KLIC-score for predicting early failure in prosthetic joint infections treated with debridement, implant retention and antibiotics

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Abstract

Debridement, irrigation and antibiotic treatment form the current approach in early prosthetic joint infection (PJI). Our aim was to design a score to predict patients with a higher risk of failure. From 1999 to 2014 early PJIs were prospectively collected and retrospectively reviewed. The primary end-point was early failure defined as: 1) the need for unscheduled surgery, 2) death-related infection within the first 60 days after debridement or 3) the need for suppressive antibiotic treatment. A score was built-up according to the logistic regression coefficients of variables available before debridement. A total of 222 patients met the inclusion criteria. The most frequently isolated microorganisms were coagulase-negative staphylococci (95 cases, 42.8%) and *Staphylococcus aureus* (81 cases, 36.5%). Treatment of 52 (23.4%) cases failed. Independent predictors of failure were: chronic renal failure (OR 5.92, 95% CI 1.47–23.85), liver cirrhosis (OR 4.46, 95% CI 1.15–17.24), revision surgery (OR 4.34, 95% CI 1.34–14.04) or femoral neck fracture (OR 4.39, 95% CI1.16–16.62) compared with primary arthroplasty, C reactive protein >11.5 mg/dL (OR 12.308, 95% CI 4.56–33.19), cemented prosthesis (OR 8.71, 95% CI 1.95–38.97) and when all intraoperative cultures were positive (OR 6.30, 95% CI 1.84–21.53). A score for predicting the risk of failure was designed using preoperative factors (KLIC-score: **K**idney, **L**iver, **I**ndex surgery, **C**emented prosthesis and **C**-reactive protein value) and it ranged between 0 and 9.5 points. Patients with scores of ≤2, >2–3.5, 4–5, >5–6.5 and ≥7 had failure rates of 4.5%, 19.4%, 55%, 71.4% and 100%, respectively. The KLIC-score was highly predictive of early failure after debridement. In the future, it would be necessary to validate our score using cohorts from other institutions.

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Introduction

Open debridement, irrigation with implant retention and antibiotic treatment (DAIR) is an accepted approach for early prosthetic joint infections (PJI) [1] but the success rate using this strategy significantly varies among different cohorts. Some authors report failure rates ≥50% disregarding the causal microorganism [2–7] whereas others report failure rates <50%, mainly using rifampin combinations [8–16]. However, even when using rifampin, success rates are around 55–75%. In addition, despite the fact that two-stage exchange is associated with a high success rate, there is evidence showing worse results when it is performed as a salvage surgical treatment after failing with debridement and irrigation [17,18]. Therefore, it is necessary to identify predictors of failure that help surgeons to

select the best initial surgical approach avoiding unnecessary interventions.

Risk factors for failure in early PJI include infections caused by *Staphylococcus aureus* [2,9,11,19,20], arthroscopic debridement [11], polymicrobial infections [15], intra-articular purulence [6], all intraoperative samples being positive [21], retention of exchangeable components [15], or longer time between initial arthroplasty and diagnosis [2,3,16]. Some of these factors are only available after performing debridement but other reliable markers that are accessible before the first surgical approach are necessary. A previous nomogram using 17 variables was described; however, four variables were related to aetiological microorganisms that in general are not available before surgery and they analysed early and late infections [22].

The aim of our study was to identify predictors of early failure in our 15-year cohort of early PJI managed with debridement, irrigation and antibiotic treatment and to select those factors that are widely available before open debridement so as to design a score that helps us to decide the best initial surgical approach.

Patients and methods

From January 1999 to May 2014, all patients with a PJI (hip or knee arthroplasties) were prospectively registered in a database and prospectively followed up. For this study PJI diagnosed within the first 90 days after joint arthoplasty and without signs of loosening of the prosthesis were included. In all cases the duration of symptoms was shorter than 21 days. PJI was defined according to Musculoskeletal Infection Society criteria [23]. Variables gathered were: demographics (age and gender), body mass index (BMI), preoperative American Society of Anesthesiologists classification, co-morbidity (having or not having one of the following entities: hypertension, ischaemic heart disease, heart failure, anticoagulant treatment, diabetes mellitus, malignancy, liver cirrhosis, chronic renal failure, steroid therapy, dementia, rheumatoid arthritis or chronic obstructive pulmonary disease), site (hip or knee prosthesis), type of surgical indication (primary or revision surgery or femoral neck fracture), laterality, cemented or non-cemented prosthesis, age of prosthesis, time between PJI diagnosis and surgical debridement, polyethylene exchange during debridement, the use of flap for skin coverage, clinical manifestations (having or not having fever, pain, redness, wound drainage, skin necrosis, fistulae or septic shock), positive blood cultures, use of antibiotic treatment before debridement, baseline (at the moment of PJI diagnosis) serum analysis including: leucocyte count (cells/mm^3), C-reactive protein (CRP) (mg/dL), creatinine (mg/dL)

and glucose (mg/dL), percentage of positive cultures during debridement (positive cultures from total cultures submitted to the Microbiology laboratory), isolated microorganisms and susceptibility pattern, and early outcome. The Ethical Committee of our institution approved the study.

Definitions

For the present study the primary end-point was early failure, which was considered when: 1) the patient needed an unscheduled surgery (second debridement or implant removal) to achieve infection control within the first 60 days after initial debridement; 2) death-related infection within the first 60 days after initial debridement or 3) the need for long-term suppressive antibiotic treatment because the patient's general condition contraindicated additional surgeries.

Surgical treatment, microbiology and antibiotic treatment protocol

In terms of debridement, pre-existing incisions were always used, necrotic tissue was excised and the joint was washed with 6−9 L of saline. The components were left *in situ* after confirming that no signs of loosening were present at the time of surgery. Three to six deep samples of synovial fluid and periprosthetic tissue were submitted to the Microbiology laboratory. In addition, blood cultures were performed in patients with fever at the time of admission for infection. An antibiogram for all the isolates was performed by microdilution. After debridement, a broad-spectrum intravenous antimicrobial regimen including vancomycin (1 g/12 h) plus ceftazidime (2 g/8 h) was started and maintained until definitive microbiological results were obtained. The protocol of our hospital recommends 10 days of intravenous antibiotics and afterwards to switch to oral biofilm-active antibiotics. The duration of oral antibiotics was not standardized and it was decided by a member of the team (A.S.) based on the clinical manifestations of each case and the CRP concentration during follow up; however, all patients received at least 6 weeks. After being discharged, patients were followed up monthly while they were receiving antibiotic treatment and every 3−6 months during the first year after finishing therapy and once per year afterwards.

Statistical analysis

Continuous variables were expressed as mean and standard deviation (SD) or median and interquartile range (IQR) and were compared using the Student's *t* test or the Mann−Whitney *U* test according to the Kolmogorov−Smirnov test of normality. Continuous variables were also categorized according to the 75th centile (age of prosthesis until debridement ≤30 days and >30 days, time between PJI diagnosis and surgical debridement ≤4 days and >4 days, preoperative leucocyte

count ≤10 000 cell/mm^3 and >10 000 cell/mm^3, preoperative CRP ≤11.5 mg/dL and >11.5 mg/dL, preoperative creatinine ≤1.1 mg/dL and >1.1 mg/dL and preoperative glucose ≤125 mg/dL and >125 mg/dL), except for BMI value, which was categorized according to the WHO's obesity classification (<35 kg/m^2 and ≥35 kg/m^2), and patient age, which was categorized according to the mean value (<70 years and ≥70 years). Qualitative variables were described by absolute frequencies and percentages and were compared using the chi-square test or Fisher's exact test when necessary. Correlation curves between continuous variables were estimated by testing linear, logarithmic, exponential and quadratic equation models. The Kaplan−Meier survival method was used to estimate the cumulative probability of treatment success of the whole cohort from debridement and log-rank test was applied to compare survival curves. A forward stepwise logistic regression model was performed to identify independent predictors of failure. Goodness of fit was explored based on the Hosmer−Lemeshow test. Based on the logistic regression findings, a predictive additive scoring tool was developed to identify preoperative clinical signs of failure. Coefficients from the logistic regression were converted to intervals of 0.5. Risk groups were defined by the inspection of the prevalence of failure given the different score values. The predictive value of the scoring tool was checked for correctly indicating the failure rate via a receiver-operating characteristic curve. Statistical significance was defined as a two-tailed p < 0.05. The analysis was performed using SPSS, version 20.0 (SPSS, Inc., Chicago, IL, USA).

Results

A total of 222 patients with early PJI met the inclusion criteria for the study. The mean (SD) age of cohort was 71.6 (10.7) years and 121 were female (54.5%). One hundred and thirty-seven (61.7%) infections were of knee prostheses and in 165 (74.3%) patients the infected arthroplasty was cemented. In 34 (15.3%) patients the indication of the infected prosthesis was a femoral neck fracture and in 42 (18.9%) the PJI was on a revision arthroplasty. The infection was polymicrobial in 85 (38.3%) patients and the most frequently isolated microorganisms were coagulase-negative staphylococci (95 cases, 42.8%), *S. aureus* (81 cases, 36.5%), *Escherichia coli* (30 cases, 13.5%), *Enterococcus* spp. (29 cases, 13.1%), *Pseudomonas aeruginosa* (22 cases, 9.9%) and *Enterobacter cloacae* (15 cases, 6.8%). Fifty-two (23.4%) patients failed within the first 60 days after first debridement. The main characteristics of the cohort according to the outcome are shown in Table 1. Heart failure (44.1% versus 19.6%, p 0.002), chronic renal failure (60.0% versus 19.8%, p < 0.001) and liver cirrhosis (47.8% versus 20.6%, p

0.004) were significantly associated with failure. Primary prosthesis had a lower failure rate (19.7%) than revision arthroplasties (38.1%) and prosthesis indicated for femoral neck fracture (35.2%, p 0.003). Patients with bacteraemia (54.5% versus 21.8%, p 0.022), CRP >11.5 mg/dL (56.0% versus 15.6%, p < 0.001), leucocyte count >10 000 cell/mm^3 (35.4% versus 18.6%, p 0.007) and creatinine >1.1 mg/dL (33.9% versus 20.4%, p = 0.038) had a significantly higher failure rate. When all intraoperative cultures were positive (32.6% versus 9.4% p < 0.001) or PJI was polymicrobial (28.2% versus 20.4%, p = 0.182) there was a higher failure rate whereas monomicrobial PJI due to coagulase-negative staphylococci presented a significantly lower failure rate (12.5% versus 26.4%, p 0.044).

Values of CRP were carefully evaluated as a predictor of bacterial inoculum and treatment failure. CRP showed a direct relationship with the percentage of positive cultures (Fig. 1, linear equation, R^2 = 0.046, p 0.002) and an inverse association with the time between the debridement and failure (Fig. 2, logarithmic equation, R^2 = 0.179, p 0.003). Fig. 3 shows the cumulative survival function within the first 2 months after debridement according to the CRP value (log-rank test, p < 0.001).

All variables studied in the univariate analysis were included in a multivariate analysis except those with ≥10% of missing data (BMI, American Society of Anesthesiologists classification and antibiotic treatment before surgery). The step-wise forward logistic regression model identified as independent predictors of failure: chronic renal failure (OR 5.92, 95% CI 1.47−23.85), liver cirrhosis (OR 4.46, 95% CI 1.15−17.24), revision surgery (OR 4.34, 95% CI 1.34−14.04) or femoral neck fracture (OR 4.39, 95% CI 1.16−16.62) compared with primary arthroplasty, CRP >11.5 mg/dL (OR 12.308, 95% CI 4.56−33.19), cemented prosthesis (OR 8.71, 95% CI 1.95−38.97) and when all intraoperative cultures were positive (OR 6.30, 95% CI 1.84−21.53) (Hosmer−Lemeshow test, p 0.839).

A score for predicting the risk of failure was designed (Table 2) including all preoperative factors identified as independent predictors of failure (KLIC-score: **K**idney, **L**iver, **I**ndex surgery, **C**emented prosthesis and **C**-reactive protein value). The scores ranged from 0 to 9.5. By checking the score, patients were divided into five groups according to their overall score (Fig. 4). Among patients with a score ≤2, the failure rate was 4.5%, compared with 19.4% in those with >2 to 3.5 points, 55% in those with 4−5 points, 71.4% in those with >5 to 6.5 points and 100% when the score was ≥7 points. Fig. 5 shows the receiver-operating characteristic curve and the area under the receiver-operating characteristic curve was 0.839 (95% CI 0.767−0.911). A score >3.5 was associated with the best balance between sensitivity (0.739) and specificity (0.861).

TABLE 1. Characteristics of patients according to the outcome

Characteristics	Remission (*n* = 170)	Failure (*n* = 52)	p
Mean age (SD) years	71.3 (10.4)	72.4 (11.6)	0.545
Age ≥70 years	102 (60.0)	33 (63.5)	0.655
Gender			
Male	76 (44.7)	25 (48.1)	0.669
Female	94 (55.3)	27 (51.9)	
Mean (SD) BMI (kg/m^2)	31.1 (6.0)	31.6 (5.4)	0.672
BMI ≥35 (kg/m^2)	32 (22.4)	7 (19.4)	0.703
Preoperative ASA Classification III–IV	45 (30.4)	18 (46.2)	0.064
Co-morbidities			
Hypertension	116 (68.2)	35 (67.3)	0.900
Ischaemic heart disease	19 (11.2)	7 (13.5)	0.654
Heart failure	19 (11.2)	15 (28.8)	**0.002**
Anticoagulant	10 (5.9)	6 (11.5)	0.217
Diabetes mellitus	31 (18.2)	8 (15.4)	0.636
Malignancy	22 (12.9)	5 (9.6)	0.521
Chronic obstructive pulmonary disease	27 (15.9)	7 (13.5)	0.671
Chronic renal failure	8 (4.7)	12 (23.1)	**<0.001**
Liver cirrhosis	12 (7.1)	11 (21.2)	**0.004**
Steroid therapy	16 (9.4)	9 (17.3)	0.115
Dementia	7 (4.1)	5 (9.6)	0.158
Rheumatoid arthritis	5 (2.9)	3 (5.8)	0.394
Indication for previous surgery			
Primary surgery	122 (71.8)	24 (46.2)	**0.003**
Revision surgery	26 (15.3)	16 (30.8)	
Hip fracture	22 (12.9)	12 (23.1)	
Laterality (Right)	82 (48.2)	31 (59.6)	0.151
Type of cementation			
Not cemented	46 (27.1)	11 (21.2)	0.394
Cemented	124 (72.9)	41 (78.8)	
Site of arthroplasty			
Hip	61 (35.9)	24 (46.2)	0.195
Knee	109 (64.1)	28 (53.8)	
Median (IQR) age of prosthesis (days) until debridement	23 [16;31]	21 [14;29.75]	0.146
Age of prosthesis >30 days	43 (25.3)	12 (23.1)	0.855
Median (IQR) days between diagnosis and debridement	2 [1;4]	2 [1;4]	0.810
Days between diagnosis and debridement >4	37 (22.8)	11 (23.4)	0.935
Polyethylene exchange during debridement	122 (73.1)	37 (72.5)	0.943
Need flap for skin coverage	6 (3.5)	4 (7.7)	0.249
Clinical signs			
Fever	34 (20.0)	15 (30.0)	0.135
Pain	57 (69.5)	19 (73.1)	0.729
Redness	74 (89.2)	24 (92.3)	1.000
Wound drainage	82 (82.8)	23 (76.7)	0.447
Skin necrosis	9 (10.0)	4 (14.3)	0.505
Presence of fistula	12 (14.1)	5 (17.9)	0.761
Bacteraemia	5 (2.9)	6 (11.5)	**0.022**
Septic shock	0 (0)	1 (1.9)	0.234
Antibiotic treatment prior debridement	22 (25.9)	6 (25.0)	0.930
Median (IQR) leucocyte count (cell/mm^3)	8400 [6600;9980]	9250 [7000;12670]	0.068
Leucocyte count >10 000 cell/mm^3	42 (24.9)	23 (44.2)	**0.007**
Median (IQR) CRP (mg/dL)	3.05 [1.51;7.03]	14.77 [4.72;23.41]	**<0.001**
CRP >11.5 mg/dL	22 (13.9)	28 (60.9)	**<0.001**
Median (IQR) creatinine	0.84 [0.70;1.08]	0.90 [0.80;1.30]	**0.003**
Creatinine >1.1 mg/dL	37 (22.2)	19 (36.5)	**0.038**
Median (IQR) glycaemia	105 [95;126.5]	111.5 [98.25;129]	0.181
Glycaemia >125 mg/dL	42 (25.5)	17 (32.7)	0.306
Median (IQR) percentage of positive cultures	100 [67;100]	100 [100;100]	**<0.001**
All cultures positive during debridement	91 (53.8)	44 (86.3)	**<0.001**
Polymicrobial infection	61 (35.9)	24 (46.2)	0.182
Presence of microorganism			
Staphylococcus aureus	60 (35.3)	21 (40.4)	0.514
Methicillin-resistant	11 (6.5)	4 (7.7)	0.756
Methicillin-sensitive	49 (28.8)	17 (32.7)	0.606
Coagulase-negative staphylococci	80 (47.1)	15 (28.8)	**0.020**
Methicillin-resistant	46 (27.1)	9 (17.3)	0.154
Methicillin-sensitive	17 (10.0)	1 (1.9)	0.080
Unknown methicillin resistance	17 (10.0)	5 (9.6)	0.935
Enterococcus spp.	19 (11.2)	10 (19.2)	0.132
Streptococcus spp.	6 (3.5)	1 (1.9)	1.000
Escherichia coli	20 (11.8)	10 (19.2)	0.168
Pseudomonas spp.	16 (9.4)	6 (11.5)	0.653
Enterobacter cloacae	11 (6.5)	4 (7.7)	0.759
Proteus spp.	12 (7.1)	3 (5.8)	1.000

Bold indicates statistically significant differences.
ASA, American Society of Anesthesiologists; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; IQR, interquartile range.

Discussion

The primary goal of debridement and irrigation is to achieve infection control with only one surgical intervention. Indeed, a recent article comparing one versus three consecutive debridements has demonstrated a worse outcome in the second arm mainly as the result of a higher re-infection rate [24]. This result suggests that every time the prosthesis is opened, there is a risk of contamination by different microorganisms and as a
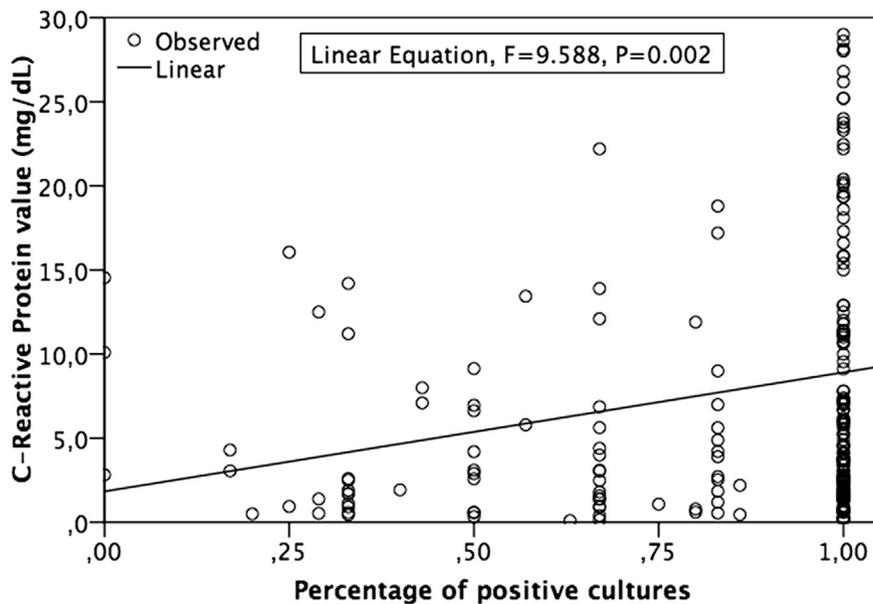
FIG. 1. Linear correlation between preoperative C-reactive protein value (mg/dL) and percentage of positive cultures obtained during debridement.

result the majority of these patients require a two-stage exchange to control the infection. Although two-stage exchange is associated with a high success rate, when it is performed as a salvage option after failed debridement the rate of success is significantly lower [17,18]. Based on these facts, it is necessary to identify not only robust predictors of failure but also those that are available early in the course of the infection. This is particularly important in early PJI because in these infections the longer the time to debridement the higher the failure rate [2,3,16].

Our results from a large single-centre cohort with a standard protocol for the management of early PJI throughout the last

15 years identified that when all cultures obtained during debridement are positive there is a high risk of failure (OR 6.30) as was also identified by Bouaziz et al. [21]. This supports the association of high bacterial inoculum with a more severe infection and a higher risk for early failure, as has been also demonstrated in patients with pneumonia [25]. A high bacterial inoculum significantly reduces the efficacy ('inoculum effect') of β-lactams [26] and glycopeptides [27,28]. In addition, it has been recently shown that *S. aureus* in synovial fluid forms clumps that are deposited on the inner surface of the synovial membrane and show a resistant pattern similar to the one described in biofilms [29]. It is reasonable to assume that the
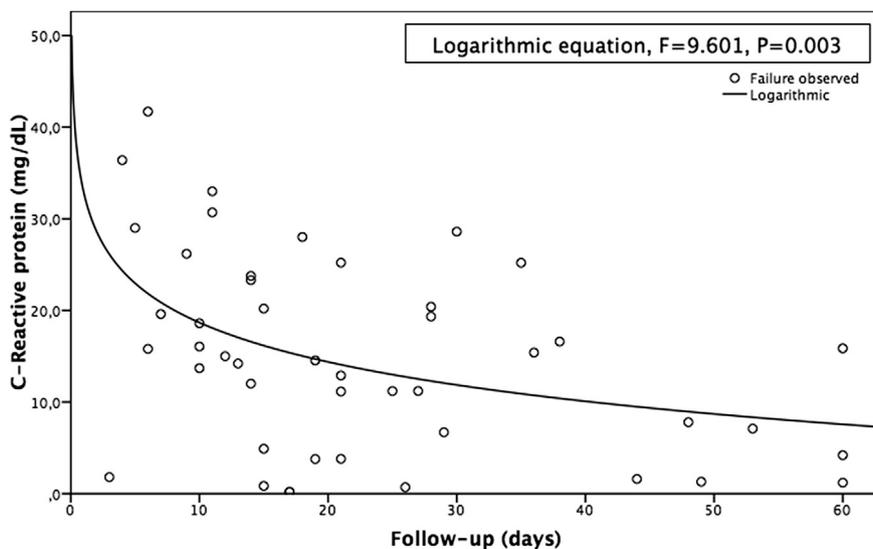

FIG. 2. Logarithmic correlation curve between preoperative C-reactive protein value and time between debridement and failure.
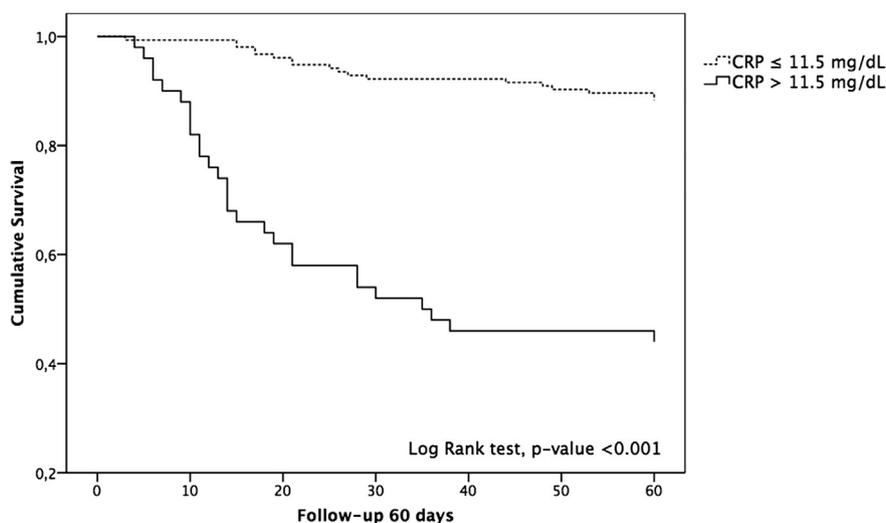
FIG. 3. Cumulative survival function within the first 2 months after debridement according to the C-reactive protein concentration (≤11.5 or >11.5 mg/dL).

higher the inoculum the higher the number of bacterial clumps, making the activity of antibiotics difficult. For this reason, it is necessary to identify preoperative predictors of bacterial inoculum. In line with this, CRP is a cheap and widely available acute-phase protein synthesized by the liver in response to factors released by macrophages. CRP binds to the bacterial surface and activates the complement system, promoting phagocytosis by macrophages, which clears bacteria. In our study, CRP showed a direct relationship with the percentage of positive cultures and an inverse correlation with the time from debridement to failure (Figs. 1 and 2), suggesting that it is a good surrogate marker for the bacterial inoculum. Another characteristic of our series is the high rate of polymicrobial infections (38%); however, it was similar to the rate reported by others in patients with similar characteristics [30,31].

Considering those predictors available before surgery like chronic renal failure, liver cirrhosis, cemented prosthesis, revision arthroplasty or arthroplasty for femoral neck fracture

TABLE 2. KLIC-score (Kidney, Liver, Index surgery, Cemented prosthesis and C-reactive protein value): scoring system to evaluate the early failure rate of prosthetic joint infections treated with debridement, irrigation and implant retention

Variable		Score
K	Chronic renal failure (**K**idney)	2
L	**L**iver cirrhosis	1.5
I	**I**ndex surgery = Revision surgery or prosthesis indicated for femoral neck fracture	1.5
C	**C**emented prosthesis	2
C	**C**-reactive protein >11.5 mg/dL	2.5

and CRP, a useful score (Table 2) to identify patients at a higher risk of failure was built-up (Fig. 4). According to the KLIC-score, patients with ≥4 points had a failure rate >60% and should be considered for alternative strategies different from standard debridement and irrigation. The potential alternatives could be: 1) multiple scheduled debridements; however, recent experience [24] demonstrated that this strategy is worse than only one debridement, 2) removing the prosthesis as a first surgical approach (one- or two-stage exchange); however, other authors did not find differences between DAIR and prosthesis exchange in early PJI [31,32], and 3) to start with more potent anti-biofilm antibiotics than vancomycin or even to locally administer high antibiotic concentrations. A recent multi-centric study evaluated the efficacy of high-dose daptomycin plus rifampin as initial treatment in 18 early PJIs due to fluoroquinolone-resistant staphylococci [33]. The overall failure rate was 50% and the relapse rate was 28%, which was better than the rates reported with vancomycin [4]. As prosthesis exchange is an aggressive surgical approach for implants that are not loosened, we consider that efforts should be focused on improving the success rate of DAIR, perhaps using additional strategies such as more potent systemic antibiotics or the administration of local antibiotics.

There are some limitations to our study; first, our score was obtained from a single-centre experience; therefore, we cannot be sure about its applicability in other centres. Second, other biomarkers such as procalcitonin or interleukin-6 could be more accurate than CRP; however, these parameters are not available everywhere whereas CRP is a cheap and widely used marker. Third, although a follow-up of 2 years is, in general, required to evaluate the outcome of PJIs, the aim of our study was to identify predictors of early failure (within the first
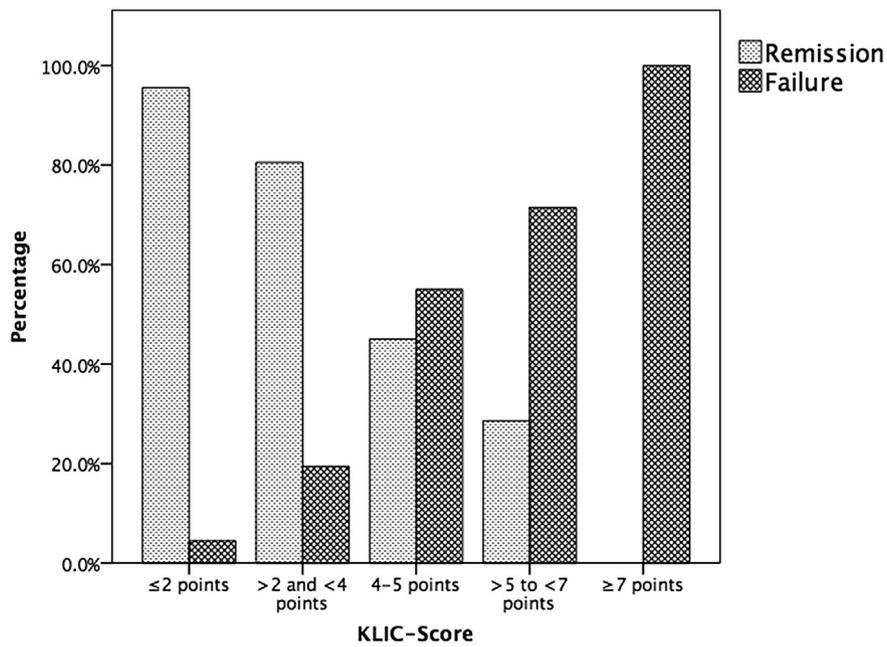
FIG. 4. Percentage of remission and failure after debridement according to the stratification derived from the KLIC-score.
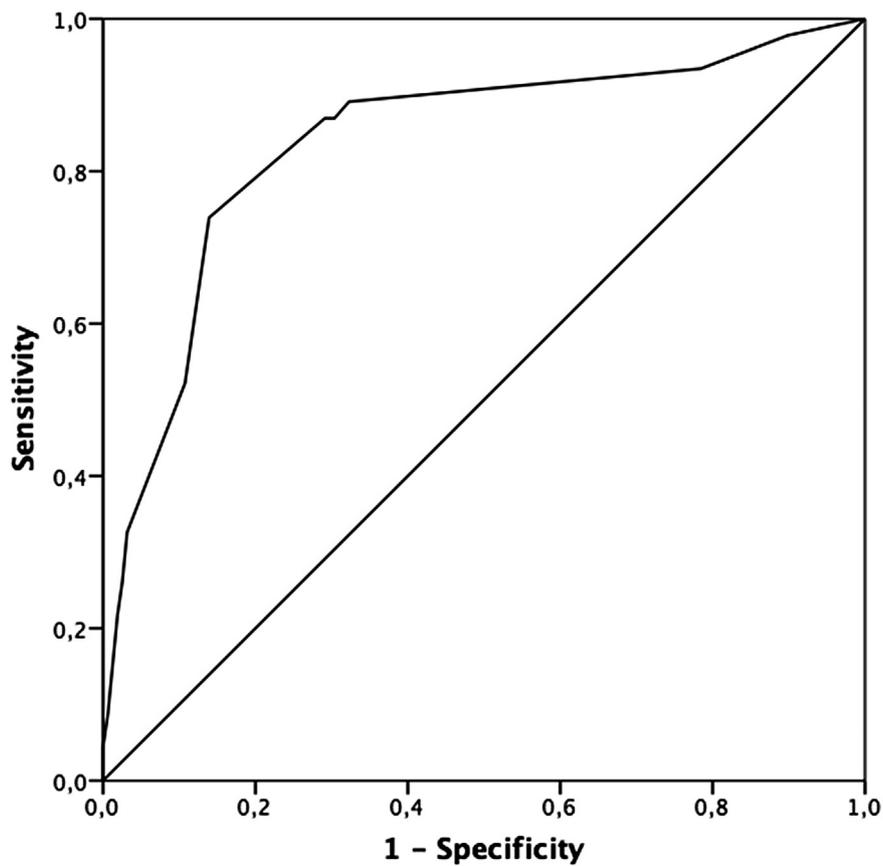

FIG. 5. Receiver-operating characteristic curve of the KLIC-score.

60 days) that lead to additional and unscheduled surgery because late failure could be influenced by many other factors. Finally, our study included only early (<3 months) PJI; therefore, the KLIC-score could not be applied for predicting the outcome of late acute haematogenous PJI.

In conclusion, the early failure rate with debridement and irrigation in a large single-centre cohort was 23.4% and the main predictors of failure were co-morbidity, the reason for arthroplasty, cemented or non-cemented prosthesis, the baseline CRP and the number of positive intra-operative cultures. Considering only those factors available before the first surgical approach, a useful score was designed with a high predictive value. In the future, it would be necessary to validate our score using cohorts from other institutions.

Transparency declaration

Acknowledgements

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