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Complications - Infection

Predicting Failure in Early Acute Prosthetic Joint Infection Treated With Debridement, Antibiotics, and Implant Retention: External Validation of the KLIC Score

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ABSTRACT

Background: Debridement, antibiotics, and implant retention (DAIR) is a widely used treatment modality for early acute prosthetic joint infection (PJI). A preoperative risk score was previously designed for predicting DAIR failure, consisting of chronic renal failure (K), liver cirrhosis (L), index surgery (I), cemented prosthesis (C), and C-reactive protein >115 mg/L (KLIC). The aim of this study was to validate the KLIC score in an external cohort.

Methods: We retrospectively evaluated patients with early acute PJI treated with DAIR between 2006 and 2016 in 3 Dutch hospitals. Early acute PJI was defined as <21 days of symptoms and DAIR performed within 90 days after index surgery. Failure was defined as the need for (1) second DAIR, (2) implant removal, (3) suppressive antimicrobial treatment, or (4) infection-related death within 60 days after debridement.

Results: A total of 386 patients were included. Failure occurred in 148 patients (38.3%). Patients with KLIC scores of $\leq$2, 2.5-3.5, 4-5, 5.5-6.5, and $\geq$7 had failure rates of 27.9%, 37.1%, 49.3%, 54.5%, and 85.7%, respectively ($P < .001$). The receiver-operating characteristic curve showed an area under the curve of 0.64 (95% confidence interval 0.59-0.69). A KLIC score higher than 6 points showed a specificity of 97.9%.

Conclusion: The KLIC score is a relatively good preoperative risk score for DAIR failure in patients with early acute PJI and appears to be most useful in clinical practice for patients with low or high KLIC scores.

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The institutional review boards of the participating hospitals approved this study. The study is conducted in accordance to the principles of the Declaration of Helsinki, the Medical Research Involving Human Subjects Act (WMO), and the Good Clinical Practice standard (GCP). In consultation with the review boards, obtaining informed consent from the participants was not required in this observational study.

This manuscript represents a multicenter study, in which authors are part of a writing committee. All authors assume responsibility for the overall content and integrity of the article. C.L. and M.W. conducted the study, in collaboration with P.J., J.P., B.K., A.V., W.Z., and B.D., E.T. and AS aided in the legitimate process of validation of the risk score.

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Total joint arthroplasty is a widely used treatment modality for osteoarthritis of the hip and knee, with 310,800 total hip arthroplasties and 639,400 total knee arthroplasties performed in the United States in 2010 [1,2]. In general, joint arthroplasty is a successful procedure with large improvement in the patient's quality of life. However, prosthetic joint infection (PJI) is a major complication after joint arthroplasty with high impact on the patient's well-being, occurring in 1%-2% of primary joint arthroplasties and up to 10% in revision arthroplasties [3,4]. Most of these infections occur within the first 3 months after implantation and are defined as early infections [5,6].

Surgical debridement, antibiotics, and implant retention (DAIR) is the recommended treatment for patients with early PJI, being most successful in early acute PJI, in which symptoms exist for less than 3 weeks [7,8]. Nevertheless, rates of infection control after DAIR vary widely from 37%-88% [9–16]. Therefore, it is important to be able to predict DAIR failure to select eligible patients before surgery, especially because performing a DAIR procedure could negatively influence the outcome of subsequent revision arthroplasty. A couple of studies showed a higher failure rate of 2-stage revisions after failed DAIR [17,18], although this has not been confirmed by others [19,20].

Previous studies identified risk factors for DAIR failure including high inflammatory parameters, infection with *Staphylococcus aureus*, longer duration of symptoms, polyethylene retention, and arthroscopic debridement [21–30]. In addition, Tornero et al [31] designed a preoperative risk score with a high accuracy for predicting failure (area under the curve [AUC] 0.84). This score consists of 5 preoperative factors, which were identified as independent predictors of failure in 222 patients with early acute PJI: (1) chronic renal failure (**K**idney), (2) **L**iver cirrhosis, (3) **I**ndex surgery (revision surgery or prosthesis indicated for a fracture), (4) **C**emented prosthesis, and (5) **C**-reactive protein (CRP) > 115 mg/L.

To implement the chronic renal failure (K), liver cirrhosis (L), index surgery (I), cemented prosthesis (C), and CRP >115 mg/L (KLIC) score in other hospitals as a standard tool for predicting DAIR failure in early acute PJI, it is important to validate the risk score in an external cohort. Therefore, we assessed the predictive value of the KLIC score in a large cohort of patients with early acute PJI treated with DAIR in the Netherlands.

Materials and Methods

Study Design

We retrospectively analyzed patients with early acute PJI who were treated with DAIR between January 2006 and December 2016 in 2 general hospitals (Martini Hospital and Medical Center Leeuwarden) and 1 university hospital (University Medical Center Groningen) in the Netherlands. Patients who developed a PJI within 3 months after joint arthroplasty and had a duration of symptoms of <21 days were included. Diagnosis of PJI was determined according to the diagnostic criteria defined by the Musculoskeletal Infection Society [32]. Patients who did not meet the Musculoskeletal Infection Society criteria were excluded from the analysis, as well as patients who underwent arthroscopic debridement instead of open surgical debridement.

Variables that were collected included demographics, body mass index, preoperative American Society of Anesthesiologists (ASA) classification, comorbidities, medication, clinical signs, serological markers, culture results and data of the index procedure, and DAIR. The same definitions and cut-off values of these variables were used as described by Tornero et al [31]. Sepsis was defined as presence of ≥2 systemic inflammatory response syndrome criteria and a suspected source of infection. Consistent with Tornero et al [31], we appointed scores to the preoperative variables of the KLIC score, adding up to a score ranging from 0-9.5 points (Table 1). The score was categorized into ≤2, 2.5-3.5, 4-5, 5.5-6.5, and ≥7 points.

Table 1
Preoperative Variables of the KLIC Score With Appointed Scores.

	Variable	Score
K	Chronic renal failure (kidney)	2
L	Liver cirrhosis	1.5
I	Index procedure (revision surgery or prosthesis indicated for a fracture)	1.5
C	Cemented prosthesis	2
C	C-reactive protein >115 mg/L	2.5

KLIC, chronic renal failure (K), liver cirrhosis (L), index surgery (I), cemented prosthesis (C), and C-reactive protein >115 mg/L.

Definition of Outcome

Primary outcome was early failure, defined as one of the following events within 60 days after initial debridement: (1) second DAIR, (2) revision surgery or implant removal, (3) infection-related death, or (4) suppressive antimicrobial treatment. In case a second DAIR procedure was solely performed for removal of gentamicin-impregnated beads, without clinical and biochemical signs of persistent infection, second debridement was not considered as failure.

Surgical and Antimicrobial Treatment

Surgical treatment consisted of DAIR, in which the wound was opened via the preexisting incision and hematoma and avital tissue were extensively excised. Subsequently, the wound was thoroughly lavaged using 3-6 L of saline. According to local protocols and the clinical judgment of the orthopedic surgeon, modular components were optionally exchanged and gentamicin-impregnated beads or sponges were inserted into the joint cavity. After obtaining multiple deep tissue biopsies for culture, broad-spectrum intravenous antimicrobial treatment was started, if necessary adjusted according to the antibiogram, and maintained for 2 weeks. Subsequently, oral antimicrobial treatment was administered for 10 weeks. Rifampin was added to the antimicrobial treatment regimen in infections caused by staphylococci.

Statistical Analysis

Categorical variables were expressed in absolute frequencies and percentages. Continuous variables were presented as mean and standard deviation or as median and interquartile range when not normally distributed. Categorical variables were compared using the chi-square test. Continuous variables were compared using the Student *t* test or the Mann-Whitney *U* test according to the Kolmogorov-Smirnov test of normality.

Failure rates were reported for each risk group of the KLIC score and a receiver-operating characteristic curve was used to examine its accuracy for predicting DAIR failure. In addition, a binary logistic regression analysis was performed to evaluate whether additional important variables were associated with failure. Multicollinearity of variables was assessed. Multivariate logistic regression analysis was performed to identify independent predictors for failure. All preoperative variables with $P < .20$ in the univariate analyses were assessed in the multivariate regression analysis. Statistical significance was defined as a 2-tailed $P < .05$. Statistical analyses were performed using IBM SPSS Statistics (version 24.0; Chicago).

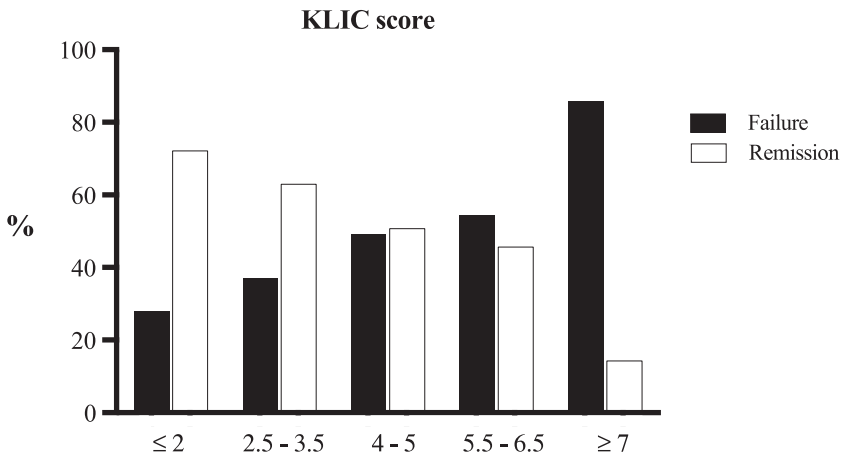

Fig. 1. Percentage of failure after debridement per group of KLIC score.

Results

Patient Population

A total of 386 patients with early acute PJI treated with DAIR were included. The mean age was 73.2 years (standard deviation ± 11.5) and 61.7% were female. Two hundred ninety-six patients (76.7%) had an infected hip prosthesis and 86 patients (22.3%) an infected knee prosthesis. 85.5% (n = 330) of the infected prostheses were primary implants. In 252 patients (65.3%), the indication for the prosthetic joint was osteoarthritis, and in 89 patients (23.1%) fracture. In 148 patients (38.3%), initial debridement failed within 60 days, of which 125 patients (84.5%) underwent a second DAIR, 5 patients (3.4%) needed suppressive antimicrobial treatment, 11 patients (7.5%) underwent revision surgery, and 7 patients (4.7%) deceased because of PJI.

Validation KLIC Score

Patients with a score ≤2 points had a 27.9% failure rate (n = 183), compared with 37.1% for patients with 2.5-3.5 points (n = 70), 49.3% with 4-5 points (n = 71), 54.5% with 5.5-6.5 points (n = 55), and 85.7% with ≥7 points (n = 7) (Fig. 1). Adjusting the stratification of the KLIC score for optimal clinical applicability showed a failure rate of 28.6% for patients with ≤3 points (n = 192), 46.5% with 3.5-6.5 points (n = 187), and 85.7% with ≥7 points (n = 7).

Binary logistic regression analysis showed that the KLIC score had good predictive value for DAIR failure ($P < .001$, odds ratio [OR] 1.32), in which one point increase in the KLIC score represents a 1.32 times higher risk of failure. The receiver-operating characteristic curve showed an AUC of 0.64 (95% confidence interval 0.59-0.69; Fig. 2). A score of 3.5 points showed the optimal cut-off point value with a sensitivity and specificity of 52.2% and 70.9%, respectively. A score higher than 6 points showed a specificity of 97.9%.

Differences Between Cohorts

Considering the lower accuracy of the KLIC score in our cohort (AUC 0.64) compared with Tornero et al (AUC 0.84), we additionally evaluated the differences between both cohorts. The incidence of variables used in the KLIC score differed. The incidence of liver cirrhosis in our cohort was significantly lower compared with Tornero et al (1.0% vs 10.4%, $P < .001$), and the incidence of cemented prostheses and CRP >115 mg/L was significantly higher (83.9% vs 74.3%, $P = .004$ and 32.4% vs 24.5%, $P = .046$, respectively). There were no differences in incidence of chronic renal failure and index procedure.

Additional notable differences between cohorts were the number of PJIs of the hip (76.7% vs 38.3%, $P < .001$) and the number of infections caused by *S. aureus* (46.9% vs 36.5%, $P = .013$). Polyethylene exchange was performed to a lesser extent in our cohort compared with that of Tornero et al (21.0% vs 72.9%, $P < .001$). Furthermore, in our cohort, gentamicin-impregnated beads and sponges were placed during a DAIR procedure in 184 patients (47.7%) and 109 patients (28.2%), respectively, whereas Tornero et al did not use any local antimicrobials. The accuracy of the KLIC score did not change in the presence or absence of the above-mentioned variables (data not shown).

Preoperative and Perioperative Variables According to Outcome

Table 2 shows the results of preoperative variables in relation to the outcome of debridement in our cohort. Various preoperative variables showed significant differences between patients with remission and failure after debridement, including CRP (78.8 vs 132.4 mg/L, $P < .001$), age (72.0 vs 75.1 years, $P = .009$), days from arthroplasty to debridement (21.0 vs 18.2 days, $P = .018$), ASA classification (2.29 vs 2.44, $P = .021$), and leukocyte count (11.0 vs 12.2 $\times 10^9$/L, $P = .027$).

Moreover, failure rates were significantly higher for the following preoperative variables: CRP >115 mg/L (55.2% vs 30.3%, $P < .001$), left-sided prosthesis (46.7% vs 31.1%, $P = .002$), presence of sepsis (52.1% vs 35.1%, $P = .007$), ischemic heart disease (50.6% vs 35.3%, $P = .013$), and prosthesis indicated for a fracture (52.8% vs 33.3%, $P = .047$). Multicollinearity analyses revealed that a left-sided prosthesis was associated with a higher percentage of positive cultures (93.6% vs 89.3%, $P = .028$), sepsis (25.0% vs 13.6%, $P = .004$), and *S. aureus* infection (57.8% vs 37.4%, $P < .001$). Presence of a fistula was associated with a significant lower failure rate after debridement (22.0% vs 40.3%, $P = .022$) and was associated with younger age (67.5 vs 73.9, $P = .001$) and a lower percentage of positive cultures (85.0% vs 92.1%, $P = .032$). Multivariate regression analysis showed that the following preoperative variables were significant independent predictors for DAIR failure in our cohort: gender (OR 2.03), ischemic heart disease (OR 1.84), laterality of the arthroplasty (OR 1.80), age (OR 1.03), CRP (OR 1.01), and days from arthroplasty to debridement (OR 0.97).

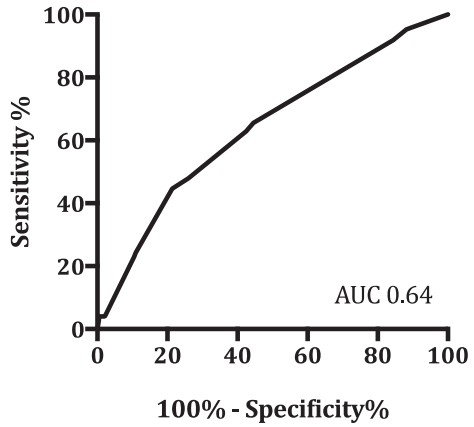

Fig. 2. Receiver-operating characteristic curve for the KLIC score.

Table 3 shows the results of perioperative variables in relation to the outcome of debridement. Positive cultures in all the obtained intraoperative tissues and bacteremia were associated with a significant higher failure rate (41.7% vs 26.2%, $P = .010$ and 57.7% vs 34.4%, $P = .008$, respectively), just as the use of gentamicin-impregnated beads or sponges (43.0% vs 23.7%, $P = .001$). Multicollinearity analyses showed that use of local antimicrobials was associated with a higher CRP value (105.9 vs 78.6 mg/L, $P = .020$) and a higher number of *S. aureus* infection (50.2% vs 36.6%, $P = .022$).

Infection with *S. aureus* showed a higher failure rate (47.5% vs 30.2%, $P < .001$), as well as infection with anaerobe microorganisms (ie, *Cutibacterium acnes* [n = 4], *Bacteroides fragilis* [n = 4], and *Finegoldia magna* [n = 4]; 66.7% vs 37.2%, $P = .021$), although anaerobe microorganisms were isolated in only a limited amount of cases (n = 15). Although gram-negative microorganisms in general were not associated with DAIR failure (42.5% vs 37.3%, $P = .390$), infection with *Proteus* species did show a significant higher failure rate (61.1% vs 37.2%, $P = .042$). However, *Proteus* species were also isolated in only a limited amount of cases (n = 18). Infection with *Corynebacterium* species and other gram-positive microorganisms showed a significant lower failure rate (23.5% vs 40.6%, $P = .020$ and 8.3% vs 39.3%, $P = .030$, respectively).

Discussion

We evaluated the preoperative predictive value of the KLIC score for DAIR failure in a large external cohort of 386 patients. Our study showed that the KLIC score is a relatively good preoperative risk score for predicting failure, but its predictive value was lower than previously described, with an AUC of 0.64 in our cohort compared with 0.84 in the study by Tornero et al [31]. This lower predictive accuracy is probably due to the retrospective design of this study and differences in local epidemiology, clinical characteristics, and surgical techniques. Although performing an additional prospective study could be useful, our results demonstrated that the KLIC score is applicable in clinical practice in patients with a low (<3.5 points) or high (>6 points) KLIC score for predicting DAIR failure.

Differences between cohorts are the most important reason that a predictive model should be validated externally before it can be implemented in clinical practice in other countries and hospitals. Therefore, validating the KLIC score in a large external cohort of patients in the Netherlands is one of the strengths of our study. In addition, by using the exact same variables, inclusion criteria, definition of failure, and cut-off values as Tornero et al, the process of validation of the KLIC score was executed legitimately.

Table 2
Preoperative Patient Characteristics According to Outcome.

Characteristics	Remission (n = 238)	Failure (n = 148)	*P* Value
Age, y			
Mean (SD)	72.01 (11.47)	75.12 (11.23)	**.009**
≥70	152 (63.9%)	105 (70.9%)	.152
Gender			
Male	79 (33.2%)	69 (46.6%)	.080
BMI, kg/m^2			
Mean (SD)	30.17 (6.48)	29.10 (5.62)	.117
≥35	50 (22.3%)	23 (17.4%)	.269
Preoperative ASA classification			
Mean (SD)	2.29 (0.65)	2.44 (0.60)	**.021**
3-4	90 (37.8%)	65 (43.9%)	.234
Comorbidities			
Hypertension	147 (61.8%)	92 (62.2%)	.938
Ischemic heart disease	38 (16.0%)	39 (26.4%)	**.013**
Heart failure	22 (9.2%)	19 (12.8%)	.265
Diabetes mellitus	46 (19.3%)	36 (24.3%)	.243
Malignancy	57 (23.9%)	30 (20.3%)	.400
COPD	43 (18.1%)	38 (25.7%)	.074
Chronic renal failure	15 (6.3%)	11 (7.4%)	.667
Liver cirrhosis	1 (0.4%)	3 (2.0%)	.130
Dementia	8 (3.4%)	8 (5.4%)	.327
Rheumatoid arthritis	17 (7.1%)	11 (7.4%)	.915
Medication			
Anticoagulants	51 (21.4%)	44 (29.7%)	.066
Steroid therapy	23 (9.7%)	21 (14.2%)	.174
Site of arthroplasty			
Knee	54 (22.7%)	32 (21.6%)	.697
Hip	181 (76.1%)	115 (77.7%)	
Laterality			
Left	96 (40.3%)	83 (56.8%)	**.002**
Indication for arthroplasty			
Osteoarthritis	168 (70.6%)	84 (56.8%)	**.047**
Fracture	42 (17.6%)	47 (31.8%)	
Type of surgery			
Primary	207 (87.0%)	123 (83.1%)	.294
Revision	31 (13.0%)	25 (16.9%)	
Type of cementation			
Not cemented	43 (18.1%)	19 (12.8%)	.274
Cemented (without antibiotics)	8 (3.4%)	8 (5.4%)	
Cemented (with antibiotics)	187 (78.6%)	121 (81.8%)	
Days from prosthesis to debridement			
Mean (SD)	21.03 (12.96)	18.24 (9.88)	**.018**
>28 d	33 (13.9%)	13 (8.8%)	.134
Days of symptoms			
Mean (SD)	6.71 (5.95)	7.21 (6.01)	.425
Clinical signs			
Fever	42 (17.6%)	31 (20.9%)	.421
Pain	77 (32.4%)	39 (26.4%)	.211
Redness	97 (40.8%)	64 (43.2%)	.630
Wound drainage	207 (87.0%)	127 (85.8%)	.745
Skin necrosis	6 (2.5%)	7 (4.7%)	.242
Presence of fistula	32 (13.4%)	9 (6.1%)	**.022**
Sepsis	35 (14.7%)	38 (25.7%)	**.007**
Antimicrobial treatment before debridement	42 (17.6%)	24 (16.2%)	.717
Leukocyte count, $\times 10^9$/L			
Mean (SD)	10.96 (4.44)	12.19 (5.79)	**.027**
>10	121 (50.8%)	85 (57.4%)	.207
CRP, mg/L			
Mean (SD)	78.80 (86.19)	132.37 (108.0)	**<.001**
>115	56 (23.5%)	69 (46.6%)	**<.001**
Creatinine, mg/L			
Mean (SD)	79.94 (30.39)	79.23 (33.94)	.831
>110	30 (12.6%)	15 (10.1%)	.454
Glycemia			
Mean (SD)	7.23 (1.85)	7.57 (2.65)	.277

Bold indicates statistically significant differences.
ASA, American Society of Anesthesiologist; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; SD, standard deviation.

Table 3
Perioperative Patient Characteristics According to Outcome.

Characteristics	Remission (n = 238)	Failure (n = 148)	*P* Value
Polyethylene exchange	47 (19.8%)	34 (23.0%)	.462
Local antimicrobials			
No antimicrobials	71 (29.8%)	22 (14.9%)	**.001**
Gentamicin beads	12 (5.0%)	16 (10.8%)	
Gentamicin sponges	113 (47.5%)	71 (48.0%)	
Gentamicin beads + sponges	42 (17.6%)	39 (26.4%)	
Need for muscle flap for skin coverage	3 (1.3%)	5 (3.4%)	.156
Bacteremia	11 (4.6%)	15 (10.1%)	**.008**
Percentage of positive cultures			
Mean (SD)	89.38 (21.6)	94.45 (16.3)	**.009**
All cultures positive	176 (73.9%)	126 (85.1%)	**.010**
Polymicrobial infection	109 (45.8%)	67 (45.3%)	.919
Microorganism			
Staphylococcus aureus	95 (39.9%)	86 (58.1%)	**<.001**
Methicillin-resistant *Staphylococcus aureus*	0 (0%)	0 (0%)	1.000
Staphylococcus epidermidis	85 (35.7%)	41 (27.7%)	.103
Corynebacterium species	39 (16.4%)	12 (8.1%)	**.020**
Enterococcus species	44 (18.5%)	26 (17.6%)	.820
Streptococcus species	44 (18.5%)	22 (14.9%)	.358
Other gram-positives	11 (4.6%)	1 (0.7%)	**.030**
Escherichia coli	11 (4.6%)	8 (5.4%)	.729
Pseudomonas species	15 (6.3%)	4 (2.7%)	.112
Enterobacter cloacae	10 (4.2%)	5 (3.4%)	.684
Proteus species	7 (2.9%)	11 (7.4%)	**.042**
Other gram-negatives	11 (4.6%)	12 (8.1%)	.159
Anaerobes	5 (2.1%)	10 (6.8%)	**.021**
Candida species	1 (0.4%)	2 (1.4%)	.311

Bold values indicate statistically significant differences.
SD, standard deviation.

Although our study demonstrated that the KLIC score does predict failure, the sensitivity, specificity, and accuracy were lower than previously described. A cause for this could be that we performed a retrospective database research while Tornero et al [31] carried out a prospective study. In addition, differences in incidence of variables in the KLIC score, a higher number of PJIs of the hip, more infections caused by *S. aureus*, and the use of local antimicrobials could be the cause of the lower accuracy of the KLIC score. Furthermore, there was a lower percentage of polyethylene exchange in our cohort, partially because of the use of certain types of arthroplasties in which polyethylene exchange was not possible (ie, AGC prostheses). Moreover, we observed an evident increase in the percentage of polyethylene exchange from 0% in 2006 to 46.3% in 2016 in our cohort, as the importance of exchanging modular components became more evident in recent years [7,22].

Most preoperative and perioperative risk factors for DAIR failure were in concordance with previous studies, including the preoperative variables: inflammatory parameters [22,25,27,28], ASA classification [29,30], and duration of symptoms [21,23,26,27,30], and perioperative variables: bacteremia, a higher percentage of positive cultures, and infection with *S. aureus* [11,29,33]. In our cohort, multivariate regression analysis revealed that additional preoperative variables other than the variables included in the KLIC score were predictive of failure, indicating the dynamics in risk scores because of differences in studied populations, thereby stressing the need for validation of risk scores in external cohorts.

A remarkable difference between the cohorts is the failure rate of debridement (38.3% vs 23.4%), which could be explained by the higher percentage of *S. aureus* infections and higher CRP values in our cohort. Over the years, the failure rate decreased gradually from 45.5% in 2006 to 31.7% in 2016 in our cohort, possibly because of the increase in polyethylene exchange. Nonetheless, our failure rate is comparable with previous studies [9,11,12,14,15].

Preoperative risk factors for DAIR failure can be used in the decision-making process to select eligible patients for debridement. The KLIC score is an easy and clinical applicable risk score which can help the clinician in discussing the risk of DAIR failure with the patient. Although a DAIR procedure is in general a good treatment modality for patients with early acute PJI, in patients with a high estimated preoperative failure risk, the physician may consider a different treatment approach with a higher chance of infection control. For example, performing revision surgery instead of debridement or starting suppressive antimicrobial treatment after debridement in patients who are not eligible for revision surgery due to severe comorbidity.

In conclusion, we demonstrated in an external cohort that the KLIC score is a relatively good preoperative risk score for DAIR failure in patients with early acute PJI. Its predictive value seems most prominent and therefore clinical applicable in patients with low or high KLIC scores. Ideally, additional validation in a prospective study should confirm these findings.

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