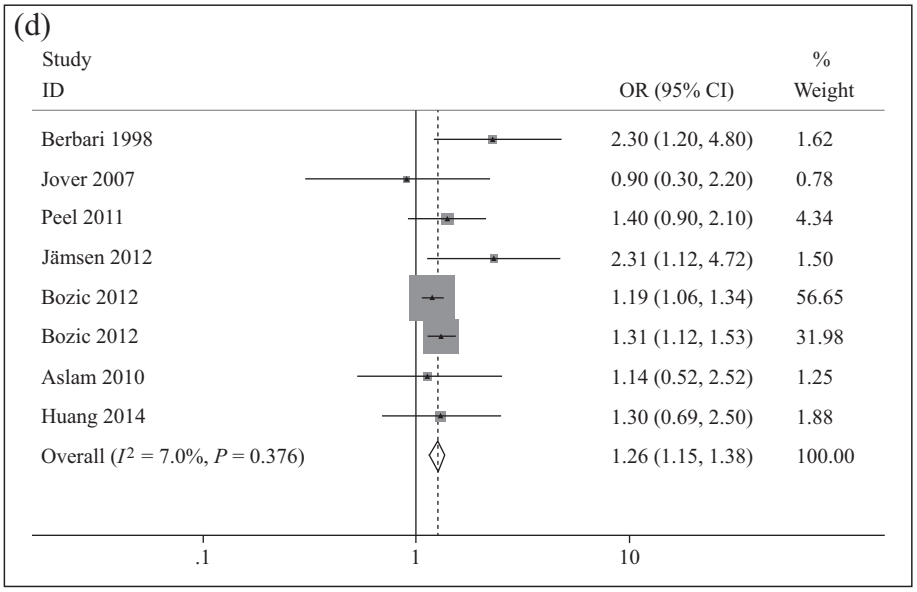
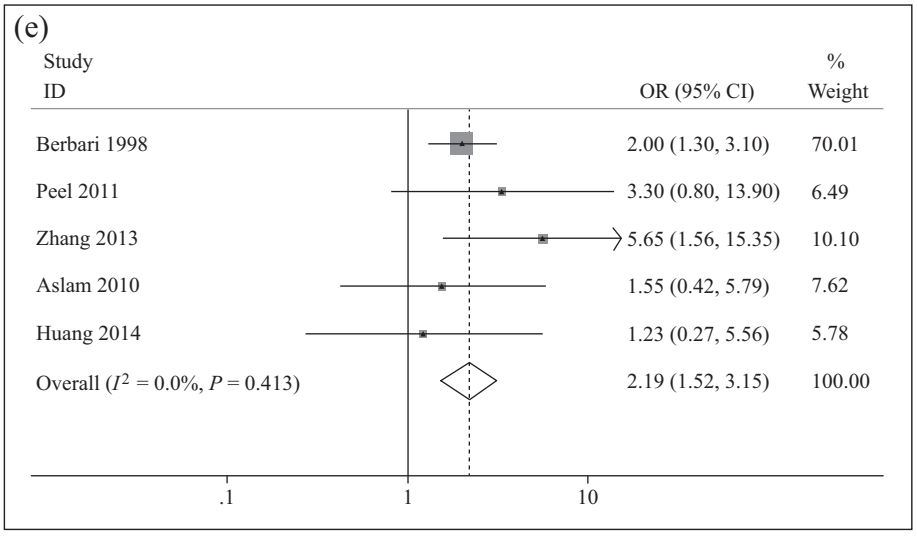
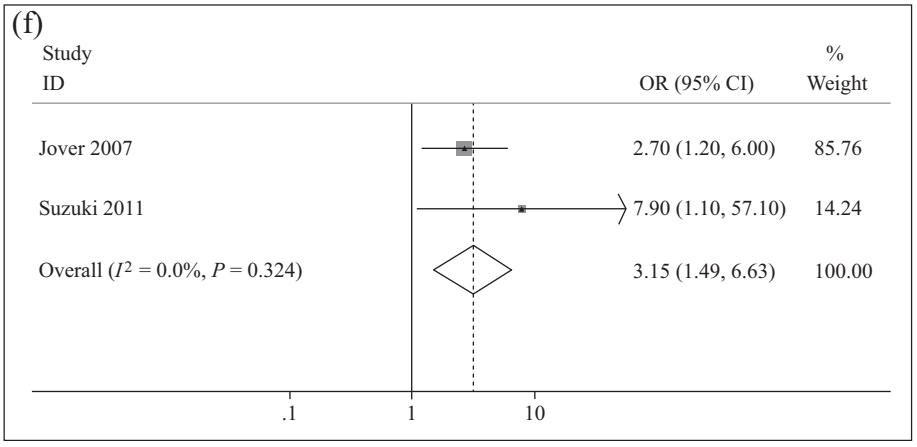


Figure 2. Forest plots of the meta-analysis of wound dehiscence (a), blood transfusion (b), surgical site infection (c), diabetes mellitus (d), steroid therapy (e), previous surgery (f) and prolonged operative time (g) as risk factors for periprosthetic joint infection after joint arthroplasty. The width of the horizontal line represents the 95% confidence interval (CI) of the individual studies, and the square represents the proportional weight of each study. Diamonds represent the pooled odds ratios (ORs) and 95% CI.







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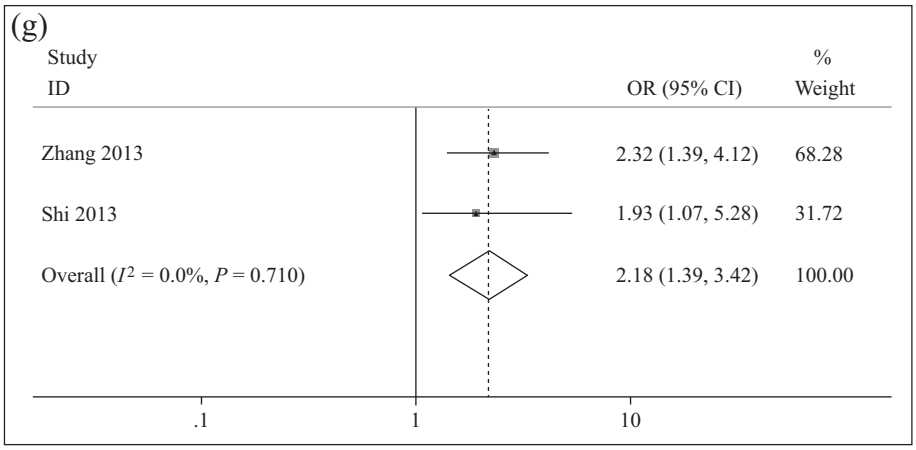

Figure 2. (*continued*).

renal disease decreased to 0 (P for heterogeneity was 0.734) and the result approached significance ($P = 0.002$). Therefore, renal disease is more likely to be a significant risk factor for TJA, although with a relatively low magnitude of association. Detailed information on the sensitivity analysis is given in Table B (see online supplementary material).

Discussion

In this systematic review and meta-analysis, the accumulated incidence of PJI after TJA was 1.1% and multiple risk factors for this complication were identified. Increased BMI, corticosteroid therapy, serum albumin level < 34 g/l, presence of a wound drain, wound dehiscence, superficial surgical site infection, other nosocomial infection, NNIS score ≥2, prolonged operative time and previous surgery were identified as strong risk factors for PJI. Diabetes mellitus, rheumatoid arthritis, blood transfusion, coagulopathy, malignancy and immunodepression were identified as moderate risk factors for PJI. None of the variables were found to have a protective effect against PJI. After sensitivity analysis, renal disease was also identified as a moderate risk factor for PJI.

Although renal disease was considered to be a risk factor in a number of studies, its potential role as a risk factor for PJI remains inconclusive. Although most investigators did not consider renal disease to be a risk factor for PJI,[8,11,15] one study did find that renal disease was a risk factor.[9] The latter study also identified numerous other comorbid conditions as risk factors.

Given the implications of PJI after TJA for patients, especially older patients and those with multiple co-morbidities, the importance of strategies to reduce the risk of PJI is self-evident. Increased appreciation of significant risk factors will allow better identification of those patients most likely to develop PJI. To refine this process, each criterion was classified as either high or moderate risk, although the limitations of this classification should be acknowledged until there is better understanding of relationships between individual risk factors. In the future, it may be possible to develop a more sophisticated PJI risk assessment tool that could provide estimates of the probability of an individual developing PJI after TJA. It is notable that although most of the risk factors cannot be changed, some risk factors, such as obesity, could be ameliorated.

A higher American Society of Anesthesiologists' (ASA) score has been considered to be a risk factor for PJI after TJA, but the methods used to measure these scores differ between studies.[2,15] Pulido *et al.* reported ASA scores in terms of frequency (ASA>2), whereas Peel *et al.* reported ASA scores as mean and standard deviation.[15] Likewise, valvular heart disease, psychosis, cerebrovascular disease and pre-operative anaemia as potential risk factors were not analysed by pooling the original result, due to the non-uniform data forms provided in individual studies. Further studies are required to explore the significance, if any, of these putative risk factors.

This meta-analysis has various limitations. Firstly, some of the ORs used in the meta-analysis were not adjusted, because many reports only provided univariate rather than multivariate statistics; likewise, some studies may have chosen not to report insignificant results or results of no interest, potentially resulting in a considerable amount of missing data. Secondly, most of the included studies were observational and retrospective with inevitable recall and interviewer biases; this may have affected the associations between risk and PJI. Thirdly, the measurements of various risk factors differed, and follow-up periods ranged widely from several months to more than 10 years. Therefore, significant heterogeneity was unavoidable in this review. Recently, US national- and state-level databases (880,786 TJAs) were used to analyse the association between liver cirrhosis and risk of PJI within 6 months of TJA; the results were inconsistent with the present study.[27] The shorter observation period may have been responsible for this difference, but this topic clearly requires further study. Fourthly, in the clinic setting, a number of the identified risk factors may apply to a single patient and may be inter-related and interdependent. For example, patients with diabetes may be more likely to present with higher BMI, patients with rheumatoid arthritis may be more likely to be receiving corticosteroids, and the need for a blood transfusion might reflect the complexity of the surgery which may be linked to prolonged operative time. However, from the data in the studies included in this meta-analysis, it is not possible to draw firm conclusions on the inter-relatedness of risk factors for PJI, as the ORs were not independent in the original studies. This is an important topic that deserves investigation in future prospective studies.

Despite these limitations, this study has some strengths. Firstly, a comprehensive search strategy based on computer-assisted and manual searching ensured, as far as is possible, that no relevant studies were omitted. Secondly, to the authors' knowledge, this is the first study to quantitatively summarize risk factors for the development of PJI after TJA.

Conclusion

This meta-analysis identified BMI $>40\ kg/m^2$, corticosteroid therapy, albumin level $<34\ g/l$, wound drainage, wound dehiscence, superficial surgical site infection, NNIS score ≥ 2, other nosocomial infection, prolonged operative time, previous surgery, diabetes mellitus, rheumatoid arthritis, blood transfusion, coagulopathy, malignancy and immunodepression as risk factors for PJI after TJA. Identification of these risk factors could contribute to screening patients at risk, thereby targeting them with relevant preventative measures.

Conflict of interest statement
None declared.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jhin.2014.10.008.

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