Circulating Biomarkers for Discrimination Between Aseptic Joint Failure, Low-Grade Infection, and High-Grade Septic Failure

Max Ettinger,[1] Tilman Calliess,[1] Jan T. Kielstein,[2] Jasmin Sibai,[1] Thomas Brückner,[1] Ralf Lichtinghagen,[3] Henning Windhagen,[1] and Alexander Lukasz[2,4]

[1]Department of Orthopaedic Surgery, [2]Department of Nephrology and Hypertension, [3]Department of Laboratory Medicine, Hannover Medical School, and [4]Department of Medicine D, Division of General Internal Medicine, Nephrology, and Rheumatology, University Hospital Münster, Germany

Background. Late-onset chronic (low-grade) periprosthetic joint infections are often accompanied by unspecific symptoms, false-negative cultures or nonspecific low values of serum biomarkers. This may lead to the unintended implantation of a revision prosthesis into an infected surgical site with the risk of short-term failure developing again. Conversely, false diagnosis of joint infection may result in multistage revision procedures, which expose the patient to unnecessary surgical procedures and inappropriate antibiotic treatment. Here, we investigated whether circulating biomarkers can preoperatively distinguish between aseptic prosthesis loosening and low-grade joint infection, and which biomarker combinations are most accurate.

Methods. Inclusion criteria for the study were indication for revision arthroplasty due to aseptic implant failure, acute high-grade infection, or (suspected) low-grade infection. C-reactive protein (CRP), procalcitonin, tumor necrosis factor α, interleukin 6 (IL-6), interleukin 10, and lipopolysaccharide binding protein were assessed preoperatively in the serum of 98 adult patients.

Results. The classification tree method revealed IL-6 and CRP as the most suitable biomarker combination for the discrimination of aseptic loosening vs low-grade joint infection. The combination of IL-6 >5.12 pg/mL and CRP >0.3 mg/dL correctly identified 15 of 16 patients as having low-grade infection (94%) whereas just one patient was aseptic (6%).

Conclusions. This is the first comprehensive prospective clinical study to our knowledge investigating the significance of a combined biomarker approach in differentiating between aseptic prosthesis loosening and low-grade joint infection. CRP plus IL-6 seems to be the most helpful combination for preoperative discrimination of aseptic loosening vs low-grade joint infection.

Keywords. low-grade; high-grade; septic joint failure; joint infection.

Total knee arthroplasty and total hip arthroplasty are very common operations and are projected to increase dramatically in numbers over the next 2 decades [1, 2], whereas the prevalence of periprosthetic joint infection (PJI) has not decreased over the past 20 years

[3]. Thus, we are facing an increasing medical and economic problem of device-related infections in the future.

Traditionally, PJIs were classified by time of appearance, as early (<3 months) or late (>3 months) postoperative infections [4]. However, recent strategies for classification of septic prosthetic failure are based on the pathogenicity and etiology of the infection. Based on these strategies, 3 classes of infection are recognized: (1) acute perioperative infections with early postoperative onset and highly virulent bacteria; (2) primary chronic low-grade infections with delayed onset and low-virulence or small colony-forming bacterial stains; and (3) late hematogenous high-grade infections. Furthermore, the standard diagnostic methods, such as blood

tests for C-reactive protein (CRP) or erythrocyte sedimentation rate or by microbiological analysis of the joint aspiration fluid, may not diagnose infections, especially low-grade infections, accurately. The current most accurate method for detection of low-grade infections is histopathological analysis of the periprosthetic membrane in conjunction with microbial analysis of periprosthetic tissue cultures [5]. In cases of joint failure, a periprosthetic membrane, which is a seam of connective tissue, is formed between the bone/cement and the implant interface and is histopathologically classified into 4 subtypes [6, 7].

The distinction between PJI and aseptic failure is crucial to make preoperative treatment decisions but can be clinically difficult due to the low virulence and biofilm-forming ability of the pathogens [8]. Clinical symptoms are not always reliable, especially for low-grade infections. False-negative and low values of serum biomarkers often occur when low-virulence pathogens are responsible for late-onset chronic (low-grade) joint infections [9]. By contrast, concomitant inflammatory conditions may cause severe elevation of these biomarkers [10, 11]. Consequently, a surgeon may decide on a 1-stage revision procedure, which may lead to the unintended implantation of a new prosthesis into an infected surgical site. Without proper debridement of the joint and sufficient antibiotic treatment, this may lead to persistence of the infection and immediate failure of the revision arthroplasty. Conversely, incorrect diagnosis of a joint infection where there is none may result in a multistage revision procedure, the consequences of which may be an extended duration of hospital stay and/or multiple admissions, as well as prolonged immobilization and rehabilitation, together with increased overall costs [3, 8, 12].

Biomarkers have been shown to be helpful for the diagnosis of PJI [13]. The purpose of this study was to determine the utility of several serum biomarkers in distinguishing between aseptic failure, low- and high-grade infections in patients undergoing revision surgery for failure of total joint arthroplasty. Using a prospective approach, we intended to detect biomarkers with optimal cutoff values to predict cause of joint failure.

PATIENTS AND METHODS

Design
Institutional review board approval was obtained for this study.

Inclusion criteria were indications for revision arthroplasty of hip, knee, or shoulder prosthesis, including aseptic implant failure, acute high-grade infection, or (suspected) low-grade infection. Patients with diseases associated with elevated inflammatory circulating biomarkers, including malignancy [14], rheumatism [15], renal failure, autoimmune disease (such as systemic lupus erythematosus or vasculitis) [16], and chronic infectious disease (such as human immunodeficiency virus or hepatitis C virus) [17] were excluded from the study. Patients with early-onset infections occurring less than 4 weeks after the index surgery and patients on antibiotics were also excluded.

Patient demographics, medical history, and clinical data including sex, age, body temperature, pulse, blood pressure, retention parameters, hemoglobin, hematocrit, leucocytes, and electrolytes were recorded. During surgery, a total of 8 tissue and fluid samples were collected for histological and microbiological examination.

The definite diagnosis of septic joint failure was carried out postoperatively with reference to the guidelines of the Musculoskeletal Infection Society [18]: (1) presence of a fistula that is connected to the prosthesis; (2) same pathogen in at least 2 separate tissue or fluid samples taken from the joint; and (3) any 3 of the following 4 criteria together: (a) CRP >0.5 mg/dL; (b) pus in the joint; (c) isolation of microorganisms in a liquid culture of the tissue or joint; and (d) positive histology (>5 neutrophils per high-power field in 5 high-power fields, or >1 neutrophil per high-power field on average after examination of 10 high-power fields in a tissue sample under ×400 magnification [19, 20], as well as membrane type II and III according to the classification of Morawietz et al [7]). The distinction between low- and high-grade infection was made clinically based on symptoms and the time-point of the infection relative to the index surgery, and the onset of symptoms in correlation with the histology and isolation of microorganisms [21, 22]. Patients with nocturnal pain, intermediate swelling, or stiffness in combination with membrane types II and III according to the Morawietz classification, or isolation of low-virulence pathogens were classified as having low-grade infection. Intraoperative tissue samples were examined by a pathologist skilled in interpretation of periprosthetic tissue.

Quantification of Biomarkers
CRP was quantified in serum samples by an immunoturbidimetric test (Roche Diagnostics, Mannheim, Germany) in line with other biochemical parameters in the Laboratory Medicine on a Cobas 6000 analyser (Roche Diagnostics), and PCT sensitivity was determined on a Brahms Kryptor analyser with an immunofluorescence assay (Thermo Fisher Scientific, Brahms GmbH, Hennigsdorf, Germany). Tumor necrosis factor α (TNF-α), interleukin (IL)-6, IL-10, and lipopolysaccharide binding protein (LBP) were quantified in serum samples using solid-phase enzyme-labeled, chemiluminiscent, sequential immunometric assays on an Immulite instrument (Siemens Healthcare, Eschborn, Germany).

Statistical Analysis
Unpaired *t*-test, 1-way analysis of variance and Bonferroni multiple comparison test were applied for comparison of quantitative variables. Two-tailed *P*-values <.05 were considered statistically significant. The classification tree method was used with the following assumptions: minimal number of cases at the superior point of 10, minimal number of cases at the

inferior point of 5, and χ^2 P-values <.05 for the distribution at break points. Categorical variables were compared using the χ^2 test. Receiver operator characteristic (ROC) curves were used to visualize cutoff values, sensitivity, and specificity of different biomarkers. Data analysis was performed using SPSS software version 22 (SPSS Inc, Chicago, Illinois). Contingency table–derived data and likelihood ratios were calculated using the StatPages website (www.statpages.org/ctab2x2.html). Figures were prepared using GraphPad Prism software version 6 (GraphPad Prism Software Inc, San Diego, California).

RESULTS

Patient Characteristics

In total, 98 adult patients were included in this study; 57 patients with no suggestion of infection were postoperatively assigned to the aseptic loosening group, while 20 were diagnosed with a low-grade infection and were postoperatively assigned to the low-grade infection group, and 21 patients received a revision on the basis of a high-grade infection.

Demographic, clinical, and laboratory characteristics and are shown in Table 1. Detailed characteristics of the 20 patients assigned to the low-grade infection group are shown in Table 2.

Leucocytes, CRP, PCT, TNF-α, IL-10, IL-6, and LBP Levels in Relation to Cause of Joint Failure

Patients with aseptic joint failure had significantly lower levels of leucocytes compared with patients with low- or high-grade infection (6.4 vs 7.6 vs $8 \times 10^3/\mu L$, $P < .01$ and $P < .01$, respectively) (Figure 1A). Patients with aseptic joint failure had significantly lower levels of CRP compared with patients with low- or

Table 1. Demographic, Clinical and Laboratory Characteristics of Patients

Characteristics	Total	Aseptic	Infectious	
			Low-grade	High-grade
Demographics (n, %)				
Number of patients	98 (100)	57 (58)	20 (20)	21 (21)
Male	42 (43)	23 (23)	9 (9)	10 (10)
Female	56 (57)	34 (35)	11 (11)	11 (11)
Age (years, median [IQR])	67 (60.3–76)	64 (60–72)	68 (66.5–77.5)	72 (61–78)
BMI	27.9 (25.4–31.9)	27.8 (24.8–31.3)	28.4 (25.7–30.9)	29.4 (25.7–35.1)
Joint (n, %)				
Hip	57 (58)	29 (30)	13 (13)	15 (15)
Knee	39 (40)	28 (29)	7 (7)	4 (4)
Shoulder	2 (2)	0 (0)	0 (0)	2 (2)
Patients with joint revision (n, %)[a]	25 (26)	8 (8)	4 (4)	13 (13)
Number of revisions (mean [IQR])[b]	1.68 (1–2)	1.63 (1–2)	1 (1–1)	1.92 (1–3)
Number of joint infections (n, %)[c]	6 (6)	0	0	6 (6)
Implant survival (days, [median, IQR])	1064 (276–2829)	1499 (595–3444)	526 (138–2226)	149 (74–1196)
Clinical parameters (median [IQR])				
Temperature (°C)	36.8 (36.5–37)	36.8 (36.4–37)	36.8 (36.5–37)	36.8 (36.5–37.2)
Heart rate (bpm)	72 (64–80)	72 (64–80)	72 (68–81)	72 (64–84)
Laboratory data (median [IQR])				
Leucocytes ($10^3/\mu L$)	6.8 (5.5–8)	6.4 (5.5–7.23)	7.6 (6.48–9.18)	8 (5.65–9.8)
CRP (mg/dL)	0.4 (0.2–1.7)	0.2 (0.1–0.4)	1.2 (0.6–6.25)	3.5 (1.45–13–35)
PCT (ng/mL)	0.04 (0.03–0.06)	0.04 (0.01–0.05)	0.04 (0.03–0.07)	0.06 (0.04–0.1)
TNF-α (pg/mL)	9.1 (7.65–11.45)	8.65 (7.2–10.98)	10.3 (8.2–14.25)	11 (8.6–12.85)
IL-10 (pg/mL)	2.4 (2–3.9)	2.4 (2–3.48)	2.6 (2–4.03)	2.9 (1.95–4.3)
LBP (µg/mL)	6.7 (4.9–9.7)	5.65 (4.28–7.2)	7.65 (6.48–11.95)	10.7 (7.75–17.45)
IL-6 (pg/mL)	4.26 (1–10.9)	2.77 (1–4.3)	11.9 (5.24–19.33)	12.8 (5.93–32.65)

Percentage related to total no. of patients.

Abbreviations: BMI, body mass index; CRP, C-reactive protein; IL-6, interleukin 6; IL-10, interleukin 10; IQR, interquartile range; LBP, lipopolysaccharide binding protein; PCT, procalcitonin; TNF-α, tumor necrosis factor α.

[a] Of the affected joint.

[b] Number of revisions of the affected joint of the patients mentioned one line above.

[c] Of the affected joint; all 6 patients had one joint infection in the past, respectively.

Table 2. Detailed Characteristics of Patients With Low-Grade Infection

Patient	Affected Joint	Temp (°C)[a]	CRP (mg/dL)	IL6 (pg/mL)	Revision Number[b]	Implant Survival, Days	Pathogen	Positive Swabs	Histology[c]	Symptoms	Synovial Fluid Culture[d]	Comorbidities
1	Knee	36.7	0.2	4.78	0	4265	Staphylococcus epidermidis	2/5	Type 2	Nocturnal resting pain, discrete swelling	Negative	Arterial hypertension
2	Hip	36.1	1.9	13.2	1	615	Staphylococcus epidermidis	2/5	Type 2	Stress-induced pain	Negative	Arterial hypertension, diabetes mellitus, hypothyreosis, auditory vertigo
3	Hip	36.8	1.0	3.2	0	591	Staphylococcus auricularis	1/5	Type 3	Stress-induced pain	Negative	Arterial hypertension
4	Hip	36.2	0.1	1.0	0	74	Micrococcus luteus	1/5	Type 2	Stress-induced pain, nocturnal resting pain	Negative	Arterial hypertension
5	Knee	37	1.4	15.2	0	5819	None		Type 3	Stress-induced pain, resting pain	Negative	Arterial hypertension, hypothyreosis
6	Hip	37	8.9	13.2	0	5455	Staphylococcus epidermidis	2/5	Type 3	Stress-induced pain, resting pain	ND	Depression, Parkinson's disease
7	Knee	36.8	0.6	5.42	0	188	Propionibacterium acnes	3/5	Type 3	Stress-induced pain, nocturnal resting pain	Negative	Chronic heart failure
8	Hip	36.2	0.3	5.22	1	154	Staphylococcus epidermidis	2/5	Type 3	Nocturnal resting pain	Negative	Arterial hypertension, diabetes mellitus
9	Hip	36	0.1	1.0	0	3647	Staphylococcus capitis	2/5	Type 3	Resting pain and nocturnal resting pain	ND	
10	Knee	36.8	2.6	16.7	0	1484	Staphylococcus haemolyticus	3/5	Type 3	Resting pain and nocturnal resting pain	Negative	Arterial hypertension, mitral regurgitation, gastroesophageal reflux
11	Hip	36.5	0.6	7.23	0	1142	Propionibacterium acnes	1/5	Type 3	Stress-induced pain, nocturnal resting pain	ND	Arterial hypertension
12	Hip	36.6	1.0	10.7	1	78	None		Type 3	Stress-induced pain, nocturnal resting pain	Negative	Arterial hypertension, coronary heart disease, restless legs syndrome, hypothyreosis
13	Hip	37	1.8	5.29	1	461	Staphylococcus capitis	3/5	Type 2	Stress-induced pain	ND	Arterial hypertension, diabetes mellitus, arterial occlusive disease
14	Knee	36.6	13.1	22.9	0	90	None		Type 3	Nocturnal resting pain, intermediate swelling	ND	Arterial hypertension, choledocholithiasis, hypothyreosis, cataract
15	Hip	37	6.4	62.2	0	70	Staphylococcus epidermidis	2/5	Type 2	Stress-induced pain	ND	Arterial hypertension, hypothyreosis
16	Hip	36.8	5.8	20.2	0	4141	Staphylococcus capitis, Staphylococcus epidermidis	2/5, 3/5	Type 2	Stress-induced pain, resting pain	ND	Arterial hypertension

Table 2 continued.

Patient	Affected Joint	Temp (°C)[a]	CRP (mg/dL)	IL6 (pg/mL)	Revision Number[b]	Implant Survival, Days	Pathogen	Positive Swabs	Histology[c]	Symptoms	Synovial Fluid Culture[d]	Comorbidities
17	Knee	36.8	7.1	27.4	0	394	Staphylococcus epidermidis	4/5	Type 2	Stress-induced pain, nocturnal resting pain	ND	Arterial hypertension, coronary heart disease, hypothyreosis, chronic heart failure
18	Hip	37.6	17.2	31.1	0	70	Staphylococcus epidermidis	4/5	Type 2	Stress-induced pain, nocturnal resting pain	ND	Arterial hypertension, coronary heart disease, atrial fibrillation, choledocholithiasis
19	Hip	37.2	1.0	13.1	0	305	Staphylococcus epidermidis	4/5	Type 2	Stress-induced pain, nocturnal resting pain	ND	Arterial hypertension, coronary heart disease
20	Knee	36.4	1.0	7.1	0	1752	Propionibacterium acnes	2/5	Type 3	Nocturnal resting pain	Propionibacterium acnes	Depression

Abbreviations: CRP, C-reactive protein; IL-6, interleukine-6; ND, not done.

[a] Preoperative temperature.

[b] Of the affected joint.

[c] According to the classification of Morawietz et al, please see "Methods" section.

[d] Preoperative.

high-grade infection (0.2 vs 1.2 vs 3.5 mg/dL, $P < .0001$ and $P < .05$, respectively) (Figure 1B). Compared with patients with low-grade or high-grade infection, patients with aseptic joint failure had significantly lower levels of PCT (0.04 vs 0.04 vs 0.06 ng/mL, $P < .05$ and $P < .05$, respectively) (Figure 1C). Patients with aseptic joint failure had significantly lower levels of TNF-α compared with patients with low-grade or high-grade infection (8.65 vs 10.3 vs 11 pg/L, $P < .05$ and $P < .05$, respectively) (Figure 1D). Patients with low-grade infection had significantly lower levels of IL-10 compared with patients with high-grade infection (2.6 vs 2.9 pg/mL, $P < .05$) but not compared to aseptic joint failure (2.4 pg/mL) (Figure 1E). Patients with aseptic joint failure had significantly lower levels of LBP compared with patients with low- or high-grade infection (5.65 vs 7.65 vs 10.7 µg/mL, $P < .0001$ and $P < .0001$, respectively) (Figure 1F). IL-6 levels were significantly higher in low-grade patients compared with aseptic patients (2.77 vs 11.9 pg/mL), whereas IL-6 levels of patients with high-grade infection were not significantly different from those of patients with low-grade joint failure (12.8 pg/mL, $P = .06$) (Figure 1G).

Predicting Cause of Joint Failure With a Joint Biomarker Model

In a prospective approach, our aim was to identify biomarkers and their optimal cutoff values in order to predict cause of joint failure. The classification tree method was used to search for biomarkers and cutoff values that would differentiate aseptic from low-grade infected joint failure. Patients with high-grade joint failure were excluded from this calculation because our aim was finding a model that would detect low-grade infections, which, in contrast to high-grade infections, are difficult to diagnose both preoperatively and intraoperatively. Within the panel of quantified biomarkers mentioned above, the classification tree method revealed IL-6 and CRP as the most suitable biomarkers. An IL-6 cutoff of ≤5.12 pg/mL divided a total of 77 patients (57 aseptic, 20 low-grade patients) into two groups. The first group, the low-risk group, consisted of 54 patients (50 aseptic [93%] and 4 low-grade [7%]). The remaining 23 patients had IL-6 >5.12 pg/mL (7 aseptic [30%] and 16 low-grade [70%]). These patients could be divided further into 2 groups by a cutoff for CRP ≤0.3 mg/dL. The medium-risk group (IL-6 >5.12 pg/mL and CRP ≤0.3 mg/dL) consisted of 6 aseptic patients (86%) and 1 low-grade patient (14%). The third group was the high-risk group (IL-6 >5.12 pg/mL and CRP >0.3 mg/dL) and consisted of 16 patients. In this group, 15 patients were correctly identified as having low-grade infection (94%), whereas just 1 patient was aseptic (6%). The classification tree method is visualized in Figure 2. Five low-grade infections patients and one aseptic patient misclassified by the classification tree method are described in detail in supplementary material (Supplementary Table 1).
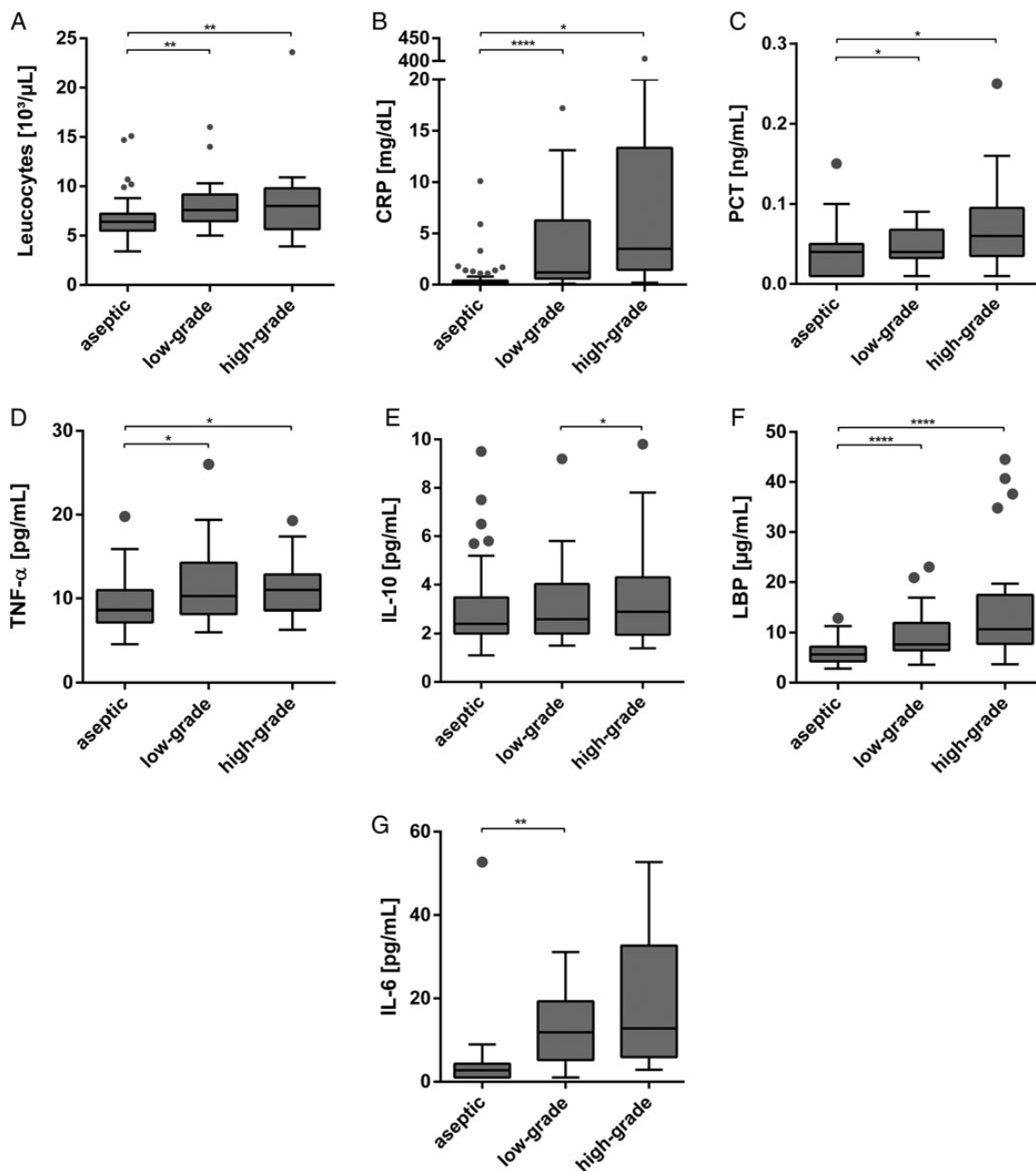
Figure 1. Leucocytes, CRP, PCT, TNF-α, IL-10, LBP, and IL-6 levels in relation to cause of joint failure. *$P<.05$; **$P<.001$; ****$P<.0001$. Abbreviations: CRP, C-reactive protein; IL-6, interleukin 6; IL-10, interleukin 10; LBP, lipopolysaccharide binding protein; PCT, procalcitonin; TNF-α, tumor necrosis factor α.

To visualize the sensitivity and specificity of the measured biomarkers to predict the cause of joint failure (aseptic vs low-grade infection), a conventional ROC curve was generated, and the area under the curve (AUC) calculated (Figure 3). The high-risk model calculated by classification tree method had an AUC of 0.878 (95% confidence interval [CI], .77–.99). The AUC of IL-6 and CRP were 0.861 (95% CI, .75–.97) and 0.828 (95% CI, .71–.95), respectively. Table 3 lists the derived sensitivities, specificities, and predictive values of the combined models and the biomarkers alone. The combined model I (IL-6 >5.12 pg/mL + CRP >0.3 mg/dL = high-risk group) had an odds ratio of 168 (95% CI, 16.36–4233.3), a negative predictive value (NPV) of 91.8%, and a positive predictive value (PPV) of 93.8%. The combined model II (IL-6 ≤5.12 or >5.12 pg/mL + CRP <0.3 mg/dL = low-risk and medium-risk groups, respectively) had an odds ratio of 24.7 (95% CI, 2.46–601.14), an NPV of 83.1%, and a PPV of 83.3% (Table 3).
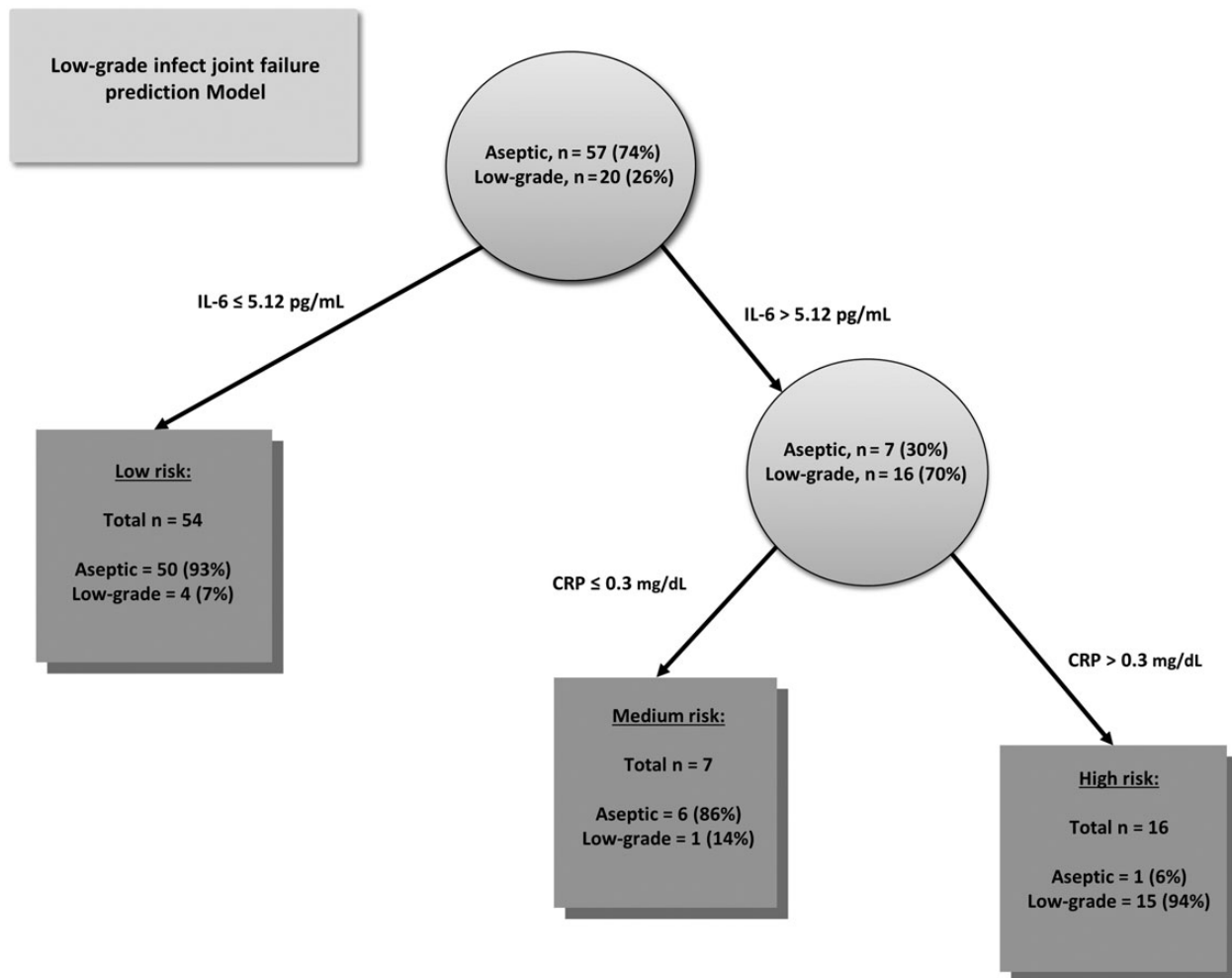
Figure 2. The classification tree method revealed interleukin 6 (IL)-6 and C-reactive protein (CRP) as the most suitable biomarkers for the discrimination of aseptic vs low-grade infection caused joint failure. The IL-6 cutoff of ≤5.12 pg/mL divided 77 patients into 2 groups. The first group, the low-risk group, consisted of 54 patients. The remaining 23 patients with an IL-6 >5.12 pg/mL were divided into 2 groups by CRP ≤0.3 mg/dL. The medium-risk group (IL-6 >5.12 pg/mL and CRP ≤0.3 mg/dL) consisted of 7 patients, and the high-risk group (IL-6 >5.12 pg/mL and CRP >0.3 mg/dL) of 16 patients. In this group, 15 patients were correctly identified as low-grade infections (94%), whereas just one patient was aseptic (6%).

DISCUSSION

The primary goal of this study was to evaluate the diagnostic value of biomarkers to distinguish not only between aseptic failure and high-grade infections in joint arthroplasty but also to detect low-grade infections against aseptic situations. To our knowledge, this is the first study that discriminates between aseptic joint failure, low-grade infection, and high-grade septic failure with reference to the guidelines of the Musculoskeletal Infection Society [18] and according to the classification of Morawietz et al [7]. Recent studies focusing on IL-6 and CRP did not distinguish between low- and high-grade infections [23–25].

Our study strictly excluded patients with inflammatory comorbidities or patients receiving antibiotic treatment, because both may have a significant effect on the diagnostic value of the biomarkers evaluated. This is in contrast to most of the other published studies [23, 25, 26].

Our study has some important limitations. Patients with any inflammatory comorbidity were excluded from this study to minimize influences other than the examined joint infections on the biomarkers measured in this cohort. Therefore, the results of our study may not be generalizable to the general population, and further studies are needed to address the relevance of the biomarkers measured in this study in patients with joint infections and inflammatory comorbidities. Furthermore, the results of our classification tree method have to be validated in further studies of patients with aseptic joint failure vs low-grade infections. Although we included a comparatively high
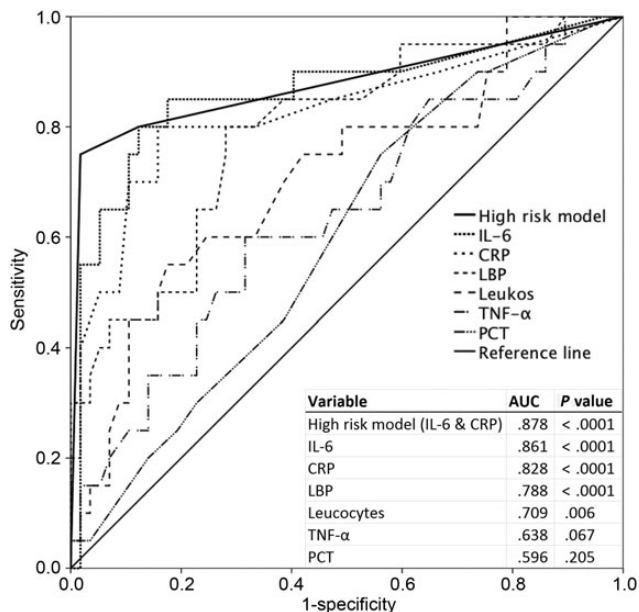
Figure 3. A conventional receiver operator characteristic (ROC) curve was generated and the area under the curve (AUC) calculated. The high-risk model (IL-6 >5.12 pg/mL and CRP ≥0.3 mg/dL) had the highest AUC (0.878, *P* < .0001). Abbreviations: CRP, C-reactive protein; IL-6, interleukin 6; LBP, lipopolysaccharide binding protein; PCT, procalcitonin; TNF-α, tumor necrosis factor α.

number of patients, the numbers in the individual groups of our cohort are low, thus larger studies are needed to propose general recommendations.

In the current literature, many different biomarkers have been evaluated regarding their ability to distinguish between aseptic and septic joint failure. Botter et al [25] showed a high specificity (98%) for PCT at a value of >0.3 ng/mL for the discrimination of aseptic loosening vs septic failure. However, the sensitivity was quite low (33%), whereas Glehr et al [27] reported a specificity of 33% and a sensitivity of 90% at a cutoff

of 0.35 ng/mL. Focusing on low-grade infections, our PCT levels showed a sensitivity of 90% and specificity of 27.8% at a low cutoff value of >0.025 ng/mL. Although the cutoff values are not comparable, because we differentiated between low-grade and high-grade infection, we came to the same conclusion, namely, that PCT alone cannot be considered as a suitable marker for the discrimination of aseptic loosening vs low-grade infection.

Data concerning the diagnostic value of LBP for the discrimination of aseptic loosening vs septic joint failure were recently published [28]. LBP showed significantly higher values in PJI compared with aseptic loosening, with a specificity of 66% and a sensitivity of 71% at a cutoff value of >7 μg/mL. Our results provide slightly higher values for the specificity (72%) and sensitivity (84%) at a cutoff value of >6.35 μg/mL, and promote the conclusion that LBP alone also cannot be considered as a suitable marker for the discrimination of aseptic loosening vs low-grade infection.

TNF-α (>40 pg/mL), is reported as having high specificity (94%), but low sensitivity (43%) in the current literature [29]. Our results confirm this observation with regard to low-grade infections. In this study, TNF-α specificity was 86% and sensitivity 35% at a cutoff value at >11.9 pg/mL when discriminating between aseptic joint failure and low-grade infection.

The diagnostic value of CRP and IL-6 has been evaluated in a variety of studies. Bottner et al [29] measured serum levels of CRP and IL-6 in 78 patients undergoing revision arthroplasty; 21 patients were categorized by intraoperative culture into the septic group. CRP and IL-6 had the highest sensitivity (95%) for the detection of a septic joint failure when levels were higher than 3.2 mg/dL and 12 pg/mL, respectively. These levels are higher than the cutoff values evaluated in our study, probably because our cutoff values were calculated with a focus on low-grade infections and excluding high-grade infections. Bottner et al did not discriminate between low- and high-grade infection and included patients with potentially inflammatory comorbidities (eg, patients receiving hemodialysis) into the

Table 3. Test Characteristics of Different Cutoff Values and Combined Models for Predicting Low-Grade Infections

	Cutoff	OR	95% CI	Sensitivity, %	Specificity, %	NPV, %	PPV, %	*P* Value
PCT	>0.025 ng/mL	3.5	.67–23.77	90	27.8	90.9	25.7	.14
TNF-α	>11.9 pg/mL	3.3	.87–12.65	35	86	79	46.7	.054
LBP	>6.35 μg/mL	14	3.19–70.61	84.2	72.4	93.3	50	**<.0001**
IL-6	>5.12 pg/mL	28.6	6.36–143.73	80	87.7	92.6	69.6	**<.0001**
CRP	≥0.3 mg/dL	7.1	1.95–28.29	80	64	92.3	37.2	**.001**
Combined model I (high risk)	IL-6 >5.12 pg/mL & CRP ≥0.3 mg/dL	168	16.36–4233.3	75	98.2	91.8	93.8	**<.0001**
Combined model II (low and med risk)	IL-6 ≤5.12 or >5.12 pg/mL and CRP <0.3 mg/dL	24.7	2.46–601.14	25	98.7	83.1	83.3	**.001**

P values in bold are provided in the chi-square test.

Abbreviations: CI, confidence interval; CRP, C-reactive protein; IL-6, interleukin 6; LBP, lipopolysaccharide binding protein; NPV, negative predictive value; OR, odds ratio; PCT, procalcitonin; PPV, positive predictive value; TNF-α, tumor necrosis factor α.

study. Glehr et al [27] excluded patients with inflammatory co-morbidities but did not discriminate between low- and high-grade infections. They reported an IL-6 sensitivity of 86% and specificity of 67% at an IL-6 cutoff of 4.7 pg/mL. Randau et al [23] compared patients with septic loosening and aseptic loosening with a control group of mechanical joint failures, and reported a sensitivity of 49% and a specificity of 88% when serum IL-6 is >6.6 pg/mL. This study did not discriminate between low- and high-grade infections, and there were no exclusion criteria. This may have caused the discrepancy to our results.

Elegeidi et al [24] excluded patients with chronic inflammatory diseases, but did not discriminate between low- and high-grade infections. They reported a sensitivity of 100% and a specificity of 91% when serum IL-6 was >10.4 pg/mL. They isolated high-virulence bacteria such as *Staphylococcus aureus*, *Escherichia coli*, or *Pseudomonas aeruginosa* in about 70% of the cases. As we isolated only low-virulence bacteria in our low-grade cohort, this may have caused the discrepancy to our results.

In comparison, our IL-6 cutoff of 5.12 pg/mL had a sensitivity of 80% and specificity of 87.7% for predicting a low-grade infection. The classification tree method showed that the combination of CRP and IL-6 was the most suitable combination for the discrimination of aseptic loosening vs low-grade infection. A patient with IL-6 >5.12 pg/mL plus CRP >0.3 mg/dL could be categorized as very likely (high-risk) to have a low-grade infection.

To summarize, this is the first study concentrating on the diagnoses of even low-grade infections against aseptic failure of knee and hip arthroplasty. We were able to calculate cutoff values for IL-6 and CRP that were much lower than in the current literature but showed a high sensitivity and specificity at detecting even low-grade infections. We consider that these findings should be useful to identify patients who require further investigation because they are very likely to have an infection when presenting with joint failure.

Supplementary Data

[Supplementary materials](http://cid.oxfordjournals.org) are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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