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Risk factors for failure of two-stage revision arthroplasty for infected hip prosthesis: review of the literature and single centre cohort analysis

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Abstract. – **OBJECTIVE: Periprosthetic joint infections (PJI) are one of the most dangerous complications in hip surgery. "Two-stage" revision surgery is the treatment of choice. Nevertheless, 5-10% of failures are reported. The aim of this study is to evaluate which factors determine the failure of the two-stage revision in patients affected by hip PJI.**

PATIENTS AND METHODS: We retrospectively enrolled 21 patients treated for hip PJI who had undergone two-stage revision surgery. The diagnosis had been made using criteria established by the Musculoskeletal Infection Society (MSIS) and readapted by the Philadelphia Consensus Conference group. The patients underwent periodic clinical and laboratory controls after the surgical procedure. The two-stage revision treatment was considered unsuccessful in the event of re-infection or in case of severe complications occurring within one year from the treatment.

RESULTS: At a mean follow-up of 23.8 months 57% healed with no complications. The reinfection rate was 19% and, after the 3rd stage, the final failure rate was 9.5%. The study has shown, with statistical significance, that a greater number of previous surgical procedures (*p*<0.05, OR=22) and BMI>25 (*p*<0.05, OR=4) represent increased risk factors in predicting the failure of two-stage revision surgery. Age, CRP, ESR and a shorter lapse (<60 days) between 1st and 2nd stage were recorded in the failure cases, and have to be considered, even if not statistically significant.

CONCLUSIONS: Knowing the factors responsible for the increased failure of two-stage revision could lead to closer monitoring and more aggressive management in those patients expected to be at greater risk of reinfection. Obesity and multiple surgeries are risk factors for failure.

Key Words
Hip prosthesis, Periprosthetic hip infection, Two-stage revision surgery.

Introduction

Total hip arthroplasty (THA) provides enduring benefits when evaluated by health, social, economic, and psychological indices[1-5]. Postoperative periprosthetic joint infection (PJI) is a devastating complication and can negate these benefits[6,7]. PJI is the most dreaded complication following hip arthroplasty, being associated with increased morbidity, mortality[8], cost[9], and reduced quality of life[10]. The incidence of PJI following primary THA is reported to be 0.5% to 2%[11] and is thought to be rising[12,13]. The 2015 New Zealand Joint Registry report identified PJI as the fifth most common reason for primary THA revision[14,15], impacting heavily on the national health system for costs related to diagnosis and treatment. In terms of health care costs, the measures taken to prevent prosthetic infections are extremely important to help reduce these burdens because the annual cost of infected revisions is estimated to reach $1.6 billion by 2020[16,17]. Significant progress has been made in the field of prevention thanks to the improvement of surgical techniques and asepsis, quality of implanted materials and antibiotic therapy. Strategies to minimize these complications are focused on 3 key areas: the patient, the surgical techniques, and the operating room (OR) environment[18]. The significant increase in the number of total joint arthroplasties, which is expected in the future due to the growing demands of an aging population[19], will certainly be followed by a consequent increase of PJI[20].

The therapeutic options for treatment and management can be challenging, and the out-

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comes may be uncertain. Surgical treatment is usually required and three different options are considered:

- Debridement, antibiotic therapy and implant retention (DAIR), which consists of the removal of all necrotic and infected tissues and allows to maintain the implant "in situ" in association with long-term antibiotic therapy;
- Direct (or one-stage) revision surgery, which involves the replacement of the prosthetic implants with a new one, after debridement, using antibiotic cement, followed by antibiotic therapy;
- Two-stage revision surgery, which consists in the removal of the infected components and the implant of a temporary antibiotic spacer, followed by the implant of a new hip prosthesis after eradication of the infection.

The two-stage revision surgery is the most widespread and has the greatest efficacy in eradicating chronic periprosthetic infections with success rates of over 90%[21,22]. In any case, management of the patient remains difficult, due to co-morbidities, inadequate residual bone stock, compromised tissue integrity, surgical complexity, lengthy surgery and compromised patient's health status (Figure 1)[23].

Currently, one of the main challenges that surgeons face is in the identification of predictive factors that can increase the risk of failure of the two-stage revision treatment. The aim of our study is to verify which factors are able to determine the failure of the two-stage revision treatment, such as the recurrence of infection or the development of serious complications within 1 year after the treatment.

Patients and methods

Starting from a database of 1230 patients, all cases of patients with infected primary hip prostheses treated with two-stage revision surgery between 2012 and 2016 in our hospital hip arthroplasty unit were identified and collected. Although there is no universally accepted definition to confirm the diagnosis of infection[24], the criteria established by the Musculoskeletal Infection Society (MSIS)[25], readapted by the Philadelphia Consensus Conference group[24] were considered

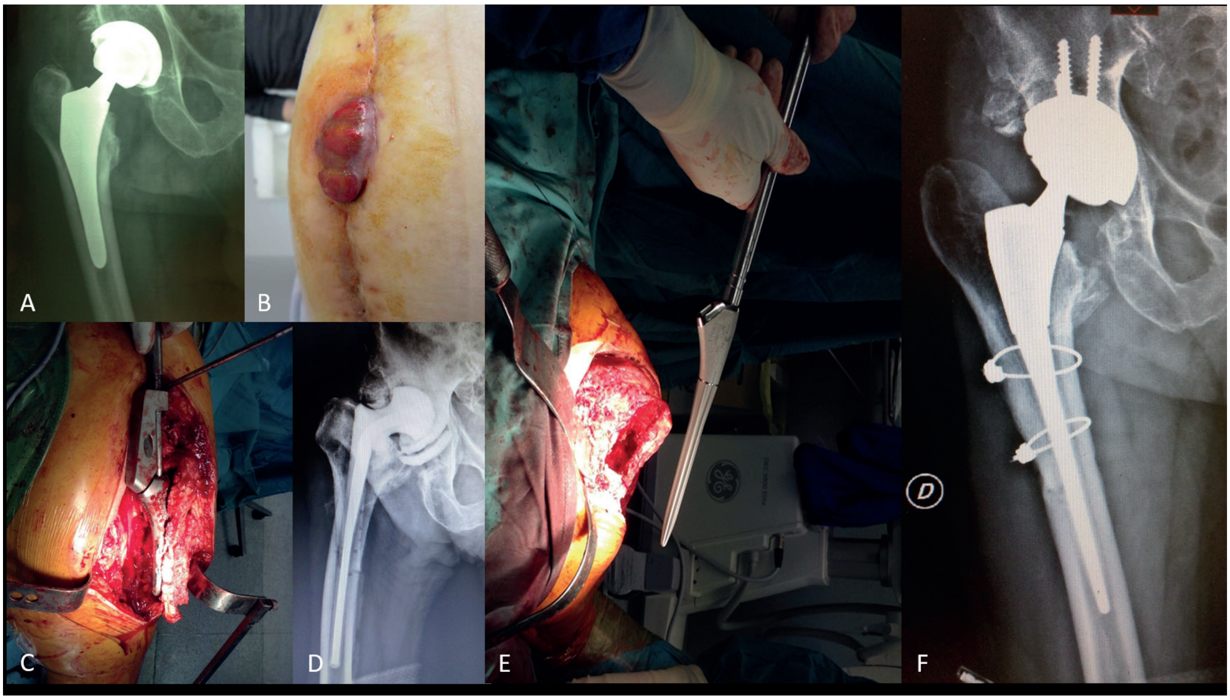

Figure 1. Two-stage revision surgery of a healed patient; a deep infection of a primary THA (**A**) was evident in the presence of an extruded and draining fistula (**B**); 1st stage implant removal required an extended trochanteric osteotomy (**C**) and the substitution with a long antibiotic gentamicin loaded spacer (**D**). 2nd stage after 3 months: a revision cementless stem was implanted in absence of any sign of infection. Two cerclages were necessary to manage the femoral osteotomy (**E**). 1-year radiographic control confirm a bony stable stem osseointegration and the osteotomy consolidation (**F**).

Table I. Musculoskeletal Infection Society (MSIS) criteria.

Major criteria (diagnosis can be made when 1 major criterion exists)	*Minor criteria (diagnosis can be made when 4/6 of the following minor criteria exist)*
– Sinus tract communicating with prosthesis	– Elevated ESR (>30 mm/h) or CRP (>10 mg/L)
– Pathogen isolated by culture from 2 separate tissue/fluid samples from the affected joint	– Elevated synovial WBC (>1.100 cells/ul for knee, >3.000 cells/ul for hip)
	– Elevated synovial PMN (>64% for knee, >80% for hip)
	– Presence of purulence in the affected joint
	– Pathogen isolation in 1 culture
	– >5 PMN/hpf in 5 hpf at X400 magnification (intraoperative frozen section of periprosthetic tissue)

diagnostic. Patients in whom at least one major criterion was found or, alternatively, three or more minor criteria, were considered affected by hip PJI (Table I). In cases where the infection is suspected even in the presence of a normal profile of blood indices or negative superficial cultures, the patient was also considered infected when the cultures obtained by multiple intraoperative biopsies were positive. The exclusion criteria considered were the following: patients undergoing revision for different indications than infection or without proven infection, patients with periprosthetic hip infection undergoing different treatment than two-stage, patients who did not survive the surgery. Therefore, we included all patients with a confirmed diagnosis of periprosthetic hip infection who had undergone 2-stage revision surgery for treatment, with the aim of identifying possible risk factors of failure. We finally obtained a cohort of 21 cases.

Patients were treated with broad-spectrum antibiotics until the cultures were obtained, followed by a microorganism-specific antibiotic. The follow-up controls were performed at 1, 3, 6, 12 months and then annually starting from the revision surgery. The follow-ups were conducted simultaneously by an orthopaedist and an infectivologist expert in periprosthetic infections. The following, potentially predictive failure variables were collected: demographic data (gender, age, body mass index), clinical history (comorbidity, time of infection and duration, interval between first and second surgical time, number of previous surgical procedures for infections or other indications at the same joint), blood parameters such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), leukocyte count, haemoglobin, haematocrit, urea nitrogen, creatinine, cultures positive for infection and antibiogram. The two-stage revision treatment was considered unsuccessful in the event of re-infection or in case of severe complications occurring within one year from treatment initiation. The following parameters defined the failure of the two-step revision treatment: recurrence of infection confirmed by positive culture tests for the same or another microorganism, persistence of the infection after the first stage that requires debridement and implantation of a new antibiotic spacer (third-stage), persistence of the infection after having performed third-stage revision surgery, such as to require more invasive rescue procedures (e.g., "Girldestone procedure"), occurrence of significant complications that could compromise the success of the implant. On the other hand, the criteria that defined success were the following: absence of signs or symptoms of infection, the two-stage revision surgery was sufficient to eradicate the infection.

Statistical Analysis

A statistical analysis was performed using the SPSS software (IBM Statistics). A comparison of all the variables collected was performed to identify significant differences between the two groups. The Student's *t*-test was chosen to study continuous variables. The chi-square test (Fisher exact test) with 2x2 contingency table was used for the study of categorical variables. The confidence interval used was 95% and a value of $p < 0.05$ was defined statistically significant.

Results

Between 2012 and 2016, a cohort of 21 patients affected by periprosthetic hip infection who had undergone two-stage revision surgery was selected. The cohort of patients consisted of 9 males (42.8%) and 12 females (57.1%). The average length of the follow-up was 23.8 months (range: 12-48; SD 16.05) for all patients, 28 (range: 12-48; SD 18.79) for the healed and 18.2 (range: 12-41; DS 9.87) for the failures. The mean age of patients at the time of primary hip arthroplasty was 69.4 years (range: 42-83; SD: 11.63) and at the first surgical time of the two-stage revision was 72 years (range: 44-86 years; SD: 11.82). The occurrence of infection from primary hip arthroplasty was 519.5 days (range: 47-1770; SD: 550.6) for the healed and 501 days (range: 46-1915; SD: 520) for the failures. The duration of the symptoms, as time elapsed between the diagnosis of infection and the spacer implantation, was of 195 days (range: 30-563; SD: 161.44) for healed and 165 days (range: 54-549; SD: 176.4) for failures. Out of 21 patients, 12 healed without complications (Figure 1). Of the others, 4 cases of reinfection (19.04%), 1 superficially healed infection (4.7%), 2 dislocations (9.5%), 1 femoral fracture (4.7%) and 1 ankylosis (4.7%) were observed. Of these, after further treatment, 2 cases evolved in persistent infection (9.5%) and 2 cases in severe functional impotence (9.5%) because of Girldestone's resection in order to obtain a complete eradication of the infection. Finally, 90.5% of the patients were permanently healed. Persistent infections have been treated by prescribing a chronic suppressive antibiotic therapy. In 2 cases the persistence of the infection following the implant of the spacer was found; however, a 3rd stage procedure, consisting in new debridement and irrigation with pulsed washing and the implant of a second spacer, permitted the eradication of the infection. In 3 cases, a definitive revision prosthesis was not implanted because of severe comorbidity or severe bone deficiency or deterioration of soft tissues (Figure 2). 8 women healed and 4 women developed reinfection or serious complications. On the other hand, 4 men healed, while 5 men failed. Consequently, we did not find a significant connection between sex and risk of failure of the two-stage revision *(p*=0.38 | *p*>0.05). The mean age at the time of first revision surgery (spacer implant) was found to be greater in the group of failures (75.1 years; SD: 6.06; range: 67-85) than in the successful group (69.32 years; SD: 14.55; range: 43-85), although the difference was not significant from a statistical point of view *(p*=0.23 | *p*>0.05) (Table II). In addition, we observed that patients in the failures group had a higher BMI than in the healed one *(p*=0.048), demonstrating a significant difference (confidence interval to 95% | *p*<0.05) between the average of 25.34 in successes (IC 95%=21.76-28.92 | DS=5.63) and 30.88 in failures (IC 95%=25.97-35.78 | DS=6.38). We also calculated by odds ratio the impact that a BMI>25 has, as a risk factor, in the failure of the two-stage revision treatment. A value of the odds ratio of 4.00 was found, although this resulted in no statistical significance *(p*=0.13). The comorbidities detected (cardiovascular disease, diabetes, and rheumatoid arthritis) were also equally represented in the two groups: there were 3 cases of heart disease, 1 of diabetes and 1 patient with rheumatoid arthritis in both groups. The time lapse between the primary hip arthroplasty surgery and the diagnosis of hip infection was on average 519.5 days (range: 46-1915; SD: 550.6) in the healed and 501 (range: 47-1770; SD: 520) in the failures but these values are due almost exclusively to the case *(p*=0.46). Likewise, the mean time spent between the diagnosis of hip infection and the spacer's implant was 194.6 days (range: 54-549; SD: 161.4) in the healed and 164.8 days (range: 30-563; SD: 176.4) in the failures *(p*=0.69 | *p*>0.05). In the failure cases, 6 patients had undergone more than two surgical procedures on the same hip while only 1 patient in the healed group had more than 2 procedures. This difference was found to have a very high level of statistical significance (IC 95% | *p*=0.0005 | *p*<0.05). In addition, we calculated that the impact as a risk factor for failure of more than 2 surgical procedures carried out on the same joint is equal to an odds ratio of 22 (IC 95%=1.85 – 260.65 | *p*=0.014). The mean interval between the first and second stage was (3 patients were excluded because of a third stage procedure) of 127.6 days (range: 56-397; SD: 90.1) in healed patients and 72.5 days (range: 27-117; SD: 33.6) in the failure ones *(p*=0.17 | *p*>0.05). Even if not significant, it was interesting. We observed lower pre-surgical CRP (33.9 *vs.* 57.5 | *p*=0.21 | *p*>0.05) and ESR (39.2 against 46.8 | *p*=0.31 | *p*>0.05) in the group of healed patients, even if in absence of statistical significance. Otherwise, no evident differences were observed between the two groups among the other blood parameters. The mean values of haemoglobin and haematocrit evaluated in the last available examination prior to the first surgical stage were found to be almost overlapping between the two groups: the mean values of haemoglobin were 11.7 g/dl (range: 10.1-15.1; SD: 1.41) in successes and 11.4 g/dl (range: 10.1-13.5; SD: 1.23) in failures (*p*=0.60 | *p*>0.05) while the haematocrit was 35.9% (range: 29.7-46.3; SD: 4.35) in the healed group and 34.6% (range: 29.6-43.4; SD: 4.35) in the failures (*p*=0.52 | *p* >0.05).

Table II. Analysis of the variables between the group of healed and failures patients.

	Healing		Therapeutic Failure		
Parameters	**N**	**Mean (SD)**	**N**	**Mean (SD)**	***p*-value°**
Age	12	69.32 (14.55)	9	75.67 (6.07)	0.23
BMI	12	25.35 (5.64)	9	30.88 (6.38)	0.048*
Weight	12	68.17 (14.13)	9	84.55 (14.40)	0.008*
Duration of symptoms (days)	12	195 (161.44)	9	165 (176.43)	0.69
Previous surgical procedures	12	0.58 (0.90)	9	2.77 (1.48)	0.0005*
Time between first and second stage (days)	12	127.66 (90.09)	9	72.50 (33.64)	0.17
CRP	12	33.89 (57.93)	9	57.54 (52.9)	0.21
ESR	12	46.77 (44.96)	9	39.23 (10.23)	0.31
White blood cells	12	8.20 (4.29)	9	7.73 (1.98)	0.71
Hb	12	11.77 (1.40)	9	11.46 (1.23)	0.60
HCT	12	35.93 (4.35)	9	34.64 (4.77)	0.52
Urea nitrogen	12	18.16 (7.33)	9	16.33 (5.76)	0.54
Creatinine	12	0.92 (0.28)	9	0.80 (0.26)	0.31

°*t*-Test and Chi Square Test were used. The p-value have been compared to the significance level of 0.05.
*Statistical significant difference.

In addition, we calculated a mean post-surgical decrease in haemoglobin of 2.1 points in the group of healed patients and of 1.7 points in the group of failures. The mean post-surgical value of the white blood cells was 11.9 cells/microliter in successes and 10.8 cells/microliter in failures (p=0.08 | p>0.05).

In the group of the healed patients, there were 3 cases of polymicrobial infection (25%) and 9 of monomicrobial infection. In the failures group, 4 (44%), had polymicrobial infections while 5 infections were due to a single pathogen. The Chi-square test did not, however, show a significant statistical difference to justify the increased infection from multiple microorganisms in patients who had encountered serious complications or reinfection (p=0.35 | p>0.05). In 8 cases (3 in failures and 5 in healed) multiple intraoperative samples were necessary in order to confirm the diagnosis of infection. Staphylococci were isolated in 11 cases (91.6%) in the healed group: *MRSA* (4 cases; 33.3%), *MRSE* (3 cases; 25%), *MSSE* (3 cases; 25%), *S. Lugdunensis* (1 case; 8.3%). In the remaining case, the infection was caused by *Enterobacter cloacae* (8.3%). In 2 cases, a second pathogen was found (*Enterococcus faecalis and Morganella morganii*) and, in 1 case, two further pathogens (*Proteus mirabilis and Enterococcus faecalis*). Staphylococci were isolated in 7 patients (77.7%) in the group of failures: *S. aureus* (2 cases; 22.2%) and *S. Epidermidis* (5 cases; 55.5%). *Escherichia coli ESBL producer* (11.1%) and *Corynebacterium striatum and jeikeium* (11.1%) were isolated in the other 2 cases. In addition, there were 3 further cases of polymicrobial infections by *Enterococcus faecalis, Proteus mirabilis,* and *Pseudomonas aeruginosa* with *Corynebacterium Striatum* (Figure 2). No significant correlation was found between the microorganism and reinfection rate although polymicrobial infections were more frequent in the failures group.

Discussion

Nowadays, the 2-stage revision surgery is the Gold-Standard treatment for periprosthetic hip infections[21] and is considered the most effective technique to eradicate and prevent reinfection or other serious complications. In our study, therefore, we wanted to investigate the re-infected or seriously complicated cases as to identify the factors that are significantly related to the failure of the two-stage revision surgery in a group of patients affected by periprosthetic hip infection. The healing rate observed in our retrospective study was 90.5%. Only 2 patients developed a persistent hip infection, value in line with those reported in the literature[26].

The recurrent rate of infection following two-stage revision in infected hip prosthesis has not

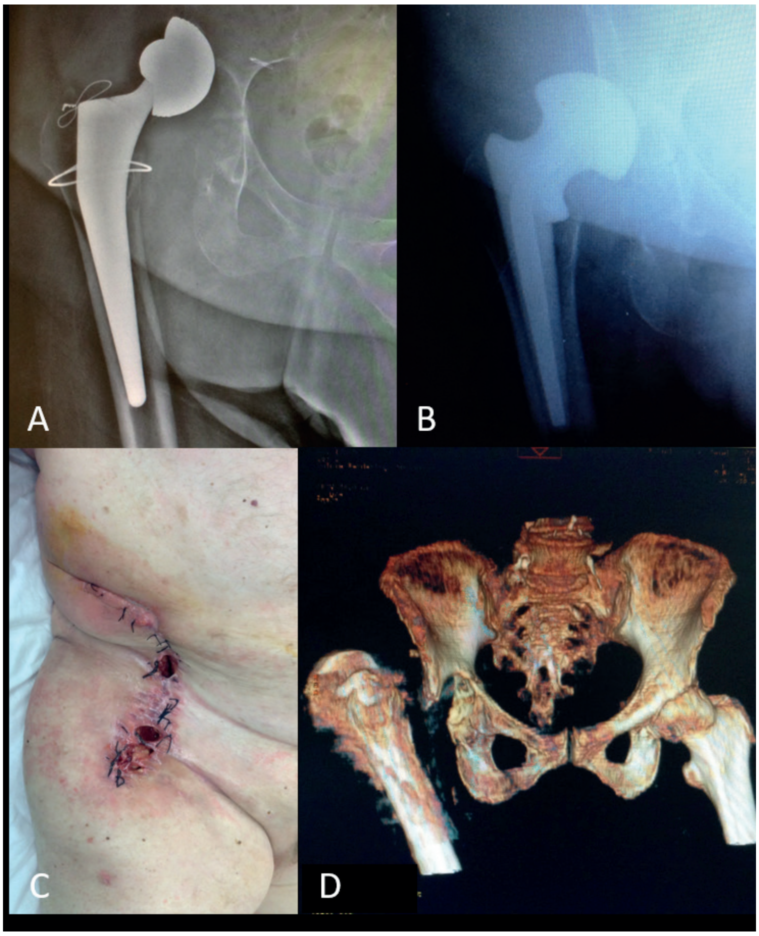

Figure 2. Girldestone procedure in a failed case of severe bone loss and soft tissues contamination in one obese (BMI=44) 70 year-old patient. A primary THA with a cup mobilization and poor bone stock (***A***), underwent to a 1st stage explantation and antibiotic spacer insertion (**B**). In the early postoperative period (21 days) abundant secretion and wound opening were evident (**C**). Poor bone stock and massive bone loss associated with soft tissues deterioration contraindicated the 2nd stage. After 3 months of multiple debridement and VAC therapy, the infection was eradicated.

undergone major variations in the last thirty years[27]. On this point, Wilson and Dorr found a 9% recurrence rate of infection following 22 patients with a minimum follow-up of 3 years in 1989[28]. In their study, Lai et al[29] reported a recurrence rate of 12.5% in a cohort of 40 patients with a mean follow-up of 4 years in 1996. In addition, Haddad et al [30] observed a recurrence rate of 8% in a group of 50 patients followed for an average period of 5.8 years. The success rate of this revision surgery reported by Durbhakula et al[31] was 100% in a group of 20 patients followed for an average time of 38 months; these studies further confirm that our data are in line with the literature. Evaluating a review published in 2012 in which 36 different studies have been included, Lange et al [32] observed a failure rate of only 10.4% for two-stage revision surgery on a total of 929 patients. Our study also showed a re-infection rate of 9.5%, in line with the main reports in the literature.

We have statistically observed a close correlation between high BMI and higher risk of failure (25.34 in successes *vs.* 30.88 in failures, $p<0.05$). Obesity, already known as a risk factor for periprosthetic hip infection[33], has also been documented in other studies as a contributing factor in the development of serious complications or reinfection after revision surgical procedures. In 2015 Houdek et al[34], in two different studies, have shown that obesity (BMI>30) is associated with a higher risk of reinfection and further revisions. Obesity acts in a multifactorial way as an independent risk factor in the failure of revision. In addition, associated systemic factors, such as immunodeficiency and reduced wound healing, involve more frequent surgical scar revision and debridement[35]. Weight loss may have a favourable effect on the state of immune system impairment[35], although an optimal approach to achieving it has not yet been established. One of the most significant aspects highlighted by our study concerns the number of surgical procedures carried out on the same joint with a very high level of statistical significance (2.78 failures *vs.* 0.58 healing, $p<0.05$). On this matter, several authors have come to our conclusion. The same result came from Chen et al[27]: in their clinical study of a cohort of 155 patients with infected hip prosthesis and treated with two-stage revision, they have identified as a risk factor for the failure of treatment multiple procedures of debridement or substitution of the spacer before the prosthetic revision implantation (survival rate free from reinfection at 10 years=72.7% | $p=0.047$). The need to practice multiple debridements implies their ineffectiveness in eliminating necrotic tissues and biofilm, and consequently, the risk of a reinfection is significantly increased. Moreover, the joint subjected to multiple surgical procedures is compromised in its healing capacity due to the presence of damaged scars, adhesions, and loss of tissues. This exposes the patient to a greater risk of reinfection or other complications such as dislocations or iatrogenic fractures for a poor quality of bone and periarticular tissues.

In our case, healed patients were re-implanted after an intercurrent period longer than the failed ones. In literature, it has not yet been established with adequate evidence what is the optimum interval between the first and second stage, which (according to the study considered), varies from two weeks to several months[24]. Lai et al[36] carry out the revision procedures in a 48-week time interval. On the other hand, Haddad et al[37] wait 3 weeks between the first and second stage. A time interval between 10 and 21 weeks (12.5 weeks on average) was chosen by Durbhakula et al[38] in their study protocol. Cordero-Ampuero et al[39] instead, used as a criterion to determine the period of waiting the time needed for the normalization of the clinical and serological parameters, commonly between 2 and 24 months (10 months on average). In their study, many authors found that less than 90 days is inadequate and constitutes an important risk factor for failure of the treatment. In fact, the revision prosthesis implantation carried out too early involves a higher risk of reinfection or serious complications, due to the insufficient local release of antibiotic by the spacer and an inadequate duration of antimicrobial activity. However, an excessive wait for the second stage is accompanied by a lower rate of recovery in ROM and function, mainly due to muscular atrophy. In our study, 127.6 days in healed and 72.5 in failures ($p=0.17$ | $p>0.05$) show that the early "Second Stage" has a greater risk of failure, even if the difference does not appear statistically significant. Following this, it is now our practice to proceed to the second stage always after at least 3 months from the first stage. The optimal period for re-implanting is between the third and the fourth month after the first stage that we called the "The Gold period for the Second Stage". After that time, a more difficult surgery, bone loss and muscle contracture, and atrophy with loss of function and lower recovery are expected.

In our study, we observed a considerable age difference between the healed patients and those who had suffered reinfection or serious complications (healed=69.32 years *vs.* failures=75.68 years), although it was not found to have any statistical significance. Anyway, in other studies, elderly patients have been found to be at major risk for failure, as shown by Lange et al[40]. A more advanced age is characterized by a more frequent coexistence of comorbidities, mostly chronic, and this constitutes an increased risk of failure. Seniority is also marked by a reduction in the immune system response and by an impairment of the healing processes. Finally, the most fragile elderly subjects require longer recovery time from surgery and face prolonged periods of immobility and complications.

In our study, the risk of failure was not found to be very different between the two sexes. This aspect has long been debated in the literature, being male in some cases related to an increased risk of reinfection or serious complications. Some authors, like Willis et al[41] and Jamsen et al[42], have shown that males are related to an increased risk of periprosthetic infection following primary hip arthroplasty. On the other hand, Triantafyllopoulos et al[43] in a study carried out on a cohort of 548 patients (283 men and 265 women), have found that females are correlated to an increased risk of failure of the revision treatment and recurrence of infection. The authors have explained this evidence because of the gynoid distribution of adipose tissue and the different hormonal profile of women. However, this apparent contradiction is explained by the fact that the study of predictive factors of reinfection or serious complications is strongly limited by the relatively few examined cases and the wide variability of the demographic characteristics of the patients.

Another clinical aspect that has not emerged from our study concerns the possible correlation between the presence of comorbidities and the risk of failure. Comorbidities (such as heart disease, diabetes or obesity), being able to compromise the organism in a systemic way, involve an increase in the ASA score (American Society of Anaesthesiologists) and the CCI (Charlson Comorbidity Index) score. In fact, Lange et al[40] have found a correlation between a higher ASA and CCI score and mortality following the two-stage revision surgery. Other authors, like Choi et al[44] however, have, highlighted how only the CCI and not the ASA score is a predictive factor of mortality. Zmistowski et al[45] have found a statistically significant association between the presence of comorbidities and mortality in the first year after the revision treatment. By individually examining the various comorbidities that we found in our study, heart disease, diabetes, and rheumatoid arthritis, commonly considered by different authors as important risk factors in the development of periprosthetic infections, these did not significantly influence the risk of reinfection, probably due to the limited number of patients. In the field of general surgery, it is also established that hyperglycaemia in the post-operative period is associated with higher rates of infection of the surgical wound[46,47].

We found higher CRP and ESR values in patients where reinfection occurred compared to cases where the infection had been successfully eradicated. Although the difference has not been found to be significant from a statistical point of view, the values of CRP and ESR are widely studied in the literature for their use in the detection of infections. The most used diagnostic algorithm, the one proposed by MSIS[25], is based on them to confirm or not the presence of infection. Nevertheless, their use is subject of debate because they do not always demonstrate the eradication of the infection[24]. In cases of low-virulent pathogen infections or chronic infections, these parameters may also be completely normal[48,49]. However, while extensive attention is dedicated to their use as diagnostic markers of infection, with high sensitivity but low specificity[24], their possible use as predictive factors of reinfection is not frequently highlighted. In a retrospective study of 189 cases of periprosthetic hip infections, Bozhkova et al[50] observed a correlation between elevated levels of CRP and the presence of polymicrobial infections. Nevertheless, the authors did not detect any statistically significant differences in the ESR values between the two groups examined. On the other hand, Mortavazi et al[51] have not found any correlation between the values of CRP and ESR and the risk of failure of the revision treatment.

Finally, in our study, we have analyzed the possible association between the failure of the two-stage revision surgery and the presence of polymicrobial infection or more aggressive pathogenic strains. We have found no differences between the healed patients and those that have been re-infected. In the past, infections caused by *Staphylococcus Methicillin Resistant (MRSA)* have been associated with a lower rate of success in revision treatment[52,53,54]. However, Laudermilch et al[55] have not found cases of re-infection in patients infected by *MRSA* treated with two-stage revision surgery and not even a significant difference in the rate of reinfection from pathogens other than *MRSA*. In our study, the infection caused by *MRSA* and *MRSE* did not emerge as a risk factor for recurrence while a higher frequency of polymicrobial infections was observed in cases where the revision treatment failed. Polymicrobial infections are traditionally considered as risk factors for failure[56]. However, in the case of the two-stage revision surgery, Marculescu et al[57] observed a 63.8% success rate in the eradication of polymicrobial infections and less than 72.8% in case of monomicrobial infection. The authors found that the 2-year survival rate in the absence of re-infection was of 83.9% and 77.7% for monomicrobial and polymicrobial infections respectively. The difference was, however, statistically insignificant due to the reduced number of samples examined (49 cases of monomicrobial infection and 9 cases of polymicrobial infections). Similar success rates have been reported by Wimmer et al[58] in a cohort of 77 cases of periprosthetic infections of the hip and knee.

Conclusions

The identification of predictive risk factors for failure of the treatment of hip PJI is crucial for the future in terms of social and economic health system costs, especially in the case of hip prostheses implant due to pathological fractures[59]. However, the study of predictive factors of reinfection or serious complications following treatment of chronic PJI is strongly limited by the relatively few examined cases and the wide variability of the demographic characteristics of patients[60]. Our study has shown with statistical significance that a greater number of previous surgical procedures performed on the same joint and the high BMI are risk factors in predicting the failure of two-stage revision surgery. We have also observed an important difference for age, CRP and ESR values and the number of isolated pathogens, but not reaching statistical significance. We have not detected a higher risk of failure for resistant methicillin pathogens. It is advisable to inform patients suffering from obesity on the increased risks of failure of the two-stage revision procedure or of serious complications or reinfection, proposing the consultation of a dietician when necessary. With regard to the diagnostic utility of CRP and ESR, in light of the evidence given by various authors in literature and from our study, we suggest an attitude of prudence in using these laboratory parameters. High preoperative values do not necessarily constitute a risk factor for failure and, in addition, these are unspecific parameters. However, to reduce the risk of two-stage revision failure given by a large number of previous surgeries a useful preoperative strategy should be planned to avoid multiple debridements and to opt directly for revision if there are the indications. The waiting interval between the first and second stage must be at least 3 months, i.e., sufficiently long such as to allow the completion of the antibiotic therapy, eradication of the infection and adequate healing of the periprosthetic tissues.

Conflict of Interests

The Authors declare that they have no conflict of interests.

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