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Risk factors for postoperative surgical site infections after anterior cruciate ligament reconstruction: a systematic review and meta-analysis

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ABSTRACT

Objectives The primary aim was to evaluate risk factors for surgical site infections after anterior cruciate ligament reconstruction (ACLR). The secondary aim was to investigate the surgical site infection incidence rate and the mean time to postoperative surgical site infection symptoms.

Design Systematic review and meta-analysis.

Data sources PubMed, Embase and Web of Science were searched from database inception to September 2021 and updated in April 2022.

Eligibility criteria Quantitative, original studies reporting potential risk factors for surgical site infections after ACLR were included.

Results Twenty-three studies with 3871 infection events from 469 441 ACLRs met the inclusion criteria. Male sex (OR 1.78, p< 0.00001), obesity (OR 1.82, p=0.0005), tobacco use (OR 1.37, p=0.01), diabetes mellitus (OR 3.40, p=0.002), steroid use history (OR 4.80, p<0.00001), previous knee surgery history (OR 3.63, p=0.02), professional athlete (OR 4.56, p=0.02), revision surgery (OR 2.05, p=0.04), hamstring autografts (OR 2.83, p<0.00001), concomitant lateral extra-articular tenodesis (OR 3.92, p=0.0001) and a long operating time (weighted mean difference 8.12, p=0.005) were identified as factors that increased the risk of surgical site infections (superficial and deep) after ACLR. Age, outpatient or inpatient surgery, bone-patellar tendon-bone autografts or allografts and a concomitant meniscus suture did not increase the risk of surgical site infections. The incidence of surgical site infections after ACLR was approximately 1% (95% CI 0.7% to 1.2%). The mean time from surgery to the onset of surgical site infection symptoms was approximately 17.1 days (95% CI 13.2 to 21.0 days).

Conclusion Male sex, obesity, tobacco use, diabetes mellitus, steroid use history, previous knee surgery history, professional athletes, revision surgery, hamstring autografts, concomitant lateral extra-articular tenodesis and a long operation time may increase the risk of surgical site infections after ACLR. Although the risk of surgical site infections after ACLR is low, raising awareness and implementing effective preventions for risk factors are priorities for clinicians to reduce the incidence of surgical site infections due to its seriousness.

INTRODUCTION

Arthroscopic anterior cruciate ligament reconstruction (ACLR) is a safe, effective and common method for ACL injury repair that can restore knee joint function and stability.[1 2] Based on data from commercial insurance providers, the incidence of ACLR is estimated to be 74.6 per 100 000 people[3]; the corresponding number from the Swedish registry estimated 40 ACLRs per 100 000 people.[4] One of the most devastating complications to manage after ACLR is surgical site infections (including skin, subcutaneous tissue, deep soft tissue/soft tissue grafts and intra-articular infections). Surgical site infections may not only result in high readmission rates and poor knee functional recovery but may also have a significant negative impact on the patient's psychology and economic health, especially for athletes, as it might affect their sports careers.[5–8] Therefore, the early identification of risk factors associated with surgical site infections following ACLR and early implementation of preventive measures are critical.

There is some evidence for specific risk factors for surgical site infections following ACLR, including male sex,[9] tobacco use,[10] diabetes,[11] inpatient ACLR,[12] and professional athletes[13]; however, other studies have reported conflicting results.[14–16] Given these controversial results and the small sample size of several studies, a meta-analysis is necessary to comprehensively evaluate the current findings. To our knowledge, the potential risk factors for surgical site infections after ACLR have never been systematically integrated. Identifying the factors that predispose individuals to surgical site infections after ACLR is critical to screening for surgical site infection risk as well as optimising ACLR procedures to minimise the risk of surgical site infections and associated serious consequences for these individuals. Therefore, the main purpose of this study was to explore risk factors for surgical site infections after ACLR. The secondary aim was to investigate the incidence rate of surgical site infections after ACLR and the mean time from surgery to the onset of surgical site infection symptoms (eg, pain, redness with increased local skin temperature, swelling and/or fever) based on studies investigating potential risk factors to provide more information for clinical practitioners.

METHODS

This systematic review was designed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses

recommendations and was preregistered with PROSPERO (CRD42021286963).

Search strategy and selection criteria

PubMed, Embase and Web of Science were comprehensively searched for English studies using the following keywords: "anterior cruciate ligament reconstruction", "risk factors" and "infections" from the inception of the database to September 2021 and updated in April 2022. The search strategy for PubMed is presented in online supplemental A1. The references of the included studies were also searched for additional relevant articles that were not captured by the initial search, and each article was manually cross-checked. Disagreements among the reviewers were resolved by discussion until a consensus was reached.

Eligibility criteria

Inclusion criteria: (1) All quantitative original studies involving male or female participants who developed subsequent surgical site infections (superficial/deep infections) and who did not develop surgical site infections following arthroscopic primary or revision ACLR. According to the Centers for Disease Control and Prevention and National Healthcare Safety Network guidelines,[17] superficial surgical site infections are attributed to the procedure within 30 days postoperatively and involve the skin and subcutaneous tissue with at least one of the following: purulent drainage from the superficial incision; organism cultured from the superficial incision; at least 1 of the following signs or symptoms of surgical site infections: localised pain or tenderness, redness, swelling or heat and opening of the superficial incision by the surgeon, with positive culture or not cultured; superficial surgical site infections are diagnosed by a surgeon or attending physician. Deep surgical site infections are defined as infections occurring within 1 year after the procedure that involve deep soft tissues (including soft tissue grafts), are intra-articular and include at least one of the following: purulent drainage from the deep incision; dehiscence of the incision or opening by the surgeon and culture positive or not cultured when the patient has a fever (>38°C) or localised redness, heat, pain or tenderness; an abscess or other evidence of surgical site infection during examination, reoperation, or histopathological or radiologic examination; deep surgical site infections are diagnosed by a surgeon or attending physician. (2) Prospective or retrospective study design. (3) Participants were not reported for undergoing intraoperative graft preparation with vancomycin as the primary antibiotic. (4) At least one risk factor associated with surgical site infections was investigated. (5) More than five infection events were recorded during the study period. (6) The study period or enrolment period of studies was mainly from 2000 until present.

Exclusion criteria: (1) studies with a total sample size less than 400; (2) case studies, review articles, conference proceedings and abstracts; and (3) studies for which data could not be extracted.

Study selection and data extraction

According to the eligibility criteria, the studies' titles, abstracts and full texts were screened by two independent reviewers to determine the final articles to be included in the study. If studies originating from the same database had more overlapping time periods than nonoverlapping time periods, the results from the study with the larger sample size were considered; otherwise, all of the studies were included. After each stage of the screening process, disagreements about inclusion were discussed, and if a consensus could not be reached, a third reviewer was consulted. The data were extracted by the other two independent researchers. The following data items were extracted from the studies: authors, publication date, source of study population, study period, sample size, sex distribution, incidence rate of postoperative surgical site infections, types of surgical site infections (superficial or deep surgical site infections) studied and the potential risk factors assessed. Disagreements were resolved through discussion, and if necessary, a third investigator made the final decision. The primary outcome of interest was to explore risk factors for surgical site infections after ACLR. The secondary outcomes were to investigate the incidence rate of surgical site infections after ACLR and the time from surgery to the onset of surgical site infection symptoms (eg, pain, redness with increased local skin temperature, swelling and/or fever) based on the literature investigating potential risk factors.

Risk of bias assessment

Registry studies were included in this meta-analysis. As there is currently no standardised method to evaluate internal bias in registry studies,[18] the Downs and Black checklist was used to evaluate the risk of bias and methodological quality of the studies.[19] Given that some of the original checklist items were not applicable to the study design of some of the included studies, an adapted version was used for assessment.[20 21] The adapted checklist had a maximum score of 19. On the basis of these scores, a summary score (the sum of each item divided by the total score) ranging from 0 to 100 was calculated, and each study was then categorised as low (<50), moderate (50–74) or high (≥75) quality. All eligible studies were independently assessed by two reviewers, with discrepancies resolved through discussion; if necessary, a third investigator made the final decision. The level of evidence for the pooled results was assessed by the method described by van Tulder *et al*,[22] which incorporates both the assigned methodological quality of the included studies and statistical outcomes. Strong evidence: the pooled results include more than half of the high-quality studies and are statistically homogeneous; Moderate evidence: the pooled results include more than half of the high-quality studies but are statistically highly heterogeneous or include at least one high-quality study and are statistically homogeneous; Limited evidence: the pooled results include at least one high-quality study but are statistically highly heterogeneous or include at least one moderate-quality study and are statistically homogeneous; Very limited evidence: the pooled results are from moderate-quality or low-quality studies and are statistically highly heterogeneous. If the analysis included more than 10 studies, a quantitative method (Egger's test) was used to explore if there was a risk of publication bias.

Data synthesis and statistical analysis

Data synthesis and statistical analysis were performed using Reviewer Manager (V.5.4; Cochrane Collaboration) and Stata (V.14; StataCorp). The effect size was calculated as the OR with 95% CIs for each risk factor for dichotomous variables. For risk factors for continuous variables, the weighted mean difference (WMD) and 95% CI were used. Where necessary, the ORs and 95% CIs were calculated from binary frequency data.[23] The outcomes incorporating data from two or more studies were presented in the meta-analysis due to the risk of bias of reporting only a single study. Heterogeneity between studies was calculated using the I^2 statistic. Heterogeneity levels >50% were considered high, and levels >80% were considered considerably high. Due to the variation in the study populations and designs, a random effects model was prespecified. If there was high heterogeneity

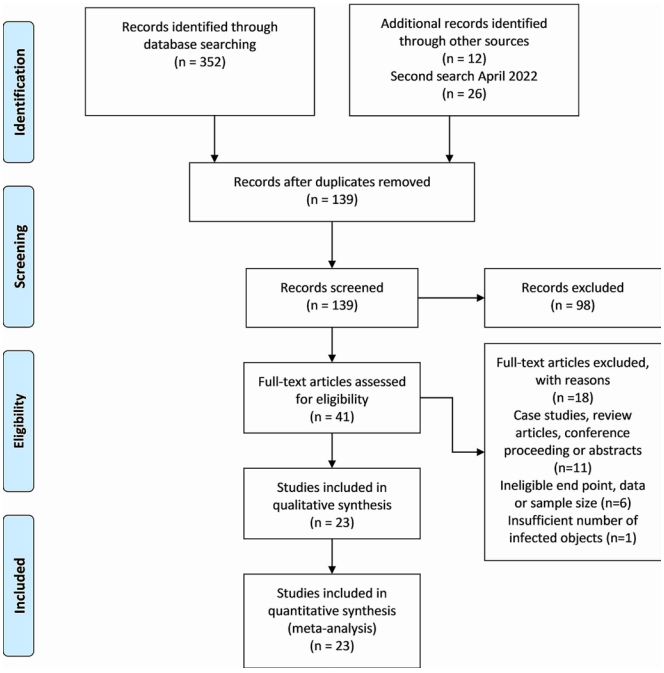

Figure 1 Flow diagram of the study selection procedure.

between studies (≥ 3 studies), a software filter was applied to remove individual studies in sequence as a sensitivity analysis to explore the reason for the heterogeneity. The number of studies removed could not exceed half of the total number of studies. The results were also recalculated using different models to evaluate the robustness of the final results. When the final results had high heterogeneity and were not robust or if the I^2 statistic was greater than 80%, the meta-analysis was abandoned, and a descriptive summary was performed. Furthermore, to obtain higher power, superficial and deep surgical site infections were pooled together for the analysis. If more than one study investigated the same risk factors for deep surgical site infections after ACLR, a subgroup analysis was performed.

RESULTS

Selection of the included studies

Through literature retrieval, a total of 389 studies were finally included. Following the review of the titles and abstracts, 41 studies were appropriate and were eligible for potential inclusion. After full text review, 23 studies[9–16 24–38] were finally included (figure 1).

Characteristics of the included studies

This analysis finally included 23 studies with a total sample size of 469 441. Of the 23 studies, 14 were from the America, 7 were from Europe and 2 were from Asia. The mean age of patients undergoing ACLR was 24–33 years, with more males than females. Fourteen potential risk factors were finally extracted for investigation. The characteristics of the included studies are presented in table 1.

Risk of bias assessment

The methodological quality of the included studies was relatively high, with more than 50% of the studies having a quality score >75 and a mean score of 74. Only one study[35] had a quality score <50. Items 12 and 15 failed to be fulfilled by the included studies (online supplemental A2 and A3). Sex, hamstring autografts (vs bone-patellar tendon-bone (BPTB) autografts) and the incidence rate of surgical site infections were the variables for which more than 10 studies were included; Egger's test yielded p=0.579, 0.322 and 0.298, respectively, indicating that there was no publication bias.

Synthesis of the results

Primary outcomes

Patient-related factors

Sex

Moderate evidence from thirteen studies[9 10 12 14–16 25 27 30 32 34 37 38] investigated the association of sex with surgical site infections. The results of the pooled analysis showed that males had significantly increased odds of surgical site infections compared with females (OR 1.78, 95% CI 1.43 to 2.21, p<0.00001, I^2=63%) (figure 2). High heterogeneity was found in the results. The sensitivity analysis showed that the study of Kawata *et al*[15] was the main source of the heterogeneity; removing this study reduced the I^2 to 38%, and the pooled analysis of the remaining studies still showed significant differences (OR 1.64, 95% CI 1.37 to 1.97, p<0.00001). The main source of heterogeneity in this study might be the short follow-up time, as patients were only observed during hospitalisation. As a result, events that occurred after discharge were not identified. Furthermore, a fixed effect model was used for the analysis, and the final result still showed statistical significance (OR 1.69, 95% CI 1.56 to 1.83, p<0.00001), indicating the robustness of the final results.

Obesity

Strong evidence from four studies[10 14 15 25] investigated the association of obesity (BMI >30 kg/m²) with surgical site infections. The meta-analysis showed that obesity was associated with an 82% increase in the odds of surgical site infections (OR 1.82, 95% CI 1.30 to 2.55, p=0.0005, I^2=0%) (figure 2).

Tobacco use

Strong evidence from nine studies[10–12 14 15 25 31 32 38] investigated the association of tobacco use with surgical site infections. The pooled analysis showed that tobacco use was associated with a 37% increase in the odds of surgical site infections (OR 1.37, 95% CI 1.08 to 1.75, p=0.01, I^2=45%) (figure 2).

Diabetes mellitus

Moderate evidence from nine studies[9–12 14 15 25 32 38] investigated the association of diabetes mellitus with surgical site infections. The results of the pooled analysis showed that patients with diabetes mellitus had significantly increased odds of surgical site infections compared with patients without diabetes mellitus (OR 3.40, 95% CI 1.56 to 7.41, p=0.002, I^2=74%) (figure 2). High heterogeneity was found in the results. The sensitivity analysis showed that the studies of Brophy *et al*[11 32] were the main source of the heterogeneity. Removing these studies reduced the I^2 to 24%, and the pooled analysis of the remaining studies still showed significant differences (OR 1.66, 95% CI 1.08 to 2.57, p=0.02). However, an investigation of the study characteristics failed to explain the heterogeneity. Furthermore, a fixed effect model was used for the analysis, and the final results still showed statistical significance (OR 1.41, 95% CI 1.17 to 1.69, p=0.0003), indicating the robustness of the final results.

Steroid use history

Strong evidence from three studies[12 15 25] investigated the association of steroid use history with surgical site infections. The

Table 1 Characteristics of the studies included in the meta-analysis

Study	Source of study population/study period	Sample size	Age mean (SD) (years)	Sex (male/female)	Incidence rate of postoperative infection	Types of infection studied	Potential risk factor(s)
Abram *et al* 2019[37]	UK 1997–2017	104 255	NR*	80 820/23 435	0.47%	Deep infection	Sex
Barker *et al* 2010[28]	USA 2002–2006	3126	NR	NR	0.58%	Deep and superficial infection	Graft choice
Bohu *et al* 2019[16]	France 2012–2016	1809	29.1 (9.8)	1249/560	0.38%	Deep infection	Sex, age, previous knee surgery history, professional athletes, out- or inpatient surgery, revision or primary surgery, a concomitant lateral extra-articular tenodesis
Brophy *et al* 2015[11]	USA 2002–2005	2198	26.8 (11)	NR	0.8%	Deep infection	Age, tobacco user, diabetes mellitus, graft choice
Brophy *et al* 2021[32]	USA 2002–2011	1423	27.8 (9.9)	832/591	0.6%	Deep infection	Sex, age, tobacco user, diabetes mellitus
Cancienne *et al* 2016[31]	USA† 2007–2011	13 358	NR*	8677/4681	1%	Deep and superficial infection	Tobacco user
Greenberg *et al* 2010[33]	USA 2005–2008	861	29.7 (11.1)	557/304	2.3%	Superficial infection	Graft choice
Gupta *et al* 2018[25]	India 2010–2015	1468	27.1 (3.1)	1358/110	1.8%	Deep and superficial infection	Sex, obesity, tobacco user, diabetes mellitus, steroid use history, graft choice
Hurvitz *et al* 2020[24]	USA† 2008–2016	15 671	24.4 (9.4)	9917/5753	0.2%	Deep infection	Graft choice
Judd *et al* 2006[29]	USA 1999–2001	418	NR	NR	5.5%	Deep and superficial infection	Previous knee surgery history, graft choice
Katz *et al* 2008[36]	USA 2001–2005	782	31.3 (10.4)	NR	0.77%	Deep infection	Age, out- or inpatient surgery, graft choice
Kawata *et al* 2018[15]	Japan 2010–2015	30 536	NR*	16 213/14 323	0.94%	Deep and superficial infection	Sex, age, obesity, tobacco user, diabetes mellitus, steroid use history
Kraus *et al* 2021[14]	Switzerland 2006–2013	25 309	26.8 (15)	14 521/10 788	1.1%	Deep infection	Sex, age, obesity, tobacco user, diabetes mellitus, outpatient or inpatient surgery, revision or primary surgery, graft choice, a concomitant meniscal suture, operating time
Krutsch *et al* 2017[26]	Germany 2008–2012	1809	31.4	NR	0.9%	Deep infection	Professional athletes
Leroux *et al* 2014[30]	Canada 2004–2010	827	30.3 (12.6)	486/341	2.2%	Deep and superficial infection	Sex
Maletis *et al* 2013[27]	USA† 2005–2010	10 626	29.5 (11.4)	6831/3795	0.48%	Deep and superficial infection	Sex, graft choice
Marom *et al* 2022[38]	USA 2010–2018	11 451	30.3 (12.3)	6384/5067	0.42%	Deep infection	Sex, age, tobacco user, diabetes mellitus, revision or primary surgery, graft choice
Murphy *et al* 2016[9]	USA 2000–2008	11 772	31.0 (12.0)	6428/5344	1%	Deep infection	Sex, age, diabetes mellitus, previous knee surgery history, graft choice
RISTIĆ *et al* 2014[35]	Serbia NR	1425	NR	NR	1.2%	Deep infection	Professional athletes, graft choice
Roecker *et al* 2021[10]	USA† 2010–2019	217 541	NR*	107 444/1 10 097	0.8%	Deep and superficial infection	Sex, obesity, tobacco user, diabetes mellitus, a concomitant meniscal suture
Sonnery-Cottet *et al* 2011[13]	France 2003–2008	1957	24.2	802/1155	0.61%	Deep infection	Professional athletes, revision or primary surgery, a concomitant lateral extra-articular tenodesis

Continued

Table 1 Continued

Study	Source of study population/study period	Sample size	Age mean (SD) (years)	Sex (male/female)	Incidence rate of postoperative infection	Types of infection studied	Potential risk factor(s)
Sonnery-Cottet *et al* 2019[34]	France 2009–2017	4421	29.1 (8.0)	3227/1194	0.34%	Deep infection	Sex, professional athletes, revision or primary surgery, a concomitant lateral extra-articular tenodesis
Westermann *et al* 2017[12]	USA 2007–2013	6398	32.8 (11.0)	4048/2350	0.61%	Deep and superficial infection	Sex, age, tobacco user, diabetes mellitus, steroid use history, out- or inpatient surgery, a concomitant meniscal suture, operating time

*The reported values are dichotomous variables.
†Both Cancienne *et al* (from 2007 to 2011) and Roecker *et al* (from 2010 to 2018) used the PearlDiver Mariner Records Database, and both Maletis *et al* (from 2005 to 2010) and Hurvitz *et al* (from 2008 to 2016) used the Kaiser Permanente ACLR registry. However, the overlapping study time periods were significantly smaller than the non-overlapping study time periods, so all the studies were included.
ACLR, anterior cruciate ligament reconstruction; NR, not reported.

meta-analysis showed that steroid use history was associated with a nearly fivefold higher risk of surgical site infections (OR 4.80, 95% CI 2.61 to 8.84, p<0.00001, I^2=0%) (figure 2).

Previous knee surgery history

Moderate evidence from three studies[9 16 29] investigated the association of previous knee surgery history with surgical site infections. The results of the pooled analysis showed that patients with a previous knee surgery history had significantly increased odds of surgical site infections compared with patients who did not have a previous history of knee surgery (OR 3.63, 95% CI 1.25 to 10.53, p=0.02, I^2=66%) (figure 2). High heterogeneity was found in the results. The sensitivity analysis showed that Bohu *et al*[16] was the main source of the heterogeneity. Removing this study reduced the I^2 to 48%, and the pooled analysis of the remaining studies still showed significant differences (OR 2.40, 95% CI 1.03 to 5.57, p=0.04). It is speculated that one of the sources of the heterogeneity was the difference in the population of this study compared with the other studies. The study populations of Judd *et al*[29] and Murphy *et al*[9] were mainly from Europe, whereas the study population of Bohu *et al*[16] was mainly from the USA. Another possible reason is the different types of previous knee surgeries in the different studies, but the lack of data makes it impossible to determine if this is the case. Furthermore, a fixed effect model was used for the analysis, and the final results still showed statistical significance (OR 2.86, 95% CI 1.62 to 5.05, p=0.0003), indicating the robustness of the final results.

Professional athletes

Limited evidence from five studies[13 16 26 34 35] investigated the association of the patient being a professional athlete with surgical site infections. The meta-analysis showed that professional athletes had significantly increased odds of surgical site infections compared with patients who were not professional athletes (OR 4.56, 95% CI 1.30 to 15.96, p=0.02, I^2=74%) (figure 2). High heterogeneity was found in the results. The sensitivity analysis failed to reveal a significant source of heterogeneity. An investigation of the study characteristics revealed that Krutsch *et al*[26] compared professional and amateur athletes (excluding no sport), while other studies compared professional and nonprofessional athletes (including no sport). The differences in the study design may have affected the final result. However, after this study was removed, the heterogeneity did not significantly change, but the pooled analysis of the remaining studies still showed a significant difference (OR 6.63, 95% CI 1.71 to 25.74, p=0.006). Furthermore, a fixed effect model was used for the analysis, and the final results still showed statistical significance (OR 4.78, 95% CI 2.65 to 8.63, p<0.00001), indicating the robustness of the final results.

Age

Strong evidence from eight studies[9 11 12 15 16 32 36 38] investigated the association of age as a continuous variable with surgical site infections. The pooled analysis showed that there was no association between age and the odds of surgical site infections (WMD −0.46, 95% CI −2.06 to 1.14, p=0.57, I^2=43%) (figure 3).

Surgery-related factors

Operating time

Strong evidence from two studies[12 14] investigated the association of the operating time as a continuous variable with surgical site infections. The pooled analysis showed that individuals who sustained a surgical site infection after ACLR had an approximately 8 min longer surgery time, on average, than those who did not (WMD 8.12, 95% CI 2.49 to 13.75, p=0.005, I^2=0%) (figure 3).

Out- or inpatient surgery

Strong evidence from four studies[12 14 16 36] investigated the association of outpatient or inpatient surgery with the incidence of surgical site infections. The results of the pooled analysis showed that there was no association between outpatient or inpatient surgery and the odds of surgical site infections (OR 0.87, 95% CI 0.46 to 1.67, p=0.68, I^2=43%) (figure 4).

Revision or primary surgery

Moderate evidence from five studies[12 14 16 36 38] investigated the association of revision or primary surgery with surgical site infections. The meta-analysis showed that revision surgery had significantly increased odds of surgical site infections compared with primary surgery (OR 2.05, 95% CI 1.03 to 4.06, p=0.04, I^2=60%) (figure 4). High heterogeneity was found in the results. The sensitivity analysis found that Kraus *et al*[14] was the main source of the heterogeneity. Removing this study reduced the I^2 to 0%, and the pooled analysis of the remaining studies still showed significant differences (OR 2.97, 95% CI 1.75 to 5.04, p<0.0001). However, the investigation of the study characteristics failed to explain the heterogeneity. Furthermore, a fixed effect model was used for the analysis, and the final results still showed statistical significance (OR 1.63, 95% CI

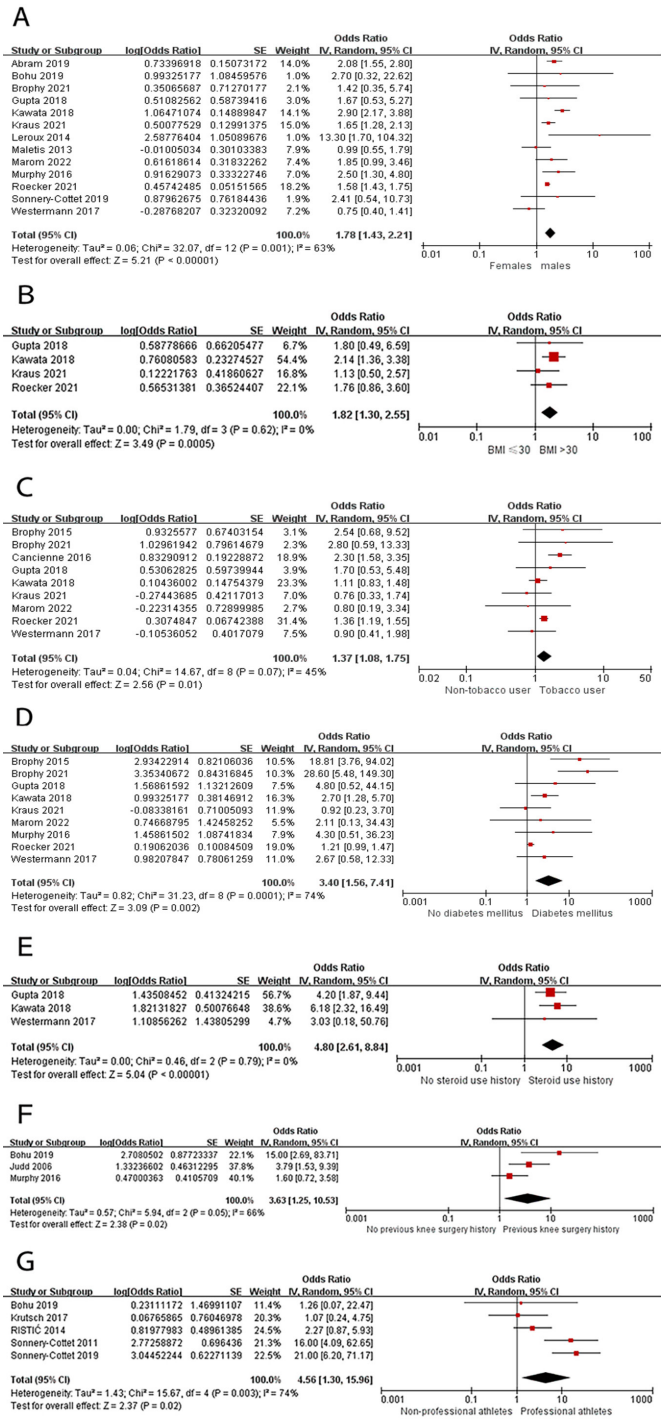

Figure 2 Forest plot detailing the association of patient-related factors as dichotomous variables with surgical site infections after anterior cruciate ligament reconstruction. (A) sex; (B) obesity; (C) tobacco user; (D) diabetes mellitus; (E) steroid use history; (F) previous knee surgery history; (G) professional athletes. IV, inverse variance.

1.13 to 2.37, p=0.009), indicating the robustness of the final results.

Graft type (for ACLR only)

Strong evidence from eleven studies[9 11 14 24 25 27–29 35 36 38] investigated the association of selecting hamstring autografts or BPTB autografts with surgical site infections. The results of the pooled analysis showed that the use of a hamstring autograft

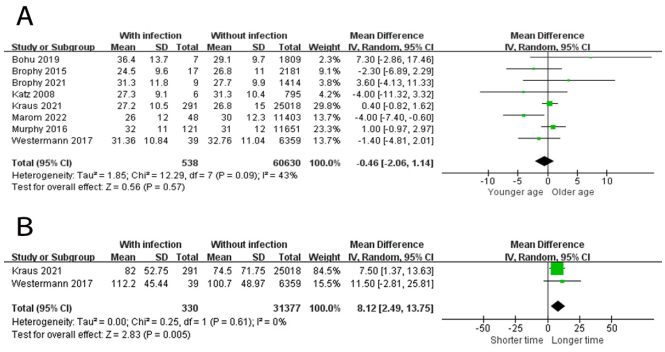

Figure 3 Forest plot detailing the association of age (A) and operating time (B) as continuous variables with surgical site infections after anterior cruciate ligament reconstruction. IV, inverse variance.

was associated with an increase in the odds of surgical site infections of more than 2.8-fold compared with a BPTB autograft (OR 2.83, 95% CI 2.22 to 3.60, p<0.00001, I^2=0%). The results of the pooled analysis of five studies[9 28 33 36 38] (strong evidence) showed that the use of a hamstring autograft was associated with an increase in the odds of surgical site infections of approximately 3.02-fold compared with an allograft (OR 3.02, 95% CI 1.62 to 5.63, p=0.0005, I^2=33%). However, based on five studies[9 27 28 36 38] (moderate evidence), BPTB autografts did not increase the odds of surgical site infections compared with allografts (OR 0.75, 95% CI 0.33 to 1.70, p=0.49, I^2=53%) (figure 4). High heterogeneity was found in the results. The sensitivity analysis found that Marom *et al*[38] was the main source of the heterogeneity; removing this study reduced the I^2 to 0%, and the pooled analysis of the remaining studies still showed no significant differences (OR 1.09, 95% CI 0.61 to 1.96, p=0.76). Based on the investigation of the study characteristics, it is speculated that the source of the heterogeneity might be the difference in types of allografts used compared with other studies. Furthermore, a fixed effect model was used for the analysis, and the final result still showed no statistical significance (OR 0.73, 95% CI 0.44 to 1.22, p=0.23), indicating the robustness of the final results.

Concomitant meniscal suture

Strong evidence from three studies[10 12 14] investigated the association of a concomitant meniscal suture with surgical site infections. The meta-analysis showed that meniscal sutures were not associated with an increased risk of surgical site infections (OR 0.95, 95% CI 0.85 to 1.08, p=0.45, I^2=0%) (figure 4).

Concomitant lateral extra-articular tenodesis (as an additional procedure)

Moderate evidence from three studies[13 16 34] investigated the association of concomitant lateral extra-articular tenodesis with surgical site infections. The meta-analysis showed that having combined lateral extra-articular tenodesis was associated with a nearly fourfold higher risk of surgical site infections (OR 3.92, 95% CI 1.96 to 7.84, p=0.0001, I^2=0%) (figure 4).

Secondary outcomes

Incidence rate

Moderate evidence from twenty-three studies investigated the incidence rate of surgical site infections after ACLR. The pooled analysis showed that the surgical site infection rate after ACLR was 1% (95% CI, 0.7% to 1.2%; I^2=98%) (online supplemental

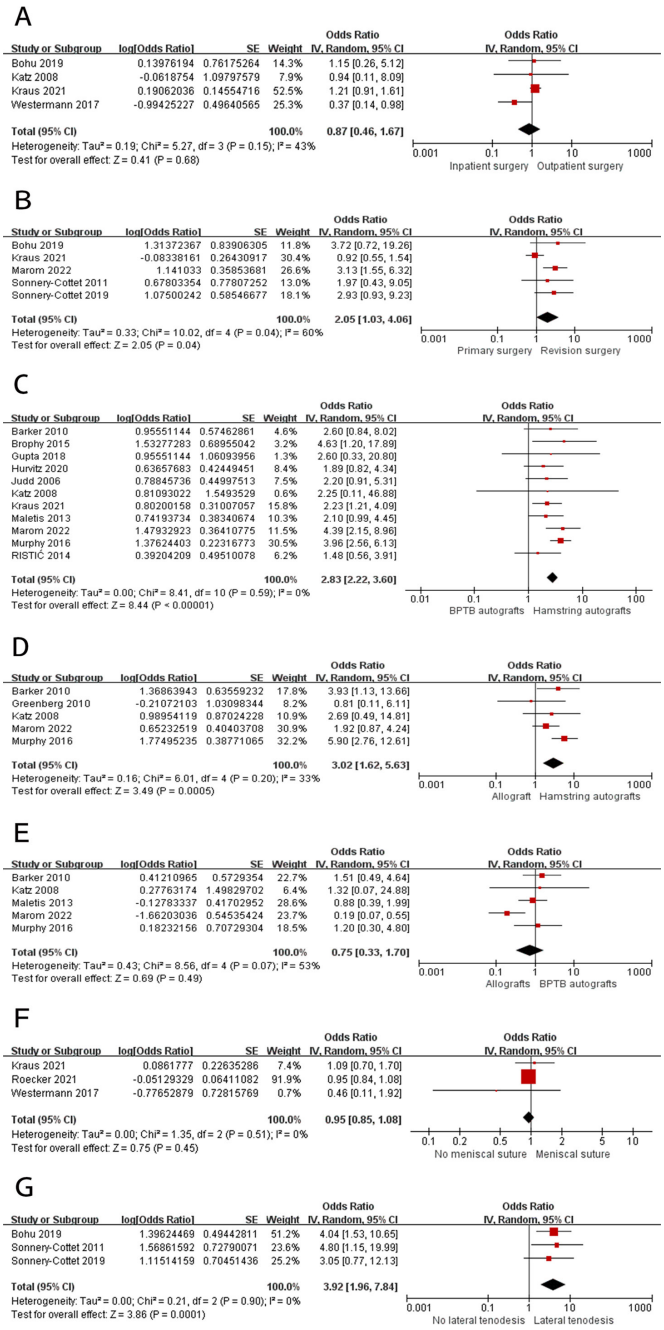

Figure 4 Forest plot detailing the association of surgery-related factors as dichotomous variables with surgical site infections after anterior cruciate ligament reconstruction. (A) Outpatient or inpatient surgery; (B) revision or primary surgery; (C) hamstring autografts or BPTB autografts; (D) hamstring autografts or allograft; (E) BPTB autografts or allografts; (F) a concomitant meniscal suture; (G) a concomitant lateral extra-articular tenodesis. BPTB, bone-patellar tendon-bone; IV, inverse variance.

A4). The sensitivity analysis failed to reveal a significant source of the heterogeneity.

Time from surgery to the onset of infection symptoms

Limited evidence from six studies[13 16 25 28 29 38] investigated the time from surgery to the onset of surgical site infection symptoms. The pooled analysis showed that the mean time from surgery to the onset of surgical site infection symptoms was 17.1 days (95% CI, 13.2 to 21.0 days; I^2=77%) (online supplemental A5). The sensitivity analysis found that Gupta *et al*[25] was the main source of the heterogeneity, and the I^2 was reduced to 38% after the study was removed. A pooled analysis of the remaining studies showed that the mean time from surgery to the onset of surgical site infection symptoms was 18.4 days (95% CI, 15.2 to 21.6 days). It is speculated that the main source of the heterogeneity was the difference in the study population. Gupta *et al*[25] is the only study from an Asian population (India), while the remaining studies are from European and US populations.

Subgroup analysis of deep surgical site infections

Sixteen studies[9 11–16 24 26 27 29 32 34–36 38] investigated the potential risk factors associated with deep surgical site infections. The results of the pooled analysis showed that male sex, diabetes mellitus, previous knee surgery history, professional athlete, revision surgery, hamstring autografts and concomitant lateral extra-articular tenodesis were associated with an increase in the odds of deep surgical site infections (online supplemental A6). However, obesity and tobacco use failed to show an association with deep surgical site infections (OR 1.99, 95% CI 0.72 to 5.47, p=0.18; and OR 1.22, 95% CI 0.85 to 1.76, p=0.28, respectively). In addition, age, outpatient surgery (vs inpatient surgery) and BPTB autografts (vs allografts) did not significantly increase the odds of deep surgical site infections. The pooled analysis showed that the incidence rate of deep surgical site infections after ACLR was 0.6% (95% CI 0.4% to 0.8%).

DISCUSSION

This meta-analysis revealed that male sex, obesity, tobacco use, diabetes mellitus, steroid use history, previous knee surgery history, professional athlete, revision surgery, hamstring autografts, concomitant lateral extra-articular tenodesis and a long operation time significantly increased the odds of surgical site infections after ACLR. Age, outpatient or inpatient surgery, BPTB autografts or allografts and concomitant meniscus suture were not associated with an increased risk of surgical site infections after ACLR. Furthermore, the incidence rate of surgical site infections after ACLR was approximately 1% (95% CI 0.7% to 1.2%), and the incidence rate of deep surgical site infections was approximately 0.6% (95% CI 0.4% to 0.8%). The mean time from surgery to the onset of surgical site infection symptoms was approximately 17.1 days (95% CI 13.2 to 21.0 days).

Patient-related factors

The analysis indicated that males had significantly higher rates of surgical site infections after ACLR than females. Similarly, the incidence rates of wound infection[39] and prosthetic joint infection (PJI)[40 41] after knee arthroplasty are significantly higher in males than in females. Experts at the 2013 International Consensus Conference on PJI also agreed that males had an increased risk of surgical site infections, particularly a higher risk of PJI after knee arthroplasty.[42] One possible reason is that sex-specific steroids have a different effect on the immune response, as testosterone reduces antibody production, while oestrogen increases antibody production.[43] Moreover, testosterone has been shown to disrupt the homoeostasis of the epidermal barrier in adults.[44 45] Endogenous testosterone inhibits skin wound healing in men and is associated with an enhanced inflammatory response.[46 47] Thus, these factors may lead to a higher incidence of postoperative surgical site infections in males than in females.

There is conflicting and controversial evidence regarding whether age influences surgical site infections after ACLR.

Roecker *et al*[10] found that patient age <40 years was a risk factor for surgical site infections after ACLR. Kawata *et al*[15] found that young age (≤19 years) was also a risk factor. Murphy *et al*[9] believed that patient age ≥20 years was a risk factor for postoperative surgical site infections. However, an association between patient age as a continuous variable and postoperative surgical site infections was not found in this study. Therefore, more research is needed regarding age as a dichotomous variable.

Obesity was also considered a risk factor associated with postoperative surgical site infections but not with deep surgical site infections. The reason may be that the thicker adipose tissue in obese patients may lead to liquefaction of postoperative fat, which increases the chance of postoperative superficial surgical site infections.[27] Additional comorbidities in obese patients may further aggravate postoperative surgical site infections. In addition, it has been suggested that obesity is a proinflammatory state associated with low-grade inflammatory responses, which may affect postoperative immune responses and increase the risk of surgical site infections.[48 49]

Tobacco use significantly increased the incidence of postoperative surgical site infections following ACLR in this analysis, but it was not associated with deep surgical site infections. In fact, many orthopaedic disorders and procedures are adversely affected by tobacco use.[50 51] Kanneganti *et al* also revealed the negative impact of tobacco use on the outcome of knee ligament surgery from both basic science and clinical perspectives.[52] Although tobacco use was not associated with deep surgical site infections in this analysis, it is worth noting that the included studies by Brophy *et al*,[11] Brophy *et al*[32] and Kraus Schmitz *et al*[14] all considered that the small sample sizes or large missing values of the included tobacco users and wide confidence intervals did not allow them to draw a reliable conclusion with enough confidence. Moreover, because a large cohort study by Cancienne *et al*[31] (13 358 participants) and a large sample size study by Roecker *et al*[10] (over 100 000 participants) did not separately study superficial and deep surgical site infections, it was not possible for these studies to be included in the analysis of deep surgical site infections. Therefore, the results for deep surgical site infections should be interpreted with caution. Whether tobacco use increases the odds of deep surgical site infections after ACLR still requires a large cohort study.

The current meta-analysis indicated that the odds of surgical site infections after ACLR and of deep surgical site infections were threefold and fivefold higher, respectively, for patients with diabetes mellitus. In many orthopaedic procedures, diabetes mellitus is considered a risk factor for postoperative surgical site infections.[53–55] Studies have reported that patients with diabetes mellitus, especially those with insulin-dependent diabetes, have a significantly increased risk of postoperative infections because high blood sugar may damage the immune system and provide a favourable environment for certain bacteria to multiply.[56 57] Although no studies have reported whether glycaemic control reduces the risk of surgical site infections after ACLR, glycaemic control significantly reduces the odds of surgical and systemic complications, length of hospital stay and mortality after knee arthroplasty.[56]

A history of steroid use was the most prominent risk factor associated with surgical site infections after ACLR. Previous studies have also found that steroid use history increases surgical site infections after arthroscopy.[58 59] Steroid use can reduce the patient's immunity to some extent,[60] which may be responsible for the increased risk of postoperative surgical site infections. Unfortunately, we were unable to determine the effects of different times and doses of preoperative steroid injections on postoperative ACLR surgical site infections due to the lack of corresponding data. Therefore, clinicians should pay more attention to individuals with a history of steroid use.

The results from the present meta-analysis showed that professional athletes were associated with increased odds of postoperative surgical site infections. Professional athletes who need to return to competition early need immediate procedures and an aggressive early rehabilitation programme,[61–63] which may increase the odds of surgical site infections after ACLR.[13] In addition, a weakened immune system has also been suggested as a major factor due to higher levels of physical stress and the demands of certain physical activities.[64–66] However, the results of the included studies were highly variable, and one of the main reasons may be the statistical underpower of the individual studies. Insufficient power is an important issue to consider, especially in the design of studies of diseases with a low incidence. Data pooling is an appropriate solution to obtain adequate statistical power. Using this methodology, 11 421 participants, including 1118 professional athletes, were recruited. The pooled analysis showed an increased risk of postoperative surgical site infections.

Surgery-related factors

In this analysis, no significant difference was found between inpatients and outpatients in terms of postoperative surgical site infections. However, different countries and populations have produced different results. Among the study population from the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database,[12] the probability of developing a surgical site infection was significantly higher after inpatient ACLR than after outpatient ACLR. However, two studies from European databases (Sweden and France)[14 16] showed no significant difference in the odds of postoperative surgical site infections between outpatient and inpatient ACLR. Therefore, more studies from other large databases are required to compare the differences in postoperative surgical site infections between these two patterns of admission. In addition, postoperative surgical site infections are only one of the aspects used to evaluate the difference between inpatient and outpatient ACLR. A comprehensive assessment of the postoperative complication rate, satisfaction, knee function and strength, and cost-effectiveness is also necessary.

A previous knee surgery history was a risk factor for surgical site infections after ACLR, and revision ACLR was also associated with an increase in the odds of surgical site infections compared with primary ACLR. Possible reasons for the increased risk of postoperative surgical site infections include a longer operation time, additional incisions, or increased foreign body load.[29 67 68] However, Brophy *et al*[32] concluded that the incidence rate of surgical site infections after revision is similar to that of primary ACLR in the literature. Conversely, the pooled analysis of the current studies showed that revision ACLR had significantly increased odds of surgical site infections compared with primary ACLR. Given that there are limited studies related to surgical site infections after revision ACLR, further studies are merited.

The present meta-analysis revealed that the odds of postoperative surgical site infections were 2.83 and 3.02 times higher with hamstring autografts than with BPTB autografts and allografts, respectively. However, no significant difference was found in postoperative surgical site infections between patellar tendon autografts and allografts. It is currently believed that the reasons for the higher surgical site infection odds of hamstring autografts include the following[11 14 27]: (1) hamstring autografts have

a greater surface exposure to potential bacteria than the patellar tendon or autologous quadriceps tendon; (2) the preparation of hamstring autografts may increase the operation time; (3) multifilament sutures, which may contain and potentially harbour bacteria, are often used to prepare hamstring autografts; (4) hamstring grafts are harvested directly at the tibial tunnel, which may create a more conducive wound environment for bacterial growth and (5) the harvest of hamstring autologous grafts may result in haematoma formation in the area of graft collection due to the extensive deep dissection needed. Future studies should pay more attention to effective preventive measures against these possible causes to reduce the odds of these graft infections. Hurvitz *et al*[24] found that hamstring autografts with screw and sheath fixation increased the risk of postoperative surgical site infections compared with hamstring autografts without screw and sheath fixation. As the screw and sheath are two separate implants with a significantly increased surface area of synthetic material to which organisms can attach, the dead space between the screw and sheath can serve as a protective space for bacteria and can cause unrestricted growth of bacteria. However, this needs to be confirmed by additional studies. In addition, further research is also needed to determine whether fixation without screws and sheaths affects the risk of ACLR revision compared with fixation with screws and sheaths, especially for populations with high-volume physical activity.

In this study, a concomitant meniscal suture was not related to the risk of surgical site infections after ACLR. Studies have also reported that concomitant open procedures increase the risk of postoperative surgical site infections, but this was not seen in arthroscopic procedures.[13 69] Austin and Sherman[70] studied 101 patients who underwent arthroscopic meniscal repair; only one patient developed a deep surgical site infection, and this infection was from isolated meniscal repair (no ACLR). No infections were found in patients who underwent simultaneous ACLR. The increased operation time associated with meniscal repair may be a factor of concern, but this procedure may be typically brief when the surgeon is already operating within the knee.[10 26] These reasons also explain why our study found a significant increase in the odds of postoperative surgical site infections with concomitant lateral extra-articular tenodesis, which is a complex open procedure requiring additional incisions. But lateral extra-articular tenodesis is an effective technique for restoring knee stability and significantly reducing persistent rotatory relaxation and graft rupture.[71 72] Sonnery-Cottet *et al*[73] reported combined ACL and anterolateral ligament reconstruction techniques and found that the reduced surgical site infection rate is an advantage of this percutaneous procedure over iliotibial band procedures that require a lateral incision. There was no difference in the odds of postoperative surgical site infections between this procedure and ACLR without combined anterolateral ligament reconstruction.[34] However, more research is needed to confirm this conclusion, considering that the complexity and prolonged duration of the procedure may lead to an increased rate of surgical site infections.

In the current meta-analysis, we found that the operation time of the group with postoperative surgical site infections was on average 8 min longer than that of the group without surgical site infections. Kraus Schmitz *et al*[14] reported that an operation time ≥70 min was associated with 83% increased odds of postoperative surgical site infections compared with an operation time of <70 min. Westermann *et al*[12] also reported that all ACLR procedures with postoperative surgical site infections had occurred for >60 min, and none of the operations with a time<60 min were associated with surgical site infections. Gowd *et al*[74] studied the relationship between arthroscopic knee procedures and operation time and found that the increase in the operation time was linearly related to the increase in surgical site infections. However, this study did not include ACLR or concomitant procedures. Agarwalla *et al*[75] investigated the relationship between the occurrence of complications after ACLR and the operation time and found that an increase in the operation time increased the risk of surgical site infections. In another systematic review, the likelihood of surgical site infections increased with increasing operation time.[76] Thus, surgeons should make efforts to maximise surgical efficiency.

Patients who are identified to have a high risk of postoperative surgical site infections (male sex, obesity, tobacco use, diabetes mellitus, steroid use history, previous knee surgery history, professional athletes, revision surgery, hamstring autografts, concomitant lateral extra-articular tenodesis and a long operation time) and their families should be informed of this risk in advance. Such patients might experience longer postoperative hospital stays, more frequent dressing changes, and higher medical costs. At the same time, clinicians should pay close attention to patients with postoperative symptoms or signs of surgical site infections, such as pain, redness with increased local skin temperature, swelling and/or fever, and laboratory results, such as continuously elevated C reactive protein (CRP) and erythrocyte sedimentation rates during the week after surgery. For patients with high suspicion of surgical site infections, early arthrocentesis and bacterial cultures should be performed, and oral and intravenous antibiotic therapy should be prolonged. However, there is currently no uniform recommendation on the duration of antibiotic therapy for postoperative surgical site infections after ACLR, and evidence-based data are not available. Some studies suggested that intravenous antibiotics should be stopped when laboratory indicators such as CRP levels return to normal, and oral antibiotics should be stopped when CRP normalises twice within an interval of a minimum of 14 days.[77–79] Schuster *et al* argued that a more individual approach is necessary. The switch to oral administration should not be based on a certain period of time but on the clinical course and bioavailability of the administered drugs.[80] Patients who are suspected to have a deep surgical site infection can undergo arthroscopic irrigation and debridement. All knee compartments should be inspected, and graft integrity should be assessed.[80–82]

The occurrence of surgical site infections after ACLR not only increases the costs of medical care but also prolongs the postoperative recovery time. Therefore, it is crucial to prevent the identified risk factors in advance. Prophylactic intravenous antibiotics are still the standard of care.[83] However, the poor vascularity of the tendons used as grafts may lead to insufficient intratendinous antibiotic levels, thereby increasing the risk of postoperative surgical site infections.[84] Recently, many researchers have found that graft vancomycin presoaking can increase local antibiotic levels, significantly decrease the risk of postoperative surgical site infections, and effectively reduce surgical site infection rates in patients with different graft types and with concomitant ligament procedures or open surgeries.[84–87] In addition, Bohu *et al*[88] found that compared with their control counterparts, more of the patients with vancomycin presoaked grafts returned to their preinjury sport. No significant difference was found in terms of the return to running and overall functional knee scores or in patient satisfaction between the vancomycin presoaked group and the control group. Offerhaus *et al*[86] found that the addition of prophylactic vancomycin presoaked grafts significantly decreased graft failure and did not increase the rate of postoperative arthrofibrosis or subjective outcome scores compared

with a control group with systemic antibiotics alone. In a study using live donors, Jacquet *et al*[89] found that presoaking human semitendinosus grafts with vancomycin (5 mg/mL) did not alter their biomechanical properties. Therefore, intravenous antibiotic prophylaxis in conjunction with vancomycin presoaking is a safe and effective preventive measure recommended by many researchers. It should be noted that the lack of high-level evidence in the current studies means that it may not be feasible to recommend vancomycin presoaking for every ACLR patient. However, when the identified risk factors for postoperative surgical site infections after ACLR are present, clinicians can attempt to use this precaution.

Incidence rate and time from surgery to the onset of surgical site infection symptoms

In this meta-analysis, the incidence rate of surgical site infections after ACLR was approximately 1%, and the incidence rate of deep surgical site infections was approximately 0.6%. A concern is that there was a large difference in the incidence rate of surgical site infections between the different studies. Local guidelines and infection prevention measures are probably of great importance. This study, therefore, provides an approximate average. The incidence of deep surgical site infections after ACLR was lower than the incidence of overall surgical site infections, which may indicate a higher incidence of superficial surgical site infections. Although the symptoms of superficial surgical site infections may be milder than those of deep surgical site infections, superficial surgical site infections are likely to develop into deep surgical site infections if not treated promptly. In addition, this study found that the onset of surgical site infection symptoms after ACLR was usually concentrated in the third week after surgery. Most patients may have been discharged during this time period, and superficial surgical site infections that present with mild symptoms are likely to worsen and lead to deep surgical site infections if the individuals do not seek medical treatment in time or if clinicians do not follow-up regularly. Therefore, clinicians should instruct discharged individuals to return to the hospital for regular check-ups, and if symptoms of surgical site infections, such as pain, redness with increased local skin temperature, swelling and/or fever, are present and laboratory tests include a significantly elevated sedimentation rate and CRP level, hospitalisation for arthrocentesis, bacterial cultures and antibiotic therapy should be performed as early as possible.

Strengths and limitations

A total of 469 441 ACLRs with 3871 infection events were included in this study, and the overall quality of the included studies was high. These strengths provide an accurate and reliable opportunity for the identification of risk factors and the determination of morbidity. In addition, potential risk factors, including patient-related factors and surgery-related factors, were comprehensively analysed and summarised in this study, and large databases and registered studies were included, which improved the representativeness and generalisability of the study. However, this study inevitably has some limitations. First, this study included a variety of ethnicities, populations and methods, which is reflected in the high heterogeneity between studies, especially in the assessment of the incidence rate. However, this calculated effect may be due to the differences in assessment populations or in the study designs rather than from real differences in the outcomes of interest.[90] Fortunately, there was no considerably high heterogeneity ($I^2 > 80$) in the results of the identification of risk factors. For the results with high heterogeneity, the robustness of the final results was also demonstrated by a sensitivity analysis and different study models. Furthermore, random effects models were used for all results analyses, as this model provides a more conservative estimate of the effect size. Second, due to the differences in design among the studies, it is difficult to determine the causal relationships between the risk factors and postoperative surgical site infections, but identifying infection-related risk factors can provide a basis for high-quality prospective cohort studies. Third, the different studies provide conflicting evidence for identifying the same risk factors, and the failure to show statistically significant results may largely reflect limitations in the sample size. This is where a meta-analysis has the advantage of reducing bias due to small sample sizes and increasing the accuracy of the results by quantitatively analysing the results of multiple independent studies. Fourth, to increase the power of the study, we pooled superficial and deep surgical site infections together for the analysis. Risk factors for deep surgical site infections were analysed by a subgroup analysis. However, it is worth noting that subgroup analyses reduce the number of studies and the sample size, which limits the strength of evidence for these projects and makes some risk factors impossible to assess. The lack of statistical significance does not mean that this risk factor is not associated with deep surgical site infections, and clinicians should rely on their clinical judgement when developing personalised prevention strategies rather than ignoring potential risk factors. Fifth, the limited number of studies on risk factors for superficial surgical site infections after ACLR prevented us from performing a subgroup analysis. Further studies are thus warranted to investigate potential risk factors. Sixth, the risk of postoperative surgical site infections may be multifactorial, and different risk factors may play a synergistic role. However, the included studies only attempted to detect an association between single variables and the risk of surgical site infections, so the relationships between multiple variables could not be evaluated. Finally, the incidence rate and the time from surgery to the onset of surgical site infection symptoms were calculated only from the studies that were included in the assessment of risk factors; the addition of other epidemiological studies that did not meet the inclusion criteria could potentially influence the reported values.

CONCLUSION

This meta-analysis revealed that male sex, obesity, tobacco use, diabetes mellitus, steroid use history, previous knee surgery history, professional athletes, revision surgery, hamstring autografts, concomitant lateral extra-articular tenodesis and a long operation time were associated with an increased odds of surgical site infections after ACLR. Early screening of individuals at high risk for surgical site infections after ACLR by identifying these risk factors will facilitate early prevention and strengthen postoperative care and follow-up. Intravenous antibiotic prophylaxis in conjunction with vancomycin presoaking is a safe and effective preventive measure that may address the identified risk factors for postoperative surgical site infections after ACLR. Surgeons should also make efforts to maximise operative efficiency by selecting the optimal surgical approach. Among the included studies, the incidence rate of surgical site infections after ACLR was approximately 1% (95% CI 0.7% to 1.2%), and that of deep surgical site infections was approximately 0.6% (95% CI 0.4% to 0.8%). The mean time from surgery to the onset of surgical site infection symptoms was approximately 17.1 days (95% CI 13.2 to 21.0 days). Although the risk of surgical site infections after ACLR is not high, surgical site infections have potentially

serious consequences, and raising awareness and implementing effective prevention strategies for risk factors are priorities for clinicians to reduce the incidence of surgical site infections.

What is already known

⇒ Surgical site infections after anterior cruciate ligament reconstruction (ACLR) are a serious complication to manage. Failure to provide timely prevention and treatment may lead to devastating outcomes.
⇒ Prevention strategies that target the early identification of risk factors are important to reduce the incidence.

What are the new findings

⇒ Male sex, obesity, tobacco use, diabetes mellitus, steroid use history, previous knee surgery history, professional athletes, revision surgery, hamstring autografts, concomitant lateral extra-articular tenodesis as well as a long operation time increase the risk of surgical site infections after ACLR.
⇒ The incidence rate of surgical site infections after ACLR was approximately 1%. The mean time from surgery to the onset of surgical site infection symptoms was approximately 17.1 days.
⇒ Although the risk of surgical site infections after ACLR is not high, surgical site infections have potentially serious consequences, and raising awareness and implementing effective preventions for risk factors are priorities for clinicians to reduce the incidence of surgical site infections.

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