What Factors Cause Hip Reimplantation to Fail after a Two-Stage Revision Hip Arthroplasty?

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ABSTRACT

Background: We analyzed the survivorship free-from-septic failure in a series of THA cases treated with a two-stage protocol at long-term follow-up, with a special focus on the relevance of positive frozen section and positive intraoperative culture taken during the reimplantation. **Methods:** We retrospectively reviewed data from 96 cases who met the Musculoskeletal Infection Society criteria for periprosthetic joint infection and who had undergone both stages of a two-stage protocol at our institution between 2008-2013. Mean follow-up was 90 months. Treatment failure was determined with a modified Delphi-based consensus definition. Kaplan-Meier estimate was used to determine survivorship free-from-septic failure. Log-Rank test was used to compare variables associated with septic failure. **Results:** Survival free-from-septic failure was 82.65% at 2 years (95%CI 73.25%-88.99%), 80.40% at 5 years (95%CI 70.70%-87.17%) and 77.32% at 6-10 years (95%CI 66.90%-84.33%). Patients with a positive culture at reimplantation had significantly more septic failures than those without it (Log-Rank test, p=0.0208), while patients with a positive frozen section at reimplantation had significantly more septic failures than those without it (Log-Rank test, p=0.0154). **Conclusions:** Reimplantations that remained at least 6 years without septic recurrences had a very low risk of further septic failure. Both positive frozen section and intraoperative culture at reimplantation were risk factors for septic failure.

Keywords: Periprosthetic joint infection; total hip replacement; two-stage revision surgery.

Level of Evidence: IV

¿Qué factores hacen fallar un reimplante de cadera luego de una revisión en dos tiempos?

RESUMEN

Introducción: El objetivo del estudio fue analizar la supervivencia sin recurrencia de infección en pacientes con reemplazo total de cadera tratados con revisión en dos tiempos, valorando el impacto del cultivo intraoperatorio y la congelación positiva en el reimplante. **Materiales y Métodos:** Estudio retrospectivo de 96 casos con infección periprotésica crónica, según los criterios de la MusculoSkeletal Infection Society, sometidos a los dos tiempos quirúrgicos en nuestra institución, entre 2008 y 2013. El seguimiento promedio fue 90 meses. La falla séptica se definió sobre la base de un consenso tipo Delphi modificado. La supervivencia sin falla séptica se definió sobre la base del estimador de Kaplan-Meier. Se compararon los resultados de supervivencia en función del cultivo intraoperatorio y de los estudios de anatomía patológica por congelación mediante la prueba del orden logarítmico. **Resultados:** La supervivencia sin falla séptica fue del 82,65% a los 2 años (IC95% 73,25-88,99%), 80,40% a los 5 años (IC95% 70,70-87,17%) y 77,32% a 6-10 años (IC95% 66,90-84,33%). Hubo significativamente más fallas en los pacientes con un cultivo positivo en el reimplante que en aquellos con un cultivo negativo (prueba del orden logarítmico, p = 0,0208), y en quienes tuvieron un estudio anatomopatológico por congelación positivo en el reimplante que en aquellos con un resultado negativo (prueba del orden logarítmico, p = 0,0154). **Conclusiones:** Los reimplantes sin recurrencias infecciosas por, al menos, 6 años tuvieron un riesgo de falla séptica muy bajo. Cuando se detectó un cultivo o una congelación positivos, la falla séptica fue significativamente mayor.

Palabras clave: Infección periprotésica; reemplazo total de cadera; revisión en dos tiempos.

Nivel de Evidencia: IV

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INTRODUCTION

Although more information is now available on the management of periprosthetic joint infection (PJI), the eradication rate has not changed in the last 20 years.[1] Considering that life expectancy is increasing, with a substantial increase in the demand for total hip replacements, a concomitant increase in the projected incidence of PJI would be a serious epidemiological problem, given the health costs absorbed by patients and health systems.[2] Two-stage revision, in which the extraction and reimplantation of the components are separated by a stage with an antibiotic-loaded cement spacer, is considered the historical gold standard for the treatment of PJI.[3]

The success rate with this protocol ranges from 65% to 90%,[4,5] which shows wide variability in the results. This has led to uncertainty in the understanding of the indications for two-stage revision surgery and imprecision in the tools for analyzing the efficacy of the treatment.[6]

At present, there are no clinical or laboratory parameters available to rule out the persistence of PJI before reimplantation. In an attempt to improve the outcomes of PJI treatment with a two-stage protocol, several studies have focused on detecting risk factors for reinfection after reimplantation, including demographic,[7] surgical[8], and laboratory variables.[9] Thus, the role of frozen section procedures or cultures (either taken previously or during the second stage) has also been extensively studied but remains a controversial topic.[10,11] Therefore, the indication to proceed with the second stage varies according to each surgeon and institution.

The objective of this study was to determine the infection-free survivorship in a series of patients with total hip replacement undergoing a two-stage revision, assessing the impact of a positive intraoperative culture or frozen section.

MATERIALS AND METHODS

A retrospective study was conducted of a consecutive series of 247 cases with chronic PJI which had undergone a revision in our institution, between 2008 and 2013. During this period, 97 cases were treated with a strict single-stage revision protocol, 30 were treated with resection arthroplasty, and 120 with a two-stage revision. Only patients >18 years who were operated on in two stages in our institution were included. We excluded 10 patients because they were clinically unfit for reimplantation (and remained chronically with a spacer) and 13 who were lost in follow-up or who did not have complete laboratory data.

The final study population included 96 hips (94 patients) with chronic PJI, of which eight had had primary surgery at our institution, while 88 had been referred from other centers. PJIs with symptoms lasting for at least 6 weeks were considered chronic. The diagnosis of PJI was made based on the *MusculoSkeletal Infection Society* (MSIS) criteria, with 1 major criterion or at least 3 of 5 minor criteria.[12] Information on surgical treatment prior to institutional referral was obtained through the digital recording of the external medical record.

The average age at the time of the first surgical stage was 63 ± 12 years (Table 1). The series included 59 women and 37 men, with an average body mass index of 32 ± 5 kg/m^2. Most had an *American Society of Anesthesiologists* (ASA) grade 3 score (58 patients [60%]). The median value of serological C-reactive protein (CRP), erythrosedimentation rate, and white blood cell count are shown in Table 1. Seven patients (7%) died after the first two years of follow-up, there were no deaths before that date. All died of causes unrelated to PJI. The average follow-up of the series was 90 ± 32 months.

Surgical procedure

The indication for a two-stage revision included at least two of the following factors: 1) confirmation of chronic PJI with MSIS criteria,[12] 2) functionally active patients, who walked unaided or with minimal assistance before surgery, 3) presence of a fistula. In all cases, a posterior approach was used in a laminar airflow operating room. The surgeries were performed by one of three hip surgeons. Preoperative antibiotic prophylaxis depended on the isolated germ before surgery, if available; otherwise, cefazolin 2 g was administered intravenously. All patients were given a preoperative dose of 1000 mg tranexamic acid, and a supplementary dose of 1000 mg was added at closure.

The first stage consisted of extraction, profuse periarticular debridement, and insertion of an antibiotic-loaded polymethylmethacrylate spacer. To achieve an adequate removal of the implant, an extended trochante-

Table 1. Demographic data and surgeries of patients before the first surgical stage

Variable	Number of hips (total hips: 96, total patients: 94)
Average age (years)	63 ± 12
Female sex (%)	59 (62.7%)
Average body mass index (kg/m^{2})	32 ± 5
ASA scale (%) 1 2 3 4	 0 (0%) 31 (33%) 58 (61.7%) 5 (5.3%)
Previous surgeries to treat periprosthetic infection (%) No Debridement Revision	 49 (51%) 21 (22%) 26 (27%)
Median serological CRP (IQR) (mg/dl)	37 (22-58)
Median serological erythrosedimentation rate (IQR) (mm/h)	48 (39-64)
Median (IQR) serological white blood cell count (cells/µl)	7600 (6200-8950)
Average synovial CRP (mg/dl)*	16 ± 6
Average follow-up (months)	90 ± 32

ASA = *American Society of Anesthesiologists*, IQR = interquartile range; CRP = C-reactive protein. *Analyzed only in 19 cases.

ric osteotomy was used in 16 cases (17%). In 68 cases (70%), the implant, interface, and cement (if any) were removed without any osteotomy (Table 2). Intraoperative frozen section with acute inflammation (positive) was reported in 86 cases (90%). Since December 2011, synovial CRP began to be measured, using a cut-off value of 9.5 mg/dl.[13] In this series, it was analyzed only in 19 cases during the first stage and the average value was 16 ± 6.5 mg/dl.

Non-articulating spacers were used in 62 cases (64%) with vancomycin for gram-positive germs and gentamicin/ceftazidime for gram-negative germs. The most frequent microorganism was coagulase-negative *Staphylococcus* (25%). In 10% of the cases, the culture was negative (Table 2).

The acetabular and femoral bone defects were classified during the first stage (Table 2).[14] After the spacer, the patients received intravenous antibiotic therapy for an average time of 11 ± 4 weeks. Antibiotic prescription depended on the isolated germ; patients with culture-negative infections received broad-spectrum treatment (vancomycin 15 mg/kg, every 12 h plus ceftazidime 2 g, every 8 h or meropenem 1 g, every 8 h).

The median time elapsed between the first and second surgical stage was 97 days (interquartile range [IQR] 72-183). This variability depended on many factors, but above all on the authorization of health insurance providers. No surgery was performed between the first and second stages. All reimplantations were performed with an antibiotic-free period of at least two weeks. The reimplantation was performed through the same incision (Table 3).

The most frequent acetabular reconstruction was made with a primary highly porous cementless cup (45 cases [46%]), while the most common femoral reconstruction was with a modular conical distal-fixation stem (29 cases [30%]).

Table 2. Results after the first surgical stage

Variable	Number of hips (total hips: 96; total number of patients: 94)
Approach (%)	
Posterior	96 (100%)
Femoral osteotomy (%)	
Trochanteric	11 (13%)
Femorotomy (slot)	1 (1%)
Extended trochanteric osteotomy	16 (17%)
No	68 (70%)
Spacer type (%)	
Non-articulating	62 (64%)
Articulating	34 (36%)
Acetabular bone defect (Paprosky) (%)	
I	23 (24%)
IIA	25 (26%)
IIB	15 (15.6%)
IIC	14 (14.6%)
IIIA	10 (10.4%)
IIIB	9 (9.4%)
Femoral bone defect (Paprosky) (%)	
I	20 (20.8%)
II	29 (30.2%)
IIIA	29 (30.2%)
IIIB	12 (12.5%)
IV	6 (6.3%)
Germ (%)	
Negative culture	10 (10.4%)
Methicillin-resistant *S. aureus*	9 (9.4%)
Methicillin-sensitive *S. aureus*	9 (9.4%)
E. faecalis	11 (11.4%)
Coagulase-negative staphylococci resistant to oxacillin	12 (12.5%)
Coagulase-negative staphylococci sensitive to oxacillin	12 (12.5%)
E. cloacae	2 (2.1%)
Corynebacterium sp.	1 (1%)
β-hemolytic *Staphyloccocus*	1 (1%)
E. coli	4 (4.2%)
P. aeruginosa	4 (4.2%)
K. pneumoniae	2 (2.1%)
S. viridans	7 (7.3%)
Providencia sp.	1 (1%)
Anaerobic	2 (2.1%)
Polymicrobial	9 (9.4%)
Positive frozen section (%)	89 (92.7%)
Median time elapsed (IQR) between the first and second stages (days)	97 (72-183)

IQR = interquartile range.

Table 3. Results after the second surgical stage

Variable	Number of hips (total hips: 96; total number of patients: 94)
Median (IQR) serological CRP (mg/dl) before reimplant	6 (4-13)
Median (IQR) serological erythrosedimentation rate (mm/h) before reimplantation	33 (22-45)
Median (IQR) serological white blood cell count (cells/µl) before reimplantation	6300 (5000-7800)
Approach (%)	
Posterior	96 (100%)
Use of allografts (%) for acetabular or femoral reconstruction	35 (36%)
Acetabular reconstruction (%)	
Primary cementless cup	45 (47%)
Primary cemented cup	18 (19%)
Trabecular metal cup/wedge	25 (26%)
Impacted bone allografts	8 (8%)
Femoral reconstruction (%)	
Primary cementless stem	3 (3%)
Primary cemented stem	17 (18%)
Conical distal-fixation cementless stem	29 (30%)
Conical distal-fixation cemented stem	8 (8%)
Revision polished long cemented stem	7 (7%)
Impacted bone allografts	26 (27%)
Proximal femoral replacement	3 (3%)
Allograft-prosthesis composite	2 (2%)
Total femoral replacement	1 (1%)
Positive frozen section (%)	17 (18%)
Positive intraoperative culture (%)	7 (7%)
A single positive culture	6 (6%)
At least 2 positive cultures of the same germ	1 (1%)

IQR = interquartile range, CRP = C-reactive protein.

Intraoperative samples obtained during reimplantation

After removing the spacer, at least six samples were obtained for freezing and culture. The samples comprised various types of tissue (bone in contact with cement, synovial membrane, capsule, interface, joint fluid) and the locations were non-standardized but included at least three from the acetabular region and three from the femoral region. The cut-off value for frozen sections was at least 5 polymorphonuclears in each of at least 10 fields of 400x magnification.[15]

Follow-up

Patients were monitored at 15 and 45 days, at 3 months, a year and, every 2 years, from then on. The functional and radiological follow-up was carried out by a specialized orthopedist and the laboratory follow-up by an infectologist. A serological analysis was performed in each monitoring visit, which included CRP and erythrosedimentation rate. Post-implant antibiotic therapy lasted between 6 and 8 weeks. Patients who had at least one positive intraoperative culture or had acute inflammation at the reimplantation frozen section, those without a downward erythrosedimentation curve and CRP in the first postoperative month, or immunocompromised patients received antibiotic therapy, extended for a variable period, according to the infectologist's criterion and the evolution of the PJI.

Outcome variables

The success of the two-stage revision was measured by defining the post-implant septic failure based on Delphi international consensus criteria.[16] This included clinical parameters (closed wound, no signs of inflammation or drainage) and surgical parameters (any surgery performed on suspicion of infection), or death related to PJI (i.e., sepsis). Like Akgün et al., it was also considered a septic failure if the patient had received suppressor antibiotic therapy >6 months.[17]

Statistical analysis

Continuous variables were expressed as median and IQR or average and standard deviation; and categorical variables, as percentage and absolute frequency. Infection-free survivorship was calculated based on the Kaplan-Meier estimator. Survivorship outcomes were compared according to the intraoperative culture and frozen section procedure using the log-rank test. A p value <0.05 was considered statistically significant. The analyses were carried out with the Stata 14 program (Stata Corp., College Station, Texas, USA).

FINDINGS

21 septic failures were found at the end of follow-up. Infection-free survivorship (Figure 1) was 89.17% at one year (95% CI 90.81-94.02%; mortality rate 3.12%), 82.65% at 2 years (95% CI 73.25-88.99%; mortality rate 4.5%), 80.40% at 5 years (95% CI 70.70-87.17%; mortality rate 6.25%) and 77.32% at 6-10 years (95% CI 66.90-84.33%; mortality rate 7.29%).

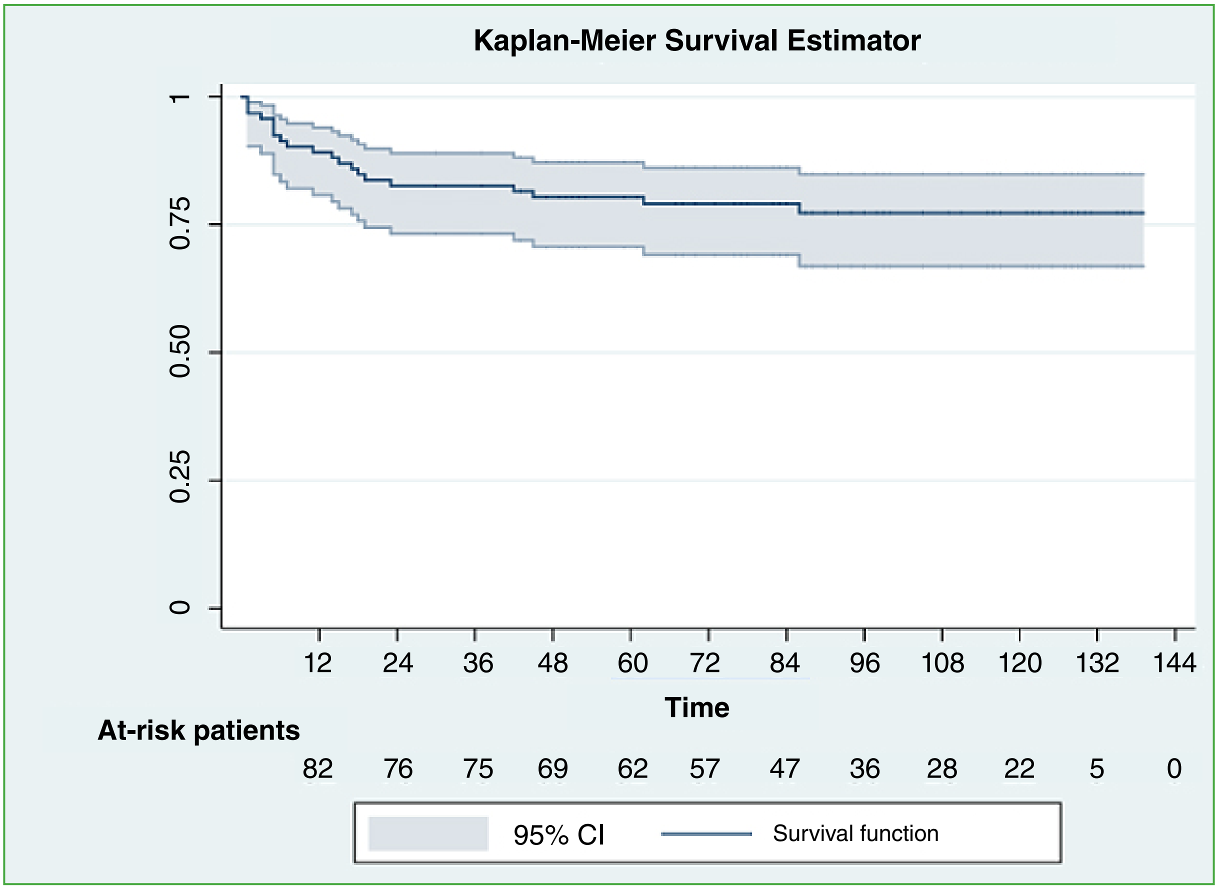

Figure 1. Plot of the infection-free survivorship as a function of time, using the Kaplan-Meier method.

Five of seven cases with a positive intraoperative culture and 18 of 89 cases without positive cultures had septic failures. The average time to septic failure in each group was 8.8 ± 9.8 and 20 ± 24.5 months, respectively. Similarly, there were septic failures in 8 of 17 cases with positive freezing and in 15 of 79 without it. The average time to septic failure in each group was 13.6 ± 14.8 and 18.5 ± 25.4 months, respectively.

When comparing infection-free survivorship between those with and without a positive culture in the reimplantation, there were significantly more failures in the former at the end of follow-up (logarithmic order test, p = 0.0208), as shown in Figure 2.

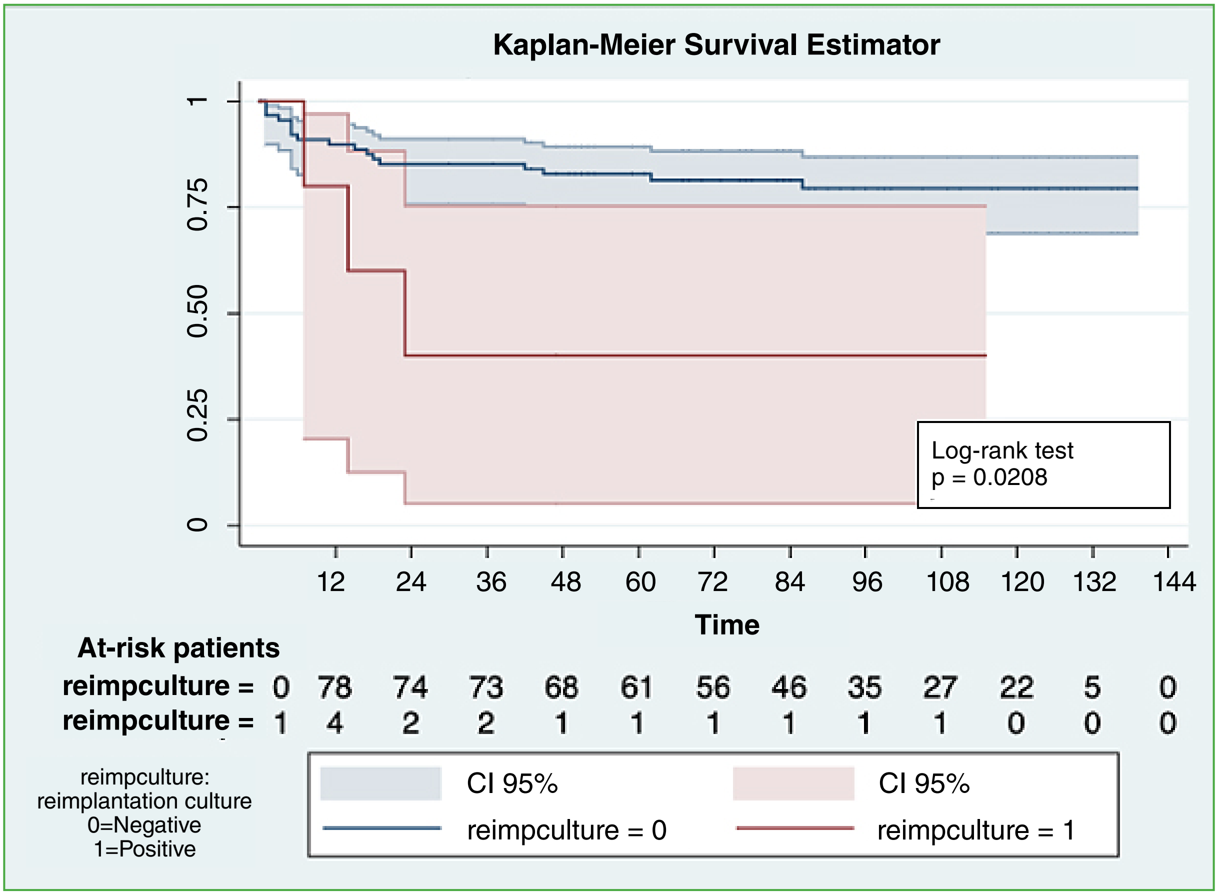

Figure 2. Plot of the infection-free survivorship as a function of time, separating the series into two groups according to the presence of a positive culture during reimplantation. The groups were compared using the log-rank test.

Similarly, when comparing infection-free survivorship among those with and without a positive frozen section in the reimplantation, there were significantly more failures in the former at the end of follow-up (logarithmic order test, p = 0.0154), as shown in Figure 3.

DISCUSSION

Various factors (dependent on the host, the doctor, the germ, and society) can alter the natural evolution of PJI leading to a therapeutic failure. In this series, most septic failures occurred in the first 6 years of post-implant follow-up. Thus, a reimplantation that reached the 6-year point of reference without any reoperation due to infection had a very low probability of suffering a septic failure in the future. These results are consistent with previous findings that measured the cumulative incidence of PJI over up to 15 years of follow-up.[18]

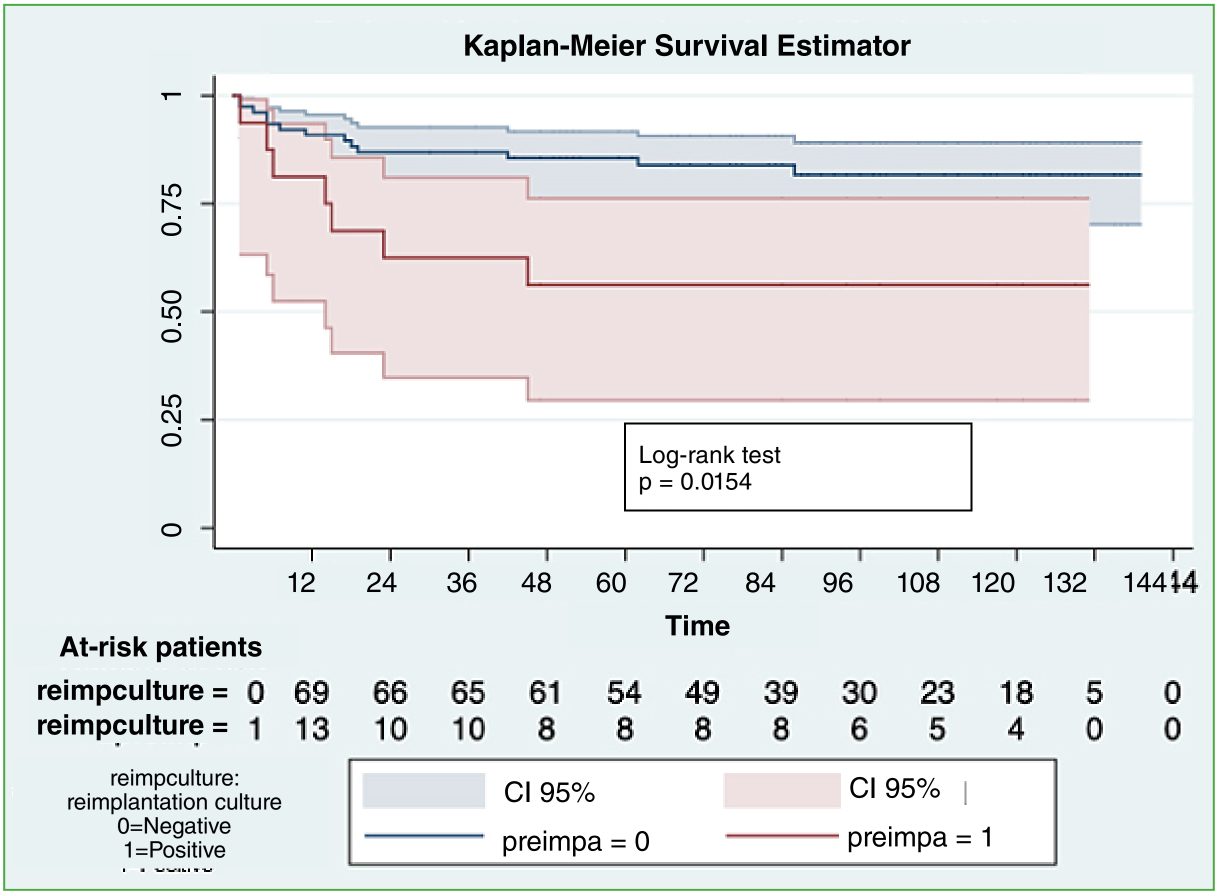

Figure 3. Plot of the infection-free survivorship as a function of time, separating the series into two groups according to the presence of a positive frozen section anatomopathological study during reimplantation. The groups were compared using the log-rank test.

Scant data on outcomes more than 5 years after reimplantation have been reported, given that PJIs usually recur in the first two years; however, we believe that these patients should be monitored for at least 5 or 6 years to consider a PJI as truly "cured".

Our study had limitations. First, the retrospective nature and the low number of patients correlated with the impossibility of generating a more appropriate survivorship analysis. However, our indication for two-stage revision has been strict and reproducible, with a low number of cases lost at follow-up and an average follow-up of 7.5 years, longer than in many similar studies.[19] Second, the clinical status of the patients has not been evaluated. Various scores have been described (*Western Ontario and McMaster Universities Osteoarthritis Index* [WOMAC], *University of California Los Angeles Index* [UCLA], *modified Harris Hip Score* [mHHS]) to measure the functionality of single- and two-stage revisions. Third, the criteria for defining a septic failure included suppressive antibiotic therapy, and this fact could alter the survivorship analysis. Since suppressive antibiotic therapy can "stretch" the life of a reimplant,[20] the modified Delphi[16] consensus criterion we used can lead to a misinterpretation of findings. It is not entirely clear whether patients with suppressive therapy should be considered failures or part of a therapeutic strategy designed to prevent future reoperations.[6]

The current evidence is controversial regarding the clinical significance of a positive intraoperative frozen section or culture in the reimplantation. In 2018, the *International Consensus Meeting* for the treatment of PJIs resolved that there is limited evidence (weak consensus) for using intraoperative frozen sections for decision-making in reimplantation.[21] Frozen section procedures are highly specific, but insensitive to detect PJI persistence,[10,11] making them unreliable. Furthermore, it is a study that depends on the pathologist, it is not available in several centers because it is expensive in our environment and its cut-off values vary according to the different institutions. Frozen section procedures could lead to safe reimplantation, unlike serological or synovial parameters that are ineffective in the presence of a spacer.[9]

The validity of the MSIS criteria for its use in reimplantations is unclear. Having two positive cultures of the same germ is a major criterion for diagnosing PJI,[12] but the diagnostic power of cultures between the two stages of treatment (i.e., with the spacer) is limited for two reasons. First, the presence of a spacer affects the sensitivity of the cultures if they were taken as an aspiration biopsy before surgery. False-negative results, reported by up to almost 15-25%, may underestimate the persistence of PJI.[22] Second, intraoperative cultures are only available after reimplantation, and isolated Gram staining techniques also have very little sensitivity.[23] However, cultures can predict septic failures. Akgün et al.[17] reported a higher failure rate in cases with a single positive culture, and suggest, as in our study, extended antibiotic therapy in those cases.

This fact calls us to use more efficient bacterial typing techniques before reimplantation. State-of-the-art sonication and genome sequencing could optimize the power of bacterial identification, but the evidence on them is too controversial to routinely indicate them. The 16S rDNA test that combines polymerase chain reaction with lateral flow immunochromatographic assays has been proposed as a novel intraoperative method to isolate bacteria in as little as 25 minutes.[24] However, its use is not available worldwide and its cost-effectiveness remains to be proven.

CONCLUSIONS

No superiority of one parameter over another in predicting the ideal time to reimplant has been described.[25] In decision-making, various factors should be considered, including signs and symptoms, adherence and response to antibiotic treatment, and serological, synovial, and pathological anatomy laboratory results. In short, this study showed that positive frozen section studies and a positive intraoperative culture were associated with PJI recurrence in the medium and long term. While frozen sections can be used as a valid parameter to defer reimplantation and suggest a new first-stage indication, the culture has, for the time being, only a prognostic value. Finally, our survivorship results suggest that if the reimplantation remains at least 6 years without infectious recurrences, the risk of future septic failure is low.

Conflict of interests: The authors declare they do not have any conflict of interests.

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