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ORIGINAL PAPER

Factors associated with infection recurrence after two-stage exchange for periprosthetic hip infection

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Abstract

Purpose Two-stage exchange is the treatment of choice for periprosthetic joint infection (PJI). Factors and outcomes associated with infection recurrence for hip PJI are limited. The primary aim of this study was to determine factors associated with infection recurrence after two-stage exchange. Secondary aims were survival, mobility, and the EuroQol five-dimension scale (EQ-5D-5L) health state.

Methods We retrospectively investigated patients with two-stage exchange for hip PJI at our institution from 2006 to 2017. Follow-up was conducted for a minimum of four years after the reimplantation.

Results We included 135 patients with 139 hip PJIs. The mean age of the patients was 69.6 years (range 32–88). The infection recurrence rate was 14.4% ($n=20$) after a mean follow-up of 8.0 years (range 4.0–13.1). Four factors for recurrence were identified at the time of the first stage: previous orthopaedic diagnoses ($p<0.001$), type of explanted prosthesis ($p=0.004$), cultured microorganisms ($p=0.033$), and sinus tract ($p=0.035$). A longer surgical reimplantation time ($p=0.015$) was the only one factor found at the second stage. The estimated Kaplan–Meier survival for the total sample was 9.0 years (95% confidence interval 8.3–9.8), without significant difference for those with infection recurrence compared to recurrence-free patients (log-rank 0.931). At the time of follow-up, 89 patients were alive. For these patients, Parker mobility score ($p=0.102$), EuroQol five-dimensional scale ($p=0.099$), and EQ Visual Analogue Scale (EQ-VAS) ($p=0.027$) were inferior in those with infection recurrence, but significance was found only for VAS.

Conclusion In this study with mid- to long-term follow-up, five factors for infection recurrence were identified. Recurrence did not affect survival, but health-related quality of life was inferior compared to recurrence-free patients. The results suggest that the period of the first stage including previous orthopaedic diagnoses requires more consideration in the future.

Keywords Hip arthroplasty · Complications · Outcome · Health-related quality of life · Survival

Introduction

Surgery and antimicrobial therapy are recommended for the treatment of periprosthetic hip joint infection (hip PJI) [1]. One-stage revision or girdlestone procedures have been reported for hip PJI, but two-stage revision surgery is considered the gold standard [2–5]. However, the optimal treatment regimen remains unclear [6]. Most recommendations are based on expert opinions or small sample sizes rather than on high-level evidence [2, 7, 8]. A systematic review reported that only 9 of 60 studies included a sample size of > 100 patients [6], and many questions remain unresolved. For example, details regarding resection, time interval between explantation and reimplantation [5, 9, 10], and duration of antibiotic therapy were not standardized among studies [10, 11]. Finally, studies on factors possibly involved in infection recurrence are limited [8, 12]. We conducted this retrospective study to compare factors and outcomes in patients with and without infection recurrence after two-stage exchange for hip PJI.

The primary aim of this study was to identify factors associated with infection recurrence and to determine effects between patients with recurrence and recurrence-free patients. The secondary aim was to assess survival, mobility, and health-related quality of life (HRQoL) for the two groups.

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Materials and methods

This study was conducted in our academic centre as a retrospective review according to the principles of the World Medical Association Declaration of Helsinki. The study was approved by the Ethics Committee (No. 19–1529-104). Data were retrieved from our electronic medical records, and informed consent was obtained from all patients who participated in follow-up.

The inclusion criteria were as follows: hip PJI based on the Working Group of the Musculoskeletal Infection Society [13], signs of infection starting a minimum of four weeks after index implantation or last aseptic exchange surgery based on the Garvin and Hanssen classification [14], and treatment with a two-stage exchange protocol. Patients who were admitted from other hospitals for subsequent treatment after starting operative infection control with one or more irrigations, debridements, modular liner exchanges, or those with additional septic or systemic infections were included. Therefore, our sample was an unselected consecutive group. Four patients with hip PJI on one side and later on the contralateral side were included twice.

Patients who underwent one-stage exchange, implant retention, or definitive resection arthroplasty were excluded. Six patients with two-stage exchange for hip PJI were excluded due to hip sarcoma ($n=2$), simultaneous acetabular fracture ($n=2$), and ipsilateral knee PJI ($n=2$); two patients were lost to follow-up.

Baseline characteristics included age, sex, affected side, and body mass index (BMI; kg/m^2). Comorbidities were assessed according to the American Society of Anesthesiologists (ASA) [15]; individual comorbidities are given in Table 1. Eighteen characteristics, including cultured microorganism, were examined at the first stage; ten characteristics were evaluated at the second stage.

Finally, at a minimum of four years after reimplantation, a telephone interview was conducted with living patients or with their relatives in cases of death. Possible missing data were assessed, and HRQoL outcomes were evaluated for living patients.

Patient mobility was assessed with the Parker score [16]. A minimum of zero points represents bedridden, and a maximum score of 9 points is given for walking ability for shopping without assistive devices.

The EQ-5D-5L® (EuroQol Research Foundation 2019, 3068 AV Rotterdam, Netherlands; registration number 43820 for this study) instrument comprises five dimensions, which each having five response levels of severity: no problems and slight, moderate, severe, or extreme problems. The calculated index values range from 1000 (best health) to − 0.205 (worst health status) for our country. The Visual Analogue Scale (EQ-VAS) ranges from the best (100 points) to the worst (0 points) current health state that the interviewed patient can imagine [17, 18].

Infection recurrence was defined as relapses (infection was due to the initial causative pathogen) or new infection (infection due to different pathogens compared to the pathogen isolated at the first stage), as per the criteria of the Working Group of the Musculoskeletal Infection Society [13].

Table 1 Baseline characteristics of the sample

Variable	No recurrence ($n=119$)	Recurrence ($n=20$)	p value
Age in years*	73.0 (10.6)	68.5 (10.6)	0.100
Male sex—no	60	15	0.053
Right side—no	59	12	0.472
Body mass index in kg/m^2*	28.9 (6.2)	28.6 (6.2)	0.971
ASA 2—no	37	7	
ASA 3—no	82	13	0.796
Comorbidities—no			
Heart failure/coronary artery disease	46	5	0.319
Hypertension	83	11	0.205
Diabetes	28	7	0.277
Alcoholism	20	7	0.070
Smoking history	15	2	1.000
Rheumatic disease/cortisone therapy	4	0	1.000
History of neoplasia	18	4	0.524

*Values are given as the mean, with the standard deviation (± SD) in parentheses

ASA American Society of Anesthesiologists

Two-stage exchange protocol

In the first stage, implants, including any cement, screws, cables, and wires, were removed. For this purpose, we used the index approach. Femoral osteotomy was performed to remove well-fixed stems. After complete implant removal, debridement and irrigation of the bone and tissue with at least 6 l of normal saline were conducted, usually with pulsatile lavage. Additionally, the surgical site was irrigated with an antiseptic solution. At least five different tissue samples were obtained for microbiological and histological analyses. Sonication of the components was not routinely performed. Cement spacers were used in selected cases, such as after proximal femoral resection. After tissue sampling, antibiotic therapy was started intra-operatively with intravenous third-generation cephalosporin and administered post-operatively according to the results of the antibiogram. In most cases, a double regimen was administered. Antibiotic therapy was given for two weeks intravenously, followed by oral therapy for four weeks. Subsequently, antibiotic therapy was stopped for two weeks, and the patients underwent joint needle aspiration to examine infection control. The criterion for reimplantation was no signs of infection or negative joint aspiration (cultivation for 2 weeks). Therefore, the time of reimplantation was routinely later than ten weeks after explantation. In cases with signs of infection between the first and second stages, debridement and irrigation were repeated.

The second stage was performed using the same surgical approach. According to the experiences of the senior surgeons and patients' bone quality, cementless Wagner® ($n=91$) or Spotorno® stems ($n=32$), cemented Müller® stems ($n=10$), or proximal femoral replacements ($n=6$) were used. Appropriate cups were used for the hip socket (cementless Allofit® cups, cemented Durasul® flat profile cups, or tripolar cups), with or without Burch-Schneider® or Müller® reinforcement cages (all implants manufactured by Zimmer Biomet, Freiburg, Germany). Three patients were treated with a custom-made partial pelvic replacement. Trabecular metals or structural bone allografts were not used. Antibiotic treatment was started intra-operatively after biopsy and with the same intravenous mode as that used after the first stage. In cases with negative tissue samples, treatment was completed within 14 days; in cases with positive cultures, the regimen was administered six weeks post-operatively. Suppressive antibiotic therapy was not employed. Patients were routinely evaluated for up to two years post-operatively with radiological and clinical examinations at our institution.

Statistical analysis

The Kolmogorov–Smirnov test was applied to determine the distribution of the variables, with some showing a normal distribution. Mann–Whitney *U* tests were used to compare two independent samples, and Fisher's exact test was used for unadjusted comparisons of proportions. Pearson's chi-squared tests were used for unadjusted comparisons of ordinal distributions. Data are presented as mean values with standard deviations or as percentages. Kaplan–Meier survival analysis was employed to evaluate survival [19] and log-rank tests to compare survival probabilities. All statistical tests were two-sided, and statistical significance was set at $p<0.05$. SPSS software for Windows (version 24.0; SPSS, Chicago, IL, USA) was used for all analyses.

Results

Baseline characteristics

Between 1 January 2006 and 31 August 2017, a total of 135 patients with 139 hip PJIs underwent two-stage exchange. After a mean follow-up of 8.0 years (range 4.0–13.1), we observed 20 infection recurrences (14.4%) with 18 relapses and two new infections. The mean patient age at the time of reimplantation was 69.6 years (range 32–88), and men ($n=75$) were more affected than women ($n=64$). The baseline characteristics are shown in Table 1, with no significant differences between the two groups.

Infection recurrence

Twenty infection recurrences were assessed at a mean period of 11.0 months (range 0–118) after reimplantation. Eleven cases occurred within one year, and four cases occurred later than four years after the second stage. Treatment for infection control included antibiotic therapy with definitive girdlestone resection ($n=10$), complete and successfully repeated two-stage exchange ($n=3$), and irrigation and debridement with component retention ($n=6$), which resulted in three fistulas. One patient was treated non-operatively for a spontaneous fistula.

First stage

Factors for recurrence at the time of the first stage were previous orthopaedic diagnoses ($p<0.001$), type of explanted prosthesis ($p=0.004$), polymicrobial infection ($p=0.033$), and sinus tract ($p=0.035$).

For the orthopaedic diagnoses (Fig. 1), the lowest recurrence rate was for a first-time infected index prosthesis implanted for hip fracture (0/13, 0%) or osteoarthritis (2/78,

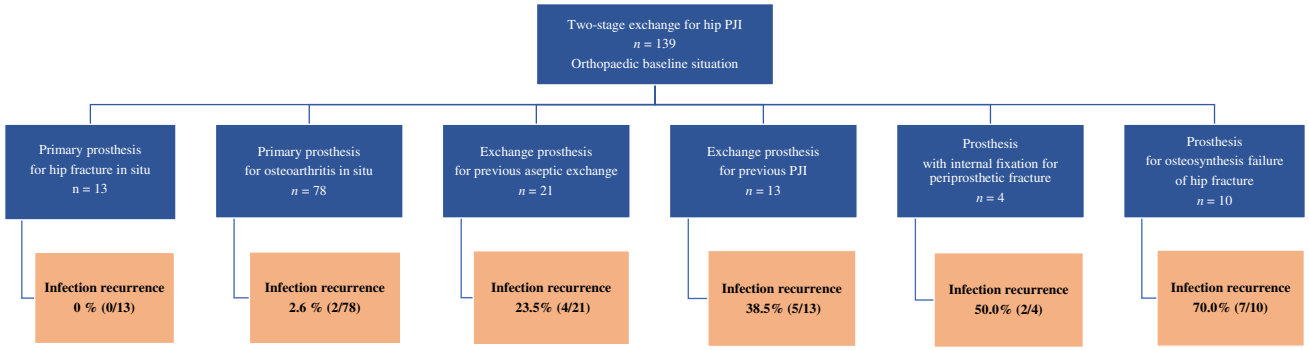

Fig. 1 Previous orthopaedic diagnoses and infection recurrence rates

2.6%). Significantly higher rates were assessed as follows: infected exchange prostheses implanted for aseptic loosening in the past (4/21, 23.5%), infection recurrence of exchange prostheses implanted for septic control in the past (5/13, 38.5%), infected prostheses with internal fixation (plates) for the treatment of periprosthetic femoral fracture in the past (2/4, 50%), and infected prostheses implanted for the treatment of osteosynthesis failure in hip fractures (7/10, 70%).

Other characteristics, such as types of stem fixation (cemented or cementless), surgical approach, or initiation of infection treatment at another hospital, were not significantly different between the two groups. The variables are presented in Table 2.

Second stage

A longer duration of surgery was the only factor associated with infection recurrence ($p = 0.015$). The duration from resection to reimplantation, need for soft tissue revision between the first stage and second stage, techniques of reimplantation (e.g., used stems and cups), preoperative blood values, perioperative red blood cell transfusions, and duration or mode of antibiotic treatment after reimplantation were not significantly different between the two groups. The variables are provided in Table 3.

Survival

The one year mortality rate for the sample size was 3.7% (5/135 patients). No patient with infection recurrence died within one year after reimplantation. The estimated Kaplan–Meier survival for the total sample size was 9.0 years (95% confidence interval (CI) 8.3–9.8 years), without differences between the groups (log-rank 0.931; Fig. 2).

Follow-up evaluation

We evaluated the outcomes of 89 patients, and all living patients were assessed (Table 4). The mean Parker score was 6.3 ± 2.6. Patients with recurrence ($n = 11$) had inferior scores compared to recurrence-free patients ($n = 78$), but the difference was not significant ($p = 0.102$). The mean calculated EQ-5D-5L index was 0.83 (95% CI 0.80–0.87), and patients with recurrence showed inferior but not significant results ($p = 0.099$). The mean EQ-VAS was 64.2 ± 15.8, and patients with recurrence had significantly lower scores ($p = 0.027$).

Discussion

In this study with mid- to long-term follow-up, we compared patients with and without infection recurrence after two-stage exchange for hip PJI. To our knowledge, this trial is the first study in which such patients are compared with the outcome measurements EQ-5D-5L and the Parker mobility score. Furthermore, mid- to long-term results are presented, and the analysis included some important variables not evaluated previously, e.g., previous orthopaedic diagnoses or the presence of contralateral hip prostheses. Finally, all living patients were assessed, and the analysis included the estimated survival time for both groups separately.

Baseline data

The baseline characteristics of this study were similar to those of published data [11, 20]. In contrast to the sex-based distribution of proximal femoral fractures [21], two-stage exchange was performed in this and other studies more frequently in men than in women [9, 11, 22, 23]. One explanation for this is that women receive more definitive girdlestone procedures [24]. In line with some previous studies, our baseline characteristics were not factors of recurrence [9, 11, 12]. In contrast, Cunningham et al. identified coronary artery disease and anaemia as recurrence risk factors [25], and Houdek et al. found a significantly higher risk of

Table 2 Factors assessed at first stage

Variable	No recurrence ($n=119$)	Recurrence ($n=20$)	p value
Previous orthopaedic diagnoses—no			<0.001
Primary prosthesis for osteoarthritis in situ	76	2	
Primary prosthesis for hip fracture in situ	13	0	
Primary prosthesis for internal failure of hip fracture in the past	3	7	
Any exchange prosthesis for aseptic loosening in the past	17	4	
Any exchange prosthesis for infection treatment in the past	8	5	
Any prosthesis with additional internal fixation for fracture in the past	2	2	
Location of index procedure—no			0.766
Another hospital	96	3	
Inside	23	17	
Type of prosthesis fixation—no			0.807
Cementless	72	13	
Cemented totally or partially	47	7	
Surgical approach—no			1.000
Lateral	109	19	
Posterior	10	1	
Type of explanted prosthesis—no			0.004
Standard prosthesis	98	12	
Revision prosthesis	14	8	
Hemiprosthesis	7	0	
Infection < 3 months after implantation—no	39	5	0.608
Time from index prosthesis to explantation in months*	75.8 (87.7)	71.3 (54.0)	0.532
Sinus tract present—no	21	8	0.035
Pus present—no	51	9	1.000
Infection treatment initiated at another hospital—no	44	7	1.000
One or more irrigations or debridements before resection—no	64	15	0.091
Any modular exchange before resection—no	42	11	0.134
Femoral osteotomy for stem explantation—no	21	4	0.759
Contralateral hip prosthesis in situ—no	46	6	0.619
Temporary antibiotic spacer—no	11	1	1.000
Systemic or septic disease—no	9	3	0.380
Cultured microorganisms—no			
Staphylococcus aureus	25	2	0.304
Staphylococcus coagulase–negative	40	6	0.807
Streptococcus spp.	22	3	0.390
Gram-negative bacteria	8	0	0.703
Gram-positive bacteria	2	0	0.546
Methicillin-resistant *Staphylococcus aureus* (MRSA)	4	3	0.089
Polymicrobial infection	13	6	0.033
Negative cultures	5	0	1.000

*Values are given as the mean, with the standard deviation (±SD) in parentheses

recurrence in patients with obesity (BMI ≥ 40 kg/m^2) [26]. In our study, seven patients had BMI ≥ 40 kg/m^2, but there was only one recurrence among them. Male sex, heart disease, and psychiatric disorders have also been reported as risk factors [20].

First stage

The most significant factors for recurrence were previous orthopaedic diagnoses. Subgroup analysis revealed a very low recurrence rate when two-stage exchange was performed in patients with a first-time infected primary

Table 3 Factors assessed at second stage

Variable	No recurrence ($n=119$)	Recurrence ($n=20$)	p value
Follow-up time in years*	7.8 (2.7)	9.2 (2.5)	0.025
Duration from explantation to reimplantation in days*	129.3 (87.4)	147.9 (112.2)	0.486
One or more revisions between explantation and reimplantation—no	44	9	0.620
Type of femoral stem used—no			0.103
Standard stem	40	2	
Revision stem	74	17	
Proximal femoral replacement	5	1	
Reinforcement cages used—no			0.070
Yes	20	7	
No	99	13	
Cups used—no			0.263
Standard cementless	51	9	
Standard cemented	48	5	
Dual mobility	20	6	
Additional trochanteric fixation (cables or plates)—no			0.904
Yes	9	4	
No	110	16	
Preoperative blood values*			
C-reactive protein (mg/L)	11.0 (17.5)	5.8 (6.4)	0.180
Haemoglobin (g/dL)	12.4 (1.9)	12.0 (2.1)	0.360
Perioperative red blood cell transfusion (units)—no	3.9	5.2	0.120
Duration of reimplantation in minutes*	149.0 (49.2)	175.5 (46.5)	0.015
Antibiotic treatment after replacement in postoperative days*			
Duration of total antibiotic treatment	20.4 (17.4)	27.9 (21.3)	0.095
Duration of intravenous antibiotic treatment	7.5 (6.6)	12.4 (9.7)	0.052
Duration of oral antibiotic treatment	12.5 (15.9)	15.6 (18.1)	0.327

*Values are given as the mean, with the standard deviation (±SD) in parentheses

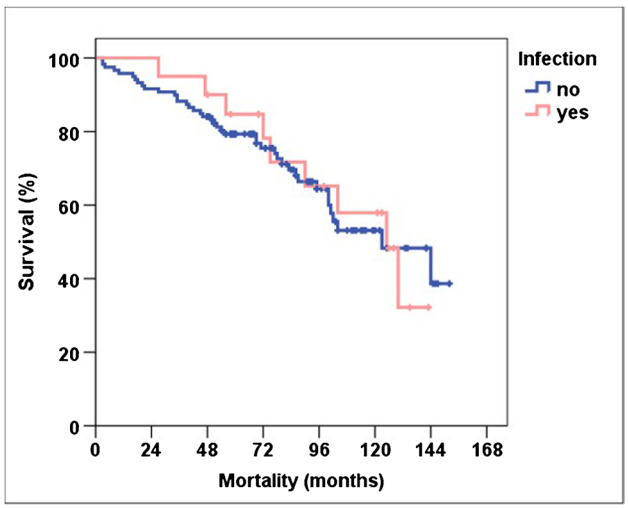

Fig. 2 Kaplan–Meier survival of patients with infection recurrence ($n=20$) and recurrence-free patients ($n=119$). The result is not significant (log-rank 0.931)

standard component, independent of the index indication (osteoarthritis or fracture) or fixation type. Therefore, we achieved favourable recurrence rates compared to other studies, with rates of 15% after ten to 15 years of follow-up and 8.8% after 4.5 years of follow-up [7, 11]. One reason for this is that our protocol was implemented for a long period of time. In cases with signs of infections after four weeks, we did not preserve the components but initiated the exchange protocol. However, in subgroup analysis of the different orthopaedic diagnoses, our infection recurrence rate reached 70% (Fig. 1). The number of cases is too low to draw any conclusion, and further studies should also include analyses of previous orthopaedic diagnoses.

Second stage

Most of the variables assessed at reimplantation were not associated with infection recurrence. The median time from resection to reimplantation was 15.1 weeks, though this interval did not predict recurrence. The mean duration of the girdlestone procedure ranges between 13 and 34 weeks [3,

Table 4 Evaluations performed at follow-up for living patients ($n = 89$)

Follow-up examination	No recurrence	Recurrence	*p* value
Living patients—no	78	11	0.451
Follow-up time in years for living patients*	7.0 (2.7)	8.5 (2.5)	0.025
Parker score/total points*	6.45 (2.5)	4.9 (3.2)	0.102
EQ-5D-5L calculated value*	0.85 (0.32)	0.69 (0.15)	0.099
EQ-VAS score*	65.9 (14.5)	51.8 (19.4)	0.027

*The values are given as the mean, with the standard deviation (± SD) in parentheses

EQ-5D-5L, EuroQol five-dimension scale; *EQ-VAS*, Visual Analogue Scale

9, 11, 12, 22, 26]. Sanchez-Sotelo et al. reported a median time of 9.4 months [23]. Rezaie et al. found that reimplantation > 26 weeks after resection was twice as likely to fail compared to that at < 26 weeks, but without significance [10]. As that study included knee prostheses, the result should not be considered for exclusive hip PJI.

Pathogens

Coagulase-negative *Staphylococcus* was the most prevalent mono-cultured microorganism. In line with previous studies, polymicrobial infection was predictive of recurrence, but not mono-microorganism infection or multi-drug resistance [10, 11, 20]. Petis et al. reported that chronic antibiotic suppression was the only factor associated with failure [11]. In our protocol, we did not administer antibiotic suppression therapy. In contrast, Akgün et al. reported a failure rate of 45% in a cohort with two-stage revision for streptococcal infections, but most cases involved knee prostheses [27].

Antibiotic treatment

All patients in our study received antibiotic treatment for 6 weeks according to the post-resection antibiogram. Therefore, we performed analyses only for the post-reimplantation period. While most studies did not report antibiotic regimens after two-stage exchange [3, 8, 10–12, 20, 25], some authors finished antibiotic therapy after reimplantation when bacterial growth was negative [6, 7, 22, 23]. A multicentre study reported that six and 12-week antibiotic regimens were comparable for treating PJI [28]. The primary outcome was infection within two years after surgery; therefore, these results have limited value. Another study showed that oral antibiotic therapy was not inferior to intravenous therapy for bone and joint infections [29]. In our study, the mean duration and mode of antibiotic therapy were not associated with infection recurrence.

Outcome

The one year mortality rate in our study was very low, and results of Kaplan–Meier analysis were not significantly different between the two groups. The finding suggests that infection recurrence does not influence survival. The result can be considered novel, as no previous study has compared survival between patients with and without infection recurrence. We assessed outcome measurements and followed up 78 living patients without recurrence and 11 with recurrence in the past. In summary, outcome measurements were inferior in the infection recurrence group, which may contribute to permanent resection arthroplasty with leg length loss, and restricted hip mobility. Our health-related results are in line with a similar study conducted by Poulsen et al. [5], who reported EQ-5D-3L after two-stage revision and found inferior scores for patients with recurrence. One review found lower HRQoL physical scores in patients after two-stage revisions but noninferior mental scores compared to the general population [30].

Limitations

This study had several limitations. First, this was a retrospective case series. Second, the sample was unselected, including patients with previously treated reinfections and periprosthetic fractures in the past. Although this facilitated a larger sample size, the recurrence group was small; therefore, regression analysis was not possible, and the results should be interpreted with caution. Third, this was a single-centre study, and the results cannot be generalized. Indeed, our components cannot be compared with others, and bias based on the surgeon's personal experiences cannot be excluded. Follow-up was performed with a telephone interview rather than by radiological and clinical evaluation. Despite long-term follow-up, many patients were alive, though relapse or new infection is possible in the future. Finally, the results of the outcome measurements reflect the morbidity and fragility of most geriatric patients rather than the outcome of the two-stage exchange strategy.

Conclusion

In this study with mid- to long-term follow-up, five factors for infection recurrence were identified. Recurrence did not affect survival, but HRQoL was inferior in those with recurrence than in recurrence-free patients. The results suggest that the period of the first stage including previous orthopaedic diagnoses requires more consideration in the future.

Author contribution All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Fabian Schwolow. The first draft of the manuscript was written by Fabian Schwolow and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability Not applicable.

Code availability Not applicable.

Declarations

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the University Regensburg, Germany (September 26, 2019/No. 19–1529-104).

Informed consent Informed consent was obtained from all individual participants in the study.

Conflict of interest The authors declare no competing interests.

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