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KNEE REVISION SURGERY

Predictors of failure of two-stage revision in periprosthetic knee infection: a retrospective cohort study with a minimum two-year follow-up

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Abstract

Purpose Despite the standardization of two-stage knee revision protocols, a high percentage of failures still occurs. Identifying the predictors of failure is necessary to determine appropriate management and counsel for patients with a periprosthetic knee infection. This study aimed to identify risk factors predicting the failure, to describe implant survival, and to report the mid-term clinical outcomes of patients undergoing two-stage revision for periprosthetic knee infection.

Methods Data of patients who underwent two-stage knee revision from 2012 to 2016 were analyzed, and 108 patients were included. The mean age was 66.6 ± 9.2 years. The mean follow-up was 52.9 ± 15.6 months. Logistic regression was conducted to identify predictors of treatment failure. Kaplan–Meier curves were generated to assess implant survival. Preoperative functional outcomes were compared to those registered at the final follow-up.

Results Difficult-to-treat infections (OR = 4.2, 95% CI 1.2–14.5, $p = 0.025$), the number of previous surgeries (OR = 1.8, 95% CI 1.2–2.6, $p = 0.005$), and the level of tibial bone defect (OR = 2.3, 95% CI 1.1–4.7, $p = 0.027$) significantly predicted the failure of two-stage knee revision. Survivorship of implants was significantly lower for patients presenting these risk factors ($p < 0.05$). Mean Knee Society Score improved from 49.0 ± 12.0 to 80.2 ± 13.6 ($p < 0.001$). Mean Oxford Knee Score improved from 22.2 ± 4.9 to 36.1 ± 6.0 points ($p < 0.001$).

Conclusion Difficult-to-treat pathogens, the number of previous surgeries, and the level of tibial bone defect were independent risk factors of two-stage knee revision failure. Overall, the two-stage protocol provided a good survival rate and functional outcome.

Keywords Two-stage revision · Knee arthroplasty · Periprosthetic knee infection · Cement spacer · PJI

Introduction

Periprosthetic joint infection (PJI) is one of the most severe complications of total knee arthroplasty (TKA), with a reported incidence of 0.7–2% [1]. As the number of total joint replacements is constantly rising, the incidence of PJI is expected to increase [2]. Several treatment strategies are available for PJI. Antibiotic suppressive therapy alone is insufficiently effective in the presence of biofilm formation; antibiotics are therefore considered only when surgery is contraindicated.

Two-stage reimplantation is the gold standard strategy for chronic infections and provides good clinical results and a high eradication rate. Despite the standardization of two-stage exchange protocols for knee PJI, failure still occurs in 4–17% of cases [3, 4].

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Several factors can influence the results of two-stage knee revisions, including comorbidities, previous surgeries, bone stock, soft tissue damage, microbiological features, and antibiotic resistance [5–9].

Identifying specific risk factors for treatment failure in two-stage TKA is important to optimize clinical outcomes and properly guide the patient's care in a way that provides the greatest chance of success. Several studies have attempted to analyze variables influencing the failure of PJIs following a two-stage protocol [5–15]. However, these studies were limited due to the use of a small number of variables, a limited series, a short follow-up, and an unstandardized definition of failure.

The purposes of this present study were as follows: (1) to identify the potential risk factors predicting the failure of two-stage revision for PJI; (2) to analyze implant survival of two-stage revision at mid-term follow-up; and (3) to analyze the clinical functional outcomes of patients who completed the two-stage procedure.

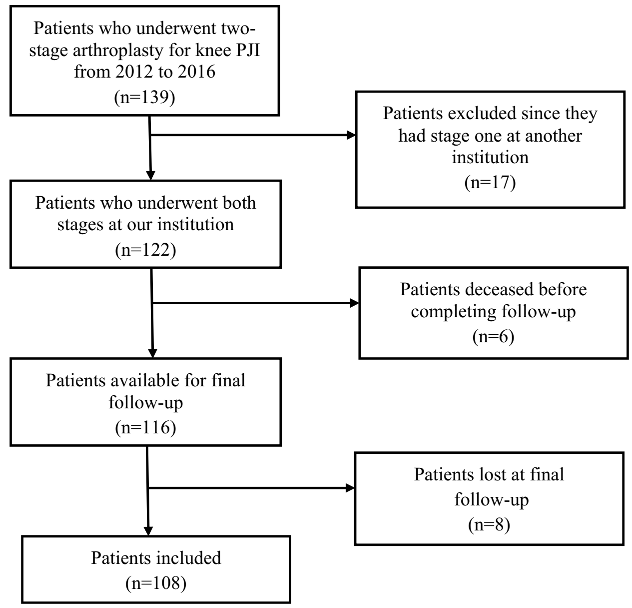

Fig. 1 Flowchart of patients selection process

Materials and methods

Study design and participants

This retrospective, single-center study was approved by the local ethical committee (181/2018), and written, informed consent was obtained from all the participants before the two-stage procedure. Data were gathered from the prospectively collected institutional arthroplasty registry.

Inclusion criteria required participants who had completed the two-stage exchange for knee PJI, had been diagnosed according to the Musculoskeletal Infection Society criteria [10, 16, 17], and who had reached a minimum two-year follow-up. Patients were excluded if they had undergone two-stage procedures for septic arthritis of the native knee, had received the first stage of the two-stage procedure outside of our institution, or had not completed the second stage for any reason, including because of a retained spacer, arthrodesis, amputation, or death. Data on 139 patients who completed the two-stage revision for chronic knee PJI between January 2012 and January 2016 were retrieved for this study. Seventeen patients were excluded because they underwent the first stage outside of our institution, six were excluded because they were deceased at the time of final follow-up, and eight patients were excluded because they were not available for final follow-up (Fig. 1).

Two-stage protocol

All procedures were performed by the same surgeon (G.B.), experienced in complex septic knee revision surgery. During the first stage, the infected TKA was removed, and extensive debridement of the residual bone and soft tissues, as well as irrigation with an antiseptic solution, were performed. Six samples of tissue were routinely retrieved for microbiological analysis. Subsequently, a preformed articulating cement spacer loaded with gentamycin was implanted. Spacers were loaded with gentamycin + vancomycin when the preoperative antibiogram detected methicillin/oxacillin-resistant pathogens or streptococci sensible to vancomycin. In cases where an extensor mechanism disruption occurred, a non-articulating antibiotic-loaded cement block was implanted. Intravenous broad-spectrum antibiotic therapy was administered for at least 2 weeks; then, based on microbiological analysis, a targeted oral or intravenous therapy was given for further 4 weeks. During the second stage, the spacer was removed and another debridement was performed. In all cases, three to six samples were collected for microbiological analysis, as were specimens for frozen section histology. Depending on the cases cultures were managed with intravenous administration of glycopeptides and fluoroquinolones for 3 weeks followed by oral fluoroquinolones for at least 4 weeks, or at least 6 weeks of antibiotic therapy based on previous antibiograms. When antibiotics were completed, the patients underwent a 2-weeks "antibiotic holiday" and were reassessed clinically, and through serum biomarker. If considered free from infection they were reimplanted.

Cases of septic recurrences during the inter-stage period were managed with a spacer exchange.

The level of bone defect was intra-operatively classified according to the Anderson Orthopedic Research Institute (AORI) [4] classification, as determined by the senior author.

After the second stage with reimplantation of the TKA, antibiotic therapy was administered until the intraoperative microbiology results were available and thereafter, if necessary. On the second postoperative day, the surgical drain was removed, and partial weight-bearing was allowed. Thromboembolism prophylaxis was administered for at least 45 days post-surgery.

Data collection and outcome measures

From the institutional arthroplasty register, patients' demographic characteristics (age, gender, body mass index [BMI], American Society of Anesthesiologists [ASA] physical status classification, and smoking status) and surgical variables (preoperative erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP], the number of previous surgeries on the assessed knee, the presence of difficult-to-treat [DTT] infections, and the AORI level of bone defects) were collected. The design of removed implants, final prosthetic design, the use of metaphyseal devices, the duration of the interstage interval, and operative times were also reported. Knee function was assessed using the Knee Society Score (KSS) [18], the Oxford Knee Score (OKS) [19], and the range of motion (ROM) registered preoperatively and at the final follow-up. Causative agents, such as enterococci, methicillin/oxacillin, or vancomycin-resistant staphylococci; extended-spectrum beta-lactamase (ESBL)-producing bacteria; multidrug-resistant organisms (MDROs); and polymicrobial and mycotic infections, were considered DTT infections [20]. Failure was defined as any re-revision or reoperation at the indexed knee occurring during the follow-up period due to septic recurrence or mechanical complication (such as aseptic loosening or dislocation), reinfection, persistent infection in the spacer, limb loss, or death due to infection by causative organism. Cases that required antibiotic suppressive therapy were considered failures. Septic recurrence was defined as a PJI of the involved joint sustained by the same microorganism (type and antibiogram) previously isolated during the staged revision.

Statistical analysis

Binomial logistic regression was conducted to ascertain the effect of age, gender, BMI, ASA, smoking status, preoperative CRP, number of previous surgeries, the degree of bone defect, and DTT infections on the likelihood that a patient will experience failure.

The receiver operating characteristic (ROC) curve was used to assess the binomial logistic regression model's level of discrimination.

Kaplan–Meier functions were generated to evaluate the survival of implants from at the final follow-up.

Preoperative values of KSS and OKS were compared to those obtained at the last follow-up using the paired *t* test. The distribution of these variables was assessed with the Shapiro–Wilk test. Categorical variables were reported as percentages or number of cases. Continuous variables were reported as mean ± standard deviation. Statistical analysis was performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). For all variables, statistical significance was set at $p < 0.05$.

Results

The final cohort included 108 patients (108 knees) with a mean follow-up of 52.9 ± 15.6 (range 26–91) months. The mean age at reimplantation was 66.6 ± 9.2 (range 43–84) years. Fifty-two (48.1%) patients were female, and 56 (51.9%) patients were male. The mean body mass index (BMI) was 27.1 ± 4.4 (range 20.6–37.9) kg/m^2. The patients' demographic features are provided in Table 1. Causative pathogens are listed in Table 2. Surgical approaches, details on previous implants, the level of bone defects, and prosthetic components implanted in the second stage are presented in Table 3.

Predictors of two-stage failure

Of the ten variables assessed, only three significantly predicted the risk of treatment failure: the presence of DTT infections (OR = 4.2, 95% CI 1.2–14.5, $p = 0.025$), the number of previous surgeries on the affected knee (OR = 1.8, 95% CI 1.2–2.6, $p = 0.005$), and the tibial AORI classification (OR = 2.3, 95% CI 1.1–4.7, $p = 0.027$), as shown in Table 4. Patients with DTT infections had a 4.2 times higher risk of treatment failure than patients without DTT infections. The logistic regression model used was statistically significant χ^2 (8) = 40.3, $p < 0.001$. The model explained 47.7% of the treatment failure variance and correctly classified 85.2% of the cases. The area under the ROC curve was 0.872 (95% CI, 0.787 to 0.957), which corresponds to an excellent level of discrimination (Fig. 2).

Survival analysis

The overall survival of two-stage failure was 77.8% at a mean follow-up of 52.9 ± 15.6 months. Failure due to septic recurrence occurred in 14 (13.0%) cases.

When patients were stratified according to the presence of DTT pathogens, the number of previous surgeries, and the level of bone defects, a log-rank test demonstrated significant different survival distributions in patients with DTT infections vs non-DTT infections, χ^2 (1) = 14.1, $p < 0.001$ (Fig. 3A), number of previous surgeries > 2 vs ≤ 2, χ^2

Table 1 Demographics and general features of the study population

Variables	Number of cases (%)	Mean (range) ± SD
Age (years)	108 (100)	66.6 (43–84) ± 9.2
BMI (kg/m^2)	108 (100)	27.1 (20.6–37.9) ± 4.4
Gender		
Female	52 (48.1)	
Male	56 (51.9)	
Side		
Left	57 (52.8)	
Right	51 (47.2)	
Smoking status		
Yes	23 (21.3)	
No	85 (78.7)	
ASA		
1	5 (4.6)	
2	37 (34.3)	
3	49 (45.4)	
4	17 (15.7)	
Number of previous surgeries	108 (100)	2.3 (1–7) ± 1.4
Preoperative CRP (mg/L)	108 (100)	5.5 (0.1–16.8) ± 4.0
Preoperative ESR (mm/hr)	56 (50.5)	51.9 (5.0–106.0) ± 29.2
Interstage interval (w)	108 (100)	21.8 (8.9–75.4) ± 12.5
Operative time (min)		
First stage	107 (99.1)	122.6 (55.0–255.0) ± 33.0
Second stage	106 (98.1)	140.0 (55.0–300.0) ± 39.1
Follow-up (m)	108 (100)	52.9 (26–91) ± 15.6

ASA, American Society of Anesthesiologists index; *BMI*, body mass index; *CRP*, C-reactive protein; *ESR*, erythrocyte sedimentation rate; *F*, female; *hr*, hours; *L*, left; *m*, months; *M*, male; *mg*, milligrams; *mm*, millimeters; *min*, minutes; *SD*, standard deviation; *w*, weeks

(1) = 22.3, $p < 0.001$ (Fig. 3B), major femoral bone defects (AORI 2B and 3) vs minor defects (AORI 1 and 2A), χ^2 (1) = 11.3, $p = 0.001$ (Fig. 3C), and major tibial defects vs minor tibial defects, χ^2 (1) = 8.5, $p = 0.003$ (Fig. 3D).

Causes of failure were septic recurrence during the interstage period (8 cases, 7.4%), which was managed in all cases with spacer exchange; septic recurrence after revision of TKA (6 cases, 5.6%), which required a further two-stage procedure in four cases and suppressive therapy in two cases; aseptic loosening of the tibial component (4 cases, 3.8%) managed through component revision; liner subluxation (4 cases, 3.8%) managed with liner substitution; and stiffness (2 cases, 1.9%), which required liner substitution and arthrolysis. No mortality or limb loss directly related with the procedure were reported.

Functional outcomes

The mean KSS significantly improved ($p < 0.001$) from a preoperative value of 49.0 ± 12.0 to 80.2 ± 13.6 points at the last follow-up (Fig. 4A). The mean OKS significantly improved ($p < 0.001$) from preoperative 22.2 ± 4.9 to 36.1 ± 6.0 points at the last follow-up (Fig. 4B). The mean extension lag decreased from preoperative 6.1 ± 6.5° to 0.8 ± 2.5° at final follow-up ($p < 0.001$) (Fig. 4C). The mean range of flexion increased from 57.2 ± 16.0° to 94.3 ± 14.1° (Table 5).

Discussion

PJI is a devastating complication of TKA, representing the main cause of revision. Two-stage revision is considered the gold-standard treatment in cases of chronic PJI since it has been demonstrated to provide high rates of infection eradication and good functional outcomes and pain control. In some specific settings, one-stage revision showed similar results [15, 21]. However, despite the standardization of diagnostic pathways and treatment protocols, failure still occurs in a considerable percentage of patients [4, 22, 23]. Addressing groups of patients at a high risk of two-stage arthroplasty failure is one of the major issues for orthopedic surgeons facing musculoskeletal infections.

Table 2 Microbiological details of pathogens involved in periprosthetic knee infections

Pathogens	Number of cases (%)
MSSA	14 (13.1)
OSSA	7 (6.5)
MSSE	8 (7.4)
OSSE	5 (4.6)
Other CoNS	9 (8.3)
Streptococci	6 (5.6)
Gram-negative	11 (10.2)
Culture-negative	16 (14.8)
DTT infections	
Resistant *Staphylococci*	13 (12.0)
ESBL	3 (2.8)
MDRO	3 (2.8)
Enterococci	4 (3.7)
Polymicrobial	7 (6.5)
Mycotic	2 (1.9)
Total	108 (100.0)

MSSA, methicillin-sensible *staphylococcus aureus*; *MSSE*, methicillin-sensible *staphylococcus epidermidis*; *OSSA*, oxacillin-sensible *staphylococcus aureus*; *OSSE*, oxacillin-sensible *staphylococcus epidermidis*; *CoNS*, coagulase-negative staphylococci; *DTT*, difficult-to-treat; *ESBL*, extended-spectrum beta-lactamase-producing bacteria; *MDRO*, multiple drug-resistant organism

In our study, three factors independently predicted an increased risk of failure: infections sustained by DTT pathogens, the number of previous surgeries (> 2), and the tibial AORI levels of bone defects. The literature shows that both patient-related and microbiological factors could influence the success of two-stage procedures. Several comorbidities, such as obesity, diabetes, smoking, chronic cardiovascular disease, and inflammatory arthritis, have been addressed as potential predictors of total knee revision failure [24–27]. These systemic comorbidities should have an influence on ASA score classification, such that an increased ASA level should reflect an increased risk of failure. Nevertheless, the statistical model used in the present study did not identify ASA index, BMI, and smoking as predictors of failure. This may be because the study was conducted in a tertiary care referral center where compromised patients with several comorbidities are frequently encountered, limiting the statistical relevance of some conditions as potential predictors. The levels of serum markers, such as ESR and CRP, are routinely used to assess patients with PJI. However, the ability of these markers to predict failure after reimplantation has not been documented. In the present study, the patient's level of serum CRP was not identified as a risk factor for failure. This finding is in accordance with previous studies that described a limited role for serological markers in staged procedures [7, 28, 29]. Recently, Hong et al. [30] proposed the CRP/albumin ratio as a reliable index to predict reimplantation success. However, the albumin levels of patients included in this study were not always available; thus, CRP/albumin index was not tested as a possible predictor. Moreover, we point out that other laboratory findings, such as levels of synovial white blood cells, serum fibrinogen, and D-dimer, which are believed to have a role in guiding reimplantation, were not always available. The present study demonstrated that patients with wide tibial defects (AORI 2A or 3) had a 2.3 times higher risk to undergo revision TKA failure (95% CI 1.1–4.7, $p = 0.027$).Previous studies have associated major bone defects (AORI 2B or 3) to poor outcomes of staged procedures, suggesting longer exposure times as the underlying cause [7]. The association between the extension of bone defects and the risk of failure

Table 3 Surgical approach, type of implants removed, level of bone defect, and final prosthetic configuration

Variables	Frequency	%
Surgical approach		
Medial parapatellar	94	87.0
Lateral parapatellar	2	1.9
Medial parapatellar + medial gastrocnemius flap	8	7.4
Medial parapatellar + TTO	4	3.7
Total	108	100.0
Level of constraint of previous implants		
UKA	9	8.3
PS	69	63.9
CCK	19	17.6
RHK	11	10.2
Total	108	100.0
AORI femur		
1	25	23.1
2A	27	25.0
2B	30	27.8
3	26	24.1
Total	108	100.0
AORI tibia		
1	31	27.4
2A	18	12.8
2B	33	33.7
3	26	26.3
Total	108	100.0
Level of constraint of final implants		
PS	16	14.8
CCK	57	52.8
RHK	35	32.4
Total	108	100.0

AORI, Anderson Orthopedic Research Institute score; *CCK*, condylar constrained knee; *PS*, posterior stabilized; *RHK*, rotating hinged knee; *TTO*, tibial tubercle osteotomy; *UKA*, unicompartmental knee arthroplasty

Table 4 Logistic regression predicting the likelihood of two-stage revision failure based on Age, gender, BMI, ASA, number of previous surgeries, preoperative CRP, type of infection, and bone defect classified according to the AORI system

Variables	*p* value	Odds ratio	95% C.I. for Odds Ratio	
			Lower	Upper
Age	0.157	0.951	0.888	1.019
Gender	0.681	0.769	0.220	2.684
BMI	0.117	10.117	0.973	1.283
Smoking status	0.525	0.618	0.140	2.721
ASA	0.813	0.908	0.409	2.016
Number of previous surgeries	0.005	1.756	1.190	2.592
Preoperative CRP	0.502	0.949	0.815	1.105
Type of infection	0.025	4.169	1.195	14.540
AORI femur	0.305	1.405	0.734	2.687
AORI tibia	0.027	2.264	1.099	4.663

AORI, Anderson Orthopedic Research Institute score; *ASA*, American Society of Anesthesiologists index; *BMI*, body mass index; *CRP*, C-reactive protein; *S.E.*, standard error

Type of infection is for DTT infection compared to non-DTT infections. Gender is for male compared to female. Smoking status is for smokers compared to non-smokers

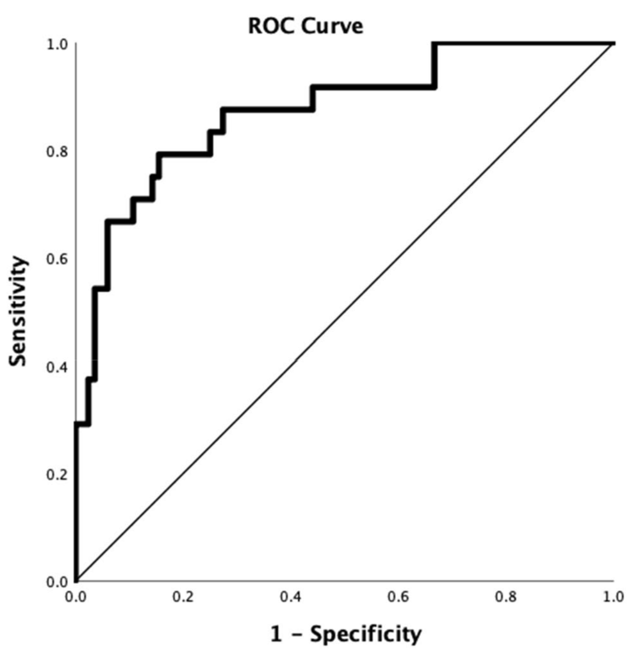

Fig. 2 ROC curve assessing the level of discrimination of the logistic model used

can be further explained considering that mechanical causes leading to reoperation (such as aseptic loosening and liner subluxation) were included in the definition of treatment failure. Moreover, massive tibial bone loss often involves tibial tuberosity, heavily impairing the knee extensor mechanism and the final outcome. This study found that patients who underwent more than two knee surgeries prior to the two-stage protocol had a 1.8 times higher risk of having a poor outcome (95% CI 1.2–2.6, $p = 0.005$). The number of previous surgeries may influence the likelihood of success in several ways. Patients who underwent a high number of surgeries on the same knee are more likely to present with wider bone defects and soft tissue disruptions. Soft tissue management in staged revision dramatically affects operative times and makes the mechanical balancing of implants more challenging. Furthermore, previously administered antibiotics in the course of earlier surgical attempts may have caused the selection of resistant pathogens. The presence of specific organisms may be associated with a high risk of septic recurrence. Resistant staphylococci, enterococci, polymicrobial, and mycotic infections have been shown to significantly reduce the rate of control of periprosthetic knee infections and are generally referred to as DTT [26, 31–34]. Our analysis demonstrated that patients suffering from DTT infections had a 4.2 times (95% CI 1.2–14.5, $p = 0.025$) higher risk of undergoing treatment failure, supporting previous evidence available in the literature. For successful management of DTT infections, multiple systemic antibiotic therapies may be required; thus, close collaboration with an infectious disease team is necessary. Although statistical significance was not reached and prediction analysis was not possible, it is important to remember that patients who have had prior trauma surgeries are vulnerable to particular critical issues. The presence of fixation devices (such as plates and screws) may contribute to ongoing infection due to biofilm formation and may complicate surgical debridement, making it more technically demanding and requiring longer operative times. Subsequently, these patients often have wide bone deficits and axial mechanical deviations that could require stepped or custom-made prosthetic components.

The survival analysis revealed 77.8% of cases to be considered successful at final follow-up. This is lower than most of the earlier results published, with some reporting success rates over 90% [4, 7, 14, 35]. We hypothesized that the main cause of this discordance is the different definitions of treatment failure. We defined failure by referring to a broad range of septic and mechanical complications requiring reintervention, whereas the treatment success of two-stage procedures is frequently defined as the absence of septic recurrences. However, it is the opinion of the authors that any mechanical complication requiring reoperation should be considered a failure since these complications have a considerable impact on the patient's quality of life, putting patients at further risk of septic recurrence.

It is important to note that significant limitations characterize this study. This was a retrospective analysis with the possibility of bias inherent in all retrospective studies.

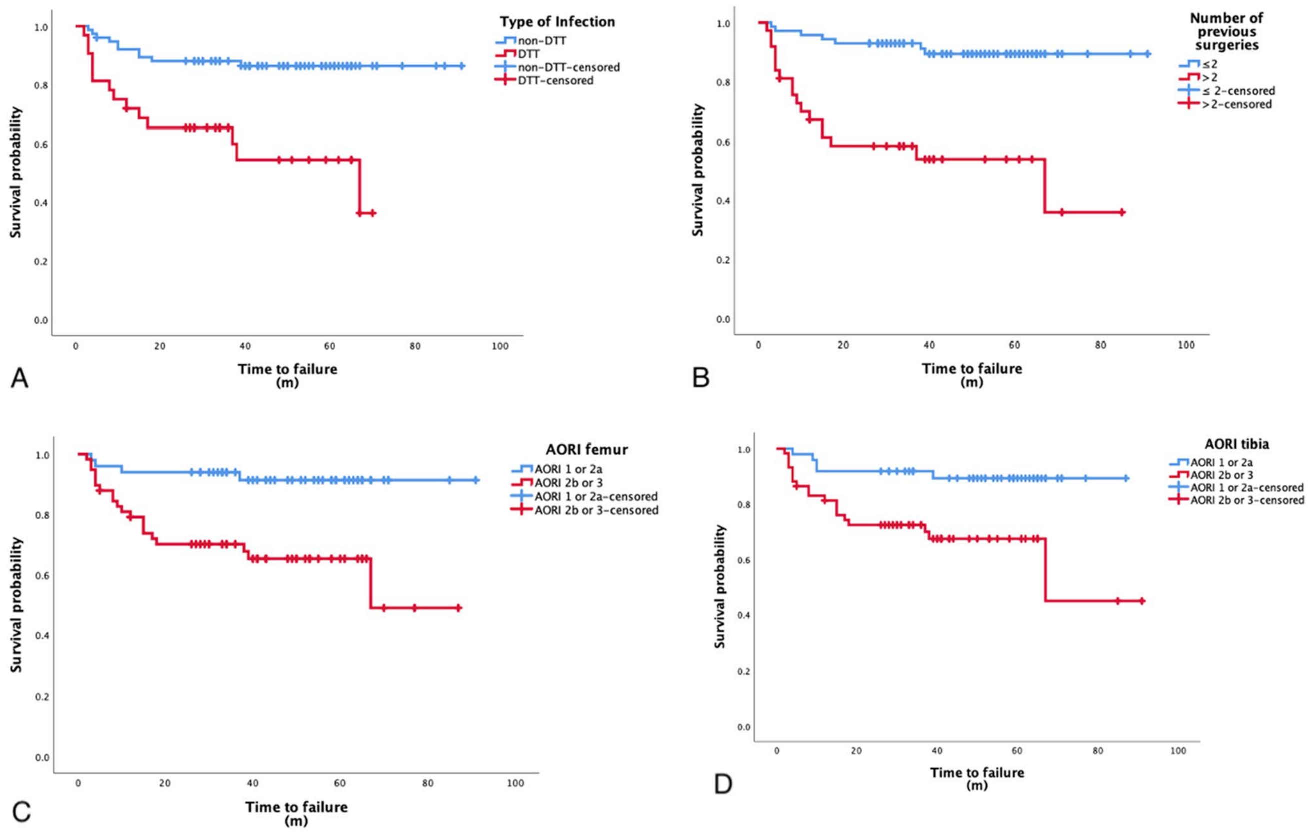

Fig. 3 **A**–**D** Survival curves of two-stage revision from treatment failure. **A** Patients were stratified for type of infection (DTT vs non-DTT). **B** Number of previous surgeries. **C** According to the femoral AORI **D** According to the tibial AORI

Patients who did not undergo reimplantation were not included in this study; thus, the investigation focused on patients deemed the best candidates to whitstand a two-stage procedure. Furthermore, the procedures were conducted in a tertiary care referral center for musculoskeletal infections, introducing a selection bias as the condition of the patients enrolled may be more complex since they were often referred to our institution after several attempts to solve the infection. However, the prospective collection of data, the fact that the standardized diagnosis and two-stage protocols were performed by the same surgeon, and the consecutiveness of patients over a restricted time interval are strengths of this analysis.

Conclusion

Despite providing good functional outcomes, two-stage revision is associated with a high treatment failure rate (22.2%). This study found the presence of DTT pathogens, the number of previous surgeries on the same joint, and the level of tibial bone defect to each independently predict the risk of failure. When counseling patients with knee PJI, surgeons must be aware of the influence of these factors on the final outcome. Further studies with larger sample sizes are needed to clearly confirm which factors can influence treatment success and to guide surgeons to the appropriate management of knee PJI.

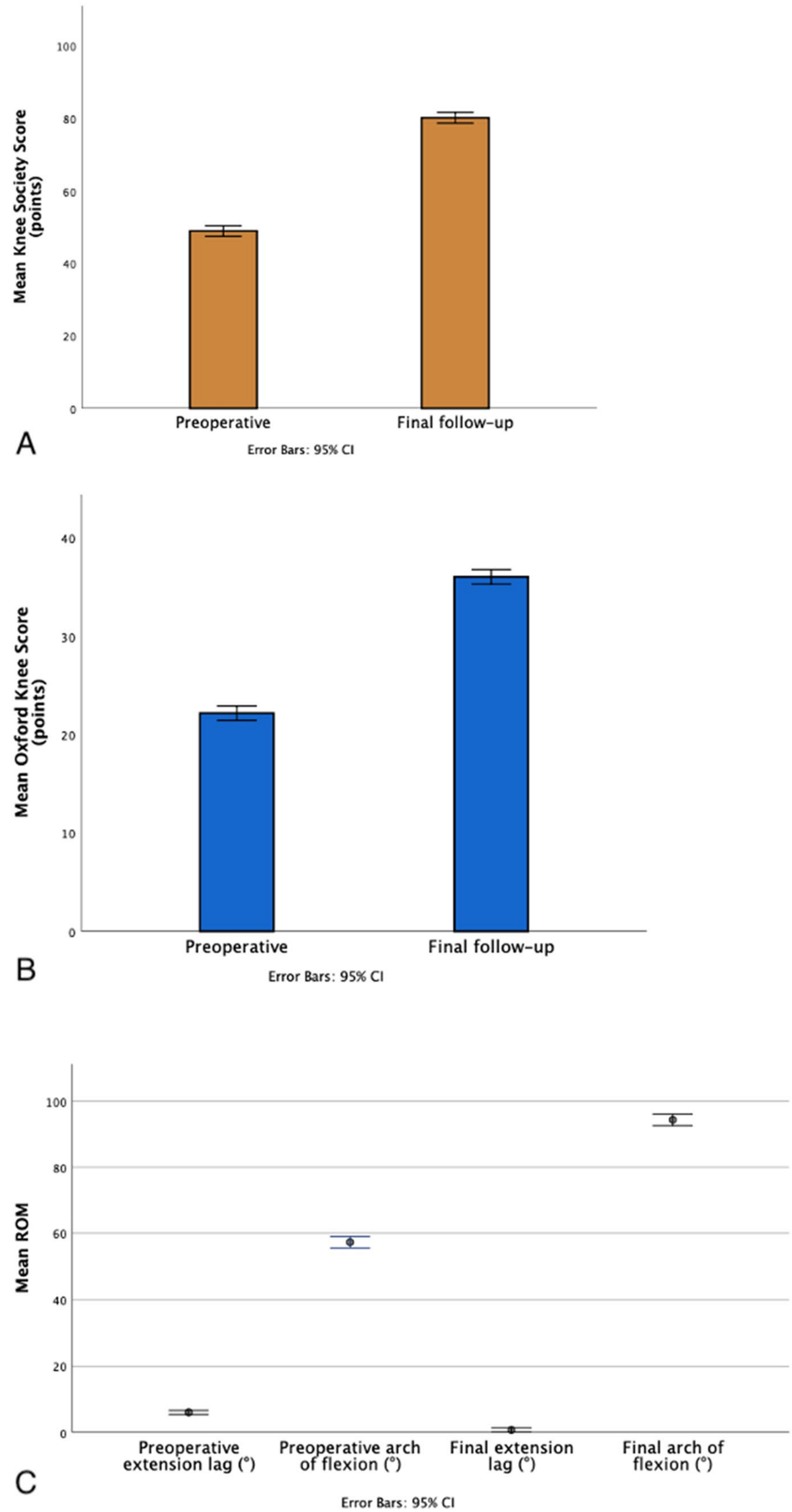

Fig. 4 **A**–**C** Bar graphs presenting statistically significant improvement ($p < 0.001$) of mean KSS, mean OKS, and ROM from preoperative values to values registered at final follow-up

Table 5 Functional outcomes and radiographic alignment registered preoperatively and at last follow-up

Variables	Number of cases (%)	Preoperative(range) ± SD	Final follow-up(range) ± SD	*p* value
Extension lag (°)	108 (100.0)	6.1 (-5.0–10.0) ± 6.5	0.8 (-5.0–10.0) ± 2.5	<.001
Arch of flexion (°)	108 (100.0)	57.2 (15.0–90.0) ± 16.0	94.3 (40.0–125.0) ± 14.1	<.001
KSS (points)	108 (100.0)	49.0 (23.0–75.0) ± 12.0	80.2 (19.0–96.0) ± 13.6	<.001
OKS (points)	108 (100.0)	22.2 (4.0–34.0) ± 4.9	36.1 (10.0–46.0) ± 6.0	<.001
FT angle (°)	108 (100.0)	4.2 (-9.0–12.0) ± 3.3	5.4 (1.0–10.0) ± 1.5	<.001

FT, femorotibial, *KSS*, Knee Society Score; *L*, left; *M*, male; *OKS*, Oxford Knee Score; *ROM*, range of motion; *SD*, standard deviation

p value refers to paired t-test comparison of mean values registered before two-stage revision and at final follow-up

Author contributions AR: data analysis, methodology, original draft writing. LC: conceptualization, original draft writing. FC: conceptualization, data collection and material organization. MA-M: review and editing of the original draft. LF and GB: supervision, project administration, review and editing of the original draft.

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Availability of data and material Complying with field standards.

Declarations

Conflict of interest The authors declare that there is no conflict of interest.

Ethics approval Approved by the local institutional review board.

Consent to participate Patients gave their informed consent to participate this study.

Consent for publication Patients gave their consent to publish clinical data contained in this study.

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