DISSERTATION

Periprothetische Gelenkinfektionen bei Patienten mit rheumatoider Arthritis – eine diagnostische Herausforderung

Periprosthetic joint infections in patients with rheumatoid arthritis – a diagnostic challenge

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List of abbreviations

ACR/EULAR	American College of Rheumatology and European Alliance of Associations for Rheumatology
ASA	American Society of Anesthesiologists
AUC	Area under the curve
CRP	C-reactive protein
DMARDs	Disease-modifying antirheumatic drugs
DOR	Diagnostic odds ratio
EBJIS	European Bone and Joint Infection Society
ESR	Erythrocyte sedimentation rate
FLS	Fibroblast-like synoviocytes
HLA	Human leukocyte antigen
ICM	International Consensus Meeting
IDSA	Infectious Diseases Society of America
IQR	Interquartile range
LE	Leukocyte esterase
MSIS	Musculoskeletal Infection Society
NGS	Next generation sequencing
NPV	Negative predictive value
PJI	Periprosthetic joint infection
PMN	Polymorphonuclear neutrophils
PPV	Positive predictive value
RA	Rheumatoid arthritis
ROC	Receiver operating curve
SLIM	Synovial-like interface membrane
TKA	Total knee arthroplasty
WBC	White blood cell

Abstract

Background: Periprosthetic joint infection (PJI) is a severe complication after primary joint arthroplasty. Its symptoms have overlap with rheumatoid arthritis (RA) with elevated inflammatory markers in both diseases. Thus, the interpretation of commonly used laboratory markers for inflammation can be challenging when PJI develops in RA patients. Even though current guidelines have good performance for diagnosing PJI, there is no specific standard to distinguish PJI from patients with active RA who had previously undergone arthroplasty.

Materials and Methods: In this study, we enrolled and retrospectively analyzed patients with or without RA who underwent revision surgery due to acute or chronic PJI of the knee. Data were gathered and analyzed including patient demographics, microbiology, laboratory tests, and prosthesis survival duration. Receiver operating curve (ROC) analysis was performed for diagnostic power.

Results: A total of 138 patients were enrolled in our study. *Staphylococcus aureus* and *Staphylococcus epidermidis* were the two major pathogens found in our cohort. For chronic PJI, laboratory tests including peripheral blood C-reaction protein, synovial white blood cell count, synovial monocyte cell count, and synovial polymorphonuclear cell count were found out to be elevated in patients with RA, and with acceptable differential diagnostic value, while parameters for acute PJI showed no significant elevation and diagnostic value between patients complicating RA or not. At the endpoint of follow-up, patients with RA had a higher chance of prosthesis failure ($p=0.03$), and a lower median prosthesis survival time ($p=0.05$) than those without RA.

Conclusion: Traditionally used laboratory markers can potentially discriminate the cases of chronic PJI with RA from without RA, but are not sufficient for differential diagnostics of RA in acute PJI cases. Considering the negative impact of autoimmune inflammation on prosthesis survival rates, RA patients should be treated particularly meticulously.

Zusammenfassung

Die periprothetische Infektion (PPI) ist eine schwere Komplikation nach primärer Gelenkendoprothetik. Die Symptome überschneiden sich mit Rheumatoider Arthritis (RA), und es wird beobachtet, dass Entzündungsparameter bei beiden Erkrankungen ansteigen. Deswegen können die Ergebnisse dieser Labortests irreführend sein, wenn sich eine PPI bei RA-Patienten entwickelt. Obwohl die aktuellen Leitlinien eine gute Sensitivität und Spezifität für die Diagnostik für PPI haben, gibt es keinen spezifischen Standard, um bei Patienten mit RA die Diagnose PPI endgültig ohne invasiven Eingriff zu sichern. In unsere Studie wurden PPI-Patienten mit und ohne RA-Vorgeschichte eingeschlossen und retrospektiv analysiert, die sich aufgrund eines akuten oder chronischen PPI am Knie einer Revisionsoperation unterzogen haben. Es wurden Daten gesammelt, einschließlich Patientendemographie, Mikrobiologie, Labortests, Überlebensdauer der Prothese. Für die diagnostische Leistung wurde eine Receiver-Operating-Curve(ROC)-Analyse durchgeführt. Staphylococcus aureus und Staphylococcus epidermidis waren die am häufigsten vorkommenden Pathogene, die in unserer Kohorte gefunden wurden. Bei chronischem PPI waren die Labortests, einschließlich des peripheren Blut-C-Reaktionsproteins, der Anzahl der synovialen Leukozyten, der synovialen Monozyten und der polymorphkernigen Zellen, bei Patienten mit RA erhöht und wiesen einen akzeptablen differenzialdiagnostischen Wert auf, während die Parameter für akute PPI keinen signifikanten Anstieg und diagnostischen Wert zwischen Patienten mit und ohne RA zeigten. Am Endpunkt der Nachbeobachtung hatten Patienten mit RA ein erhöhtes Risiko für ein Prothesenversagen ($p=0,03$) und eine geringere mediane Prothesenüberlebenszeit ($p=0,05$) im Vergleich zu Patienten ohne RA. Zusammenfassend lässt sich sagen, dass im Falle einer chronischen PPI bei Patienten mit RA traditionell verwendete Labormarker keine sichere Diagnosestellung der PPI erfolgen kann.

The scientific research here includes the results from my previous publication [1].

1. Introduction

1.1 An overview of periprosthetic joint infection (PJI)

Joint replacement surgery is characterized as an effective index surgery for end-stage arthrosis with consistent pain and/or deformity after unsuccessful conservative medications. In the last few decades, utilization of this technique has been increasing with the demand for quality of life-increasing interventions. In 2020, the annual number of total knee arthroplasty performed was around one million and the number of hip arthroplasty performed at half a million. According to a national statistical prediction, the need for primary knee/hip replacement will grow three to four hundred percent in the next twenty years [2, 3].

It is essential to avoid postoperative complications such as periprosthetic joint infections (PJI). Together with aseptic loosening, PJI represents one of the most common complications after joint replacement, and is also one of the most challenging complication to treat [4]. In case of PJI, fast and accurate diagnosis is mandatory to limit the high mortality rates and severely impacted functional outcome. With an incidence reported to be about 1-2% after primary arthroplasties, it remains a challenging issue even with adequate perioperative disinfection measures [5, 6]. Risk factors for PJI include obesity, diabetes, malnutrition, prior septic arthritis on the affected side, any active infection, and immunodestructive disease, or medications. PJI is manifested with moderate to strong fever, pain, wound swelling, secretion, and in rare cases even wound rupture. Treatment strategies should combine a systemic antibiotic therapy, usually for at least twelve weeks, and revision surgery. After revision, the risk for impaired ambulatory function is increased.

PJI can be categorized depending on the onset and symptoms (chronic vs acute) or mode of transmission (direct invasion vs hematogenous spread). Based on the symptoms and the onset time from surgery, acute PJI is defined as a morbidity with acute onset of symptoms within 4 weeks after the index arthroplasty due to colonization of high-virulent microorganisms, while chronic PJI is due to pathogens with low to medium microbial virulence, in which symptoms can be milder but also long-lasting. In both cases, there is a risk for sepsis and subsequent death in patients that are not treated. PJI is initiated by

direct attachment of pathogens on the prosthesis in the operation room, through any kind of skin lesion (periprosthetic open fracture or incompletely healed wounds), or by spreading from an infection origin nearby (soft tissue), which contributes to over two thirds of all PJI cases [6]. Additionally, hematogenous transmission from other organs, such as the bladder, oral cavities, the respiratory tract, or skin is another main pathomechanismus for the development of PJI [5, 6] . Pathogens can attach on the prosthesis surface, then proliferate and form a biofilm that prevents successful antibiotic treatment without surgical intervention.

Laboratory tests to establish the diagnosis of PJI are of great relevance as the clinical presentation of PJI cannot reliably be distinguished from other relevant diagnoses such as aseptic loosening or rheumatoid arthritis. Moreover, an accurate diagnosis is decisive to decide on the correct surgical and medical treatment [7]. In particular, for patients presenting with symptoms of acute PJI, fast and reliable diagnostic tools are essential to prevent sepsis and retain the implanted prosthesis. One- or two-stage operation is recommended for chronic PJI. Unrecognized PJI will steadily deteriorate the surrounding tissue structures, releases pathogens locally, or to spread into the bloodstream, which potentially leads to systemic infection, reported to occur in 0.22% of all patients after total knee arthroplasty (TKA) and 5.37% after revision TKA due to PJI [8]. In a worst scenario, amputation has to be considered in uncontrollable deadly sepsis in around 0.1% of all cases [9]. To this end, it is imperative for clinicians to consider PJI by a properly developed diagnostic procedure based on laboratory tests.

1.2 Current diagnostic strategies for PJI

There is currently no single examination or laboratory test that can identify PJI with absolute accuracy. Even for patients with high susceptibility of PJI, result of pathogen culture can be negative. In clinical practice, orthopedic surgeons should give comprehensive consideration based on meticulous physical examinations combined with serological and microbiological tests, as well as histological classification of periprosthetic tissue.

Over the last several years, international working groups established several definitions for diagnostic standards for PJI. Current definitions of PJI include those convened by the Musculoskeletal Infection Society (MSIS) in 2011 [7], the International Consensus Meeting (ICM) in 2013 [10], the Infectious Diseases Society of America (IDSA) in 2013

[11], and the European Bone and Joint Infection Society (EBJIS) in 2021 [12]. In 2018, both MSIS and ICM further renewed their 2011 definitions with a new scoring systems [13, 14]. These definitions were designed to be fast and reliable diagnostic tools with excellent clinical utility to identify infections. However, sensitivity and specificity displayed in these definitions were shown to be different in distinct settings [13, 15, 16]. Parvizi et al. showed in 2018 that the MSIS definition has a sensitivity of 97.7% and specificity of 99.5% [13]. In one recent study, Sigmund et al. reported improved preoperative diagnostic performance by utilizing the EBJIS definition, with a sensitivity of 81.2% and specificity of 100%, compared with the 2018 ICM and 2013 IDSA, indicating that EBJIS showed high sensitivity and no marked loss in specificity. With the EBJIS definition, the number of patients with inconclusive diagnosis that could neither be rules septic nor aseptic was also reduced [17]. Yet by considering the variation in diagnostic efficacy and laboratory workup of these definitions, the applicability of these definitions can vary among different local clinics due to local standards and accessibility to the involved discriminative tests [18].

The need for a quick and accurate diagnosis remains a significant challenge. In particular, microbiological cultures from synovial fluid or periprosthetic tissues are of high clinical diagnostic and therapeutic relevance but first test results are only available after several days. Additionally, test results may be compromised if antibiotics have been administered before arthrocentesis. In addition, there is PJI cases with negative cultures, but with typical related symptoms and changes in inflammatory markers in the blood. Recently, next generation sequencing (NGS) has been suggested as an innovative diagnostic tool to not only reduce the time till final results and to accurately reveal the organism responsible in culture negative PJI [19]. Nevertheless, there is still limited access to NGS, and further studies are necessary to explore its value in clinical settings.

At present, in addition to clinical presentations and microbiological culture, identification of laboratory markers derived from peripheral blood and synovial fluid is an essential part to diagnose PJI [20-22]. Current findings suggest higher sensitivity with serum markers and high specificity for markers from synovial fluid, necessitating a combination of both for precise diagnosis. The 2011 MSIS definition of PJI contains serum erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), synovial fluid leukocyte count, and percentage of polymorphonuclear neutrophils (PMN%). Later in the 2018 ICM and MSIS, serological D-dimer, synovial fluid CRP, leukocyte esterase (LE), and alpha-defensin were introduced as additional minor criteria.

Laboratory markers included in the consensuses are still relevant screening tests. It is an ongoing debate which marker has the best diagnostic power. Shahi et al. compared the performance of these typical tests [22]–among them LE was found to have the highest diagnostic odds ratio (DOR) at 30.06 suggesting both high test sensitivity and specificity. Additionally, synovial fluid white blood cell (WBC), serum CRP, synovial fluid PMN%, and serum ESR were found to have DORs of 29.4, 25.6, 25.5, and 14.6, respectively. Other studies pointed out alpha-defensin, an antimicrobial peptide from neutrophils, and synovial PMN% to be excellent diagnostic markers [20, 23]. The optimal diagnostic test and cut-off value remains an ongoing debate regarding acute PJI [24, 25]. This discussion was further complicated by the introduction of other novel tests to improve accuracy in difficult cases [20, 21].

1.3 Rheumatoid arthritis

Rheumatoid arthritis (RA) is one of the most prevalent autoimmune diseases. It affects 0.5-1% of the global population, with a female/male ratio of 2.5 to 3. Several genetic and environmental factors have been correlated to disease commencement and progression. In particular, gene polymorphisms in the human leukocyte antigen (HLA) system, especially HLA-DRB1, increase the risk to develop RA. Also, a positive family history, smoking, and peridontal diseases have been found to increase the likelihood for RA.
In most cases, the joints are the first affected body part. RA mostly affects the interphalangeal joints of the hand, but can also occur in major joints such as the knee and hip. Clinical signs include joint pain, swelling, morning stiffness, loss of mobility, and deformity in the end stage. RA can also impact other organs, such as the heart, lung, and kidney. Diagnosis relies on physical examination, blood tests, as well as X-rays of the joints. Rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs) are two feature serological markers used for the diagnosis. Treatment goal is to control the overactivated autoimmunity and prevent diseases progression with permanent damage to the affected organs. Medications available include glucocorticoids, disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, and biologic agents. Additionally, nonsteroidal anti-inflammatory drugs (NSAIDs) are often prescribed for pain management [26].

1.4 Diagnosis of PJI in patients with rheumatoid arthritis

Patients with RA are at higher risk of infection because long-term application of immunosuppressants is the therapeutic approach to reduce immune overactivity. Patients with auto-inflammatory arthritis that receive immunosuppressive therapy have been found to have an increased risk of PJI [27, 28]. However, it is recommended for patients to take elective joint arthroplasty without cessation of DMARDs or glucocorticoids during the perioperative period to limit RA symptoms [29, 30]. In PJI, proinflammatory cytokines induced by infection may also be a factor triggering RA initiation or recurrence [31].

The clinical manifestations between RA and PJI have partial overlap, which complicates the diagnosis of PJI in RA patients. In an active RA flare, systemic and local inflammatory markers are elevated–mainly CRP, ESR, and leukocytes. These markers are also reliable markers for PJI in most affected patients and thus are applied in the current diagnostic criteria including 2018 MSIS and 2021 EBJIS definition. However, patients with autoimmune diseases were not specifically considered in the listed criteria above. In patients with RA and suspected PJI, the recommended cut-off values might not be applicable.

In this study, we retrospectively analyzed blood and synovial fluid laboratory test results of culture-positive PJI cases with or without diagnosed RA who required prosthesis revision to determine cut-off values that can differentiate this morbidity. This study provides supplementary knowledge to what we know from the current existing literature. It is the first clinical research to assess the variation of typical serum and synovial markers for PJI diagnosis between populations with and without RA.

2. Methods

2.1 Study design

This retrospective study was approved by the Charité University Hospital ethics committee (EA2/083/19). All procedures in this study were carried out on the basis of the guidelines and regulations from Declaration of Helsinki.

2.2 Inclusion & exclusion criteria

We retrospectively analyzed all patients who received total knee revision surgery between 2013 and 2021 due to acute or chronic PJI at the Charité University Hospital in Berlin, Germany. Acute PJI was defined as PJI with onset of infection within four weeks after primary knee arthroplasty surgery, or no more than four weeks from the onset of characteristic PJI-related manifestations to the time for diagnosis and treatment. Patients with an onset of symptoms after more than four weeks after primary arthroplasty or onset of characteristic PJI-related symptoms were classified as chronic PJI. All patients received an interdisciplinary and standardized treatment approach in our orthopedic department. PJI diagnosis was based on the physical examination, laboratory blood results, serum inflammatory markers, synovial fluid tests, microbiology culture, and pathohistological observation of the tissue surrounding the prosthesis, also called synovial-like interface membrane (SLIM). In our hospital, patients with suspicion of PJI were allocated for microbiological examination from synovial fluid samples from arthrocentesis or arthroscopic surgery.

In our department, diagnosis of PJI is based on the modified EBJIS criteria (1st electronic English version 2016). Criteria used include: microbiological examination of aspiration fluid (positive culture), intraoperatively acquired fluids and tissues (same identified microorganism from at least two positive samples; in case that an organism with high virulence was identified, or patients were prescribed with antibiotics, one positive sample confirmed infection), or positive culture after sonication (> 50 CFU/ml of any organism); plus at least one of the following: (1) a sinus tract with evident communication into the joint, or purulence around the prosthesis; (2) synovial fluid leukocyte count of >2000/ul, or PMN percentage over 70%; (3) histology of preoperative biopsy or intraoperative periprosthetic membrane/SLIM with a Krenn and Morawietz Classification [32] type II or type III, or presence of more than five neutrophils in five high power fields or more.

According to the Krenn and Morawietz revised histopathological classification, there are six pathology types for SLIM in total, including type II which is characterized as infection induced periprosthetic membrane or synovitis, and type III with a combination of wear particle- and infection-induced synovitis. All patients who met the criteria above were included.

Patients who met one of the following characteristics were excluded: (1) PJI patients with negative result from the abovementioned microbiological culture; (2) primary osteomyelitis or purulent knee joint infection with no prosthesis involved; or (3) PJI after hip but not knee replacement surgery. In total, we enrolled and analyzed the data of 138 patients that have been treated at our clinic.

Diagnosis of RA was recorded from previous medical history before the inpatient treatment for PJI. Patients with RA have been diagnosed by a certified rheumatologist in line with the 2010 American College of Rheumatology and European Alliance of Associations for Rheumatology (ACR/EULAR) Classification Criteria, a point scoring system to evaluate affected joints, serological markers, acute-phase reactants, and the duration of symptoms [33]. All of these patients were treated systemically by board-certified rheumatologists before the occurrence of PJI.

2.3 Group division

We divided the enrolled patients into two groups depending on if they were diagnosed with RA (group A) or had no such diagnosis (group B). Furthermore, both group A and B were divided into subgroups depending on their onset of PJI symptoms (subgroup 1 for acute PJI, subgroup 2 for chronic PJI):

A1, acute PJI cases with RA;

A2, chronic PJI cases with RA;

B1, acute PJI cases without RA;

B2, chronic PJI cases without RA.

2.4 Data collection

We recorded basic demographic data, including age, sex, body mass index (BMI), and the American Society of Anesthesiologists' (ASA) classification. We also analyzed the Krenn and Morawietz pathology classification, microbiology and lab tests including serum CRP, WBC, and synovial fluid WBC, monocyte, and PMN count, and percentage.

Additionally, surgery related data were analyzed–acute versus chronic PJI, the number of prior revision surgeries on the affected knee (septic and aseptic), and, if applicable, the time from revision surgery till prosthesis failure due to either aseptic loosening or recurrent PJI for survival analysis.

2.5 Statistics and plots

In our study, all data were collected, categorized, and controlled by two individuals using Microsoft Excel 2016 (Redmond, WA USA). We adopted R studio software (Version 3.6.3, Vienna, Austria) to analyze all the data, and generated the plots using Graphpad Prism (version 9.0.0, San Diego, CA). P value lower than 0.05 was considered as significant statistical difference.

Continuous data were presented as median and interquartile range (IQR) and analyzed using Mann-Whitney U nonparametric test. Statistical difference in categorical data between two groups were compared using Chi-square test. Data are presented as numbers and bar plots.

To determine optimal cut-off values, receiver operating characteristic (ROC) curve was carried out. The value of area under the curve (AUC) represents the power of the tests to discriminate between PJI patients with RA and without RA. On the ROC curve, the x-value of each point represents “1-specificity”, and the y-value “sensitivity”. We used the Youden index (J) method to calculate the diagnostic cut-off value by determining the maximal value of “sensitivity + specificity-1” from all points on the ROC curve [18]. The diagnostic value was categorized depending on AUC from high to low: AUC >0.900 as excellent, 0.800-0.899 as good, 0.700-0.799 as fair, 0.600-0.699 as poor, and 0.500-0.599 as no diagnostic value.

Based on cut-off values, the sensitivity and specificity as well as the negative predictive value (NPV) and positive predictive value (PPV) were determined according to the formulas below:

Sensitivity= (True Positive)/(True Positive + False Negative)

Specificity= (True Negative)/(True Negative + False Positive)

PPV= (True Positive)/(True Positive + False Positive)

NPV= (True Negative)/(True Negative + False Negative)

For survival analysis, we retrieved the last time point at which a patient underwent their revision surgery. Prosthesis failure was defined as either aseptic loosening or recurrent

PJI with subsequent revision surgery. Kaplan–Meier survival curves were used to visualize prosthesis survival.

3. Results

3.1 Patient demographics and characteristics

A total of 138 patients were included in this study. Seventeen patients with RA and PJI made up group A and the remaining 121 patients with PJI but without RA were allocated into group B. In group A, nine patients were diagnosed with acute (group A1) and eight with chronic PJI (group A2). In group B, fifty-four patients were classified as acute (group B1) and sixty-seven as chronic PJI (group B2). The demographic data of the enrolled patients is detailed in Table 1. Average age of all participants was 69.54 years, in group A 72.94 years and in group B 69.07 years. In both groups, most of the patients had an ASA score lower than 4 (88.24% in group A, 95.86% in group B). Twelve patients in group A (70.59%) received more than one prior revision surgery, while there were 75 patients in group B (61.98%, p=0.49). None of the enrolled patients were diagnosed with a sinus tract.

Table 1: Patient Demographics and Characteristics (table modified from [1])

	Group A	Group B
Characteristics		
Sex (male/female)	12 (70.6%) / 5 (29.41%)	64 (52.9%) / 57 (47.1%)
BMI (kg/m2)	29.8±7.0	30.6±5.8
Age (years)	72.9±7.1	69.1±10.8
Surgery related		
PJI onset		
Acute	9 (52.9%)	54 (44.6%)
Chronic	8 (47.1%)	67 (55.4%)
Revision surgery		
One	5 (29.4%)	46 (38.0%)
More than one	12 (70.6%)	75 (62.0%)
ASA score		
1-3	15 (88.2%)	112 (94.2%)
4-6	1 (5.9%)	5 (4.1%)

BMI, body mass index; ASA, American Society of Anesthesiologists.

3.2 Pathohistological analysis of the periprosthetic membrane

In this study, 15 patients (88.24%) with RA (group A) and 94 patients (77.69%) without RA (group B) were classified as Krenn-Morawietz type II or III indicating infection. Among these, five patients in group A (29.41%) and 52 patients in group B (42.98%) were diagnosed with low-grade infection, while ten patients in group A (58.82%) and 42 patients in group B (34.71%) had a high-grade infection. The remaining two patients in group A (11.76%) and 27 in group B (22.31%) were classified as type I (wear particle induced SLIM) or type IV (periprosthetic membrane of fibrous type without evidence of wear particle or infection) (Figure 1).

Subgroup analysis within acute PJI showed all nine cases in group A1 (100%) and 49 patients in group B1 (90.74%) had type II or III classification, with three (33.3%) and 26 (48.15%) cases assessed as high-grade infection, respectively. For chronic PJI, six patients in group A2 (75%) and 45 in group B2 (67.16%) were classified as type II or III. High-grade infection was found in two patients (25.00%) in A2 and 16 (23.88%) in B2.

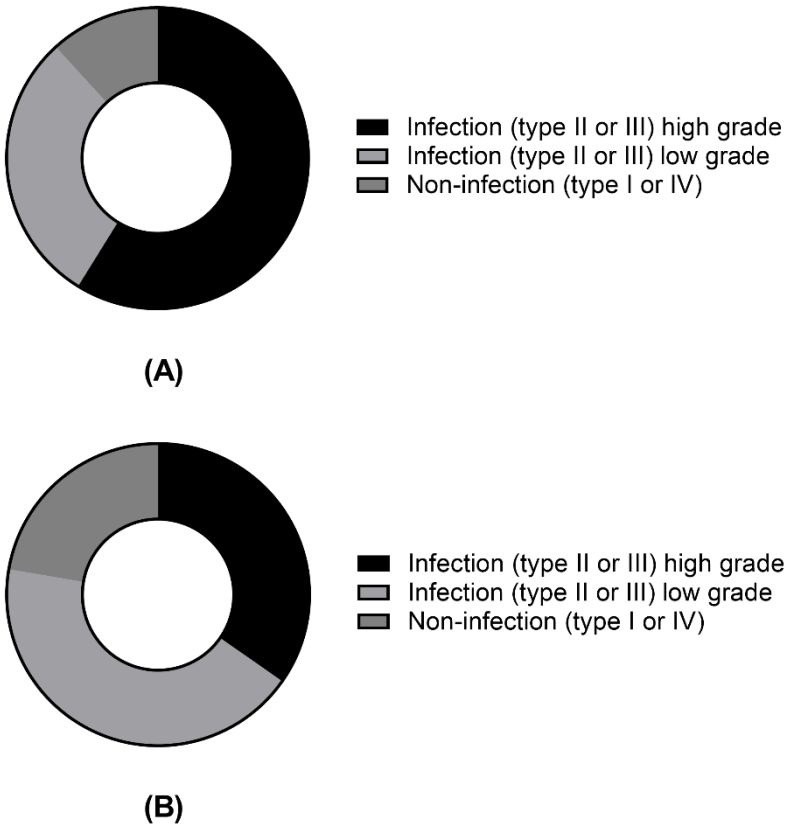

Figure 1: Histological classification of periprosthetic membrane. (figure self-created)

3.3 Causative Pathogens

In both groups, *Staphylococcus aureus* and *Staphylococcus epidermidis* ranked first and second highest in incidence rates, respectively. While eight patients in group A (47.06%) and 40 patients in group B (33.06%) were affected by *Staphylococcus aureus*, six patients in group A (35.29%) and 24 patients in group B (19.83%) were diagnosed with *Staphylococcus epidermidis*. Other common pathogens identified in our study included *Cutibacterium acnes*, *Enteroccocus faecalis*, *Streptococcus anginosus*, and *Streptococcus dysgalactiae* (Figure 2).

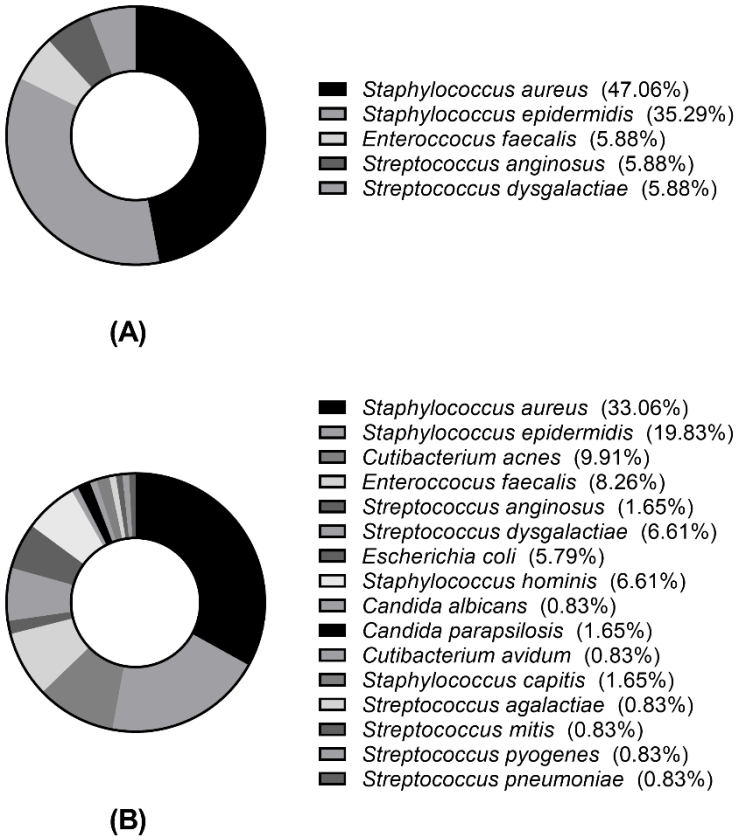

Figure 2: Causative pathogens identified in group A (A) and group B (B). *Staphylococcus aureus* and *Staphylococcus epidermidis* are the most common pathogens found in the cohort. (figure self-created)

Staphylococcus aureus was found in six patients in group A1 (66.67%) and in 25 patients in group B1 (46.30%). In the chronic PJI subgroup, group A2 consisted of six patients infected by *Staphylococcus epidermidis* (75.00%) and two patients by *Staphylococcus aureus* (25.00%). In group B2, *Staphylococcus epidermidis* was diagnosed in 22 patients (32.84%) and *Staphylococcus aureus* in 15 patients (22.39%).

3.4 Laboratory tests for serum and synovial fluid markers

3.4.1 Group A vs B

When comparing laboratory test results regardless of acute or chronic disease onset, we found patients with RA compared to without to have significantly elevated synovial WBCs (group A, 57.99 cells/nL, 37.81 to 122.41; group B, 21.72 cells/nL, 2.28 to 64.36; p=0.02), PMNs (group A: 55.89 cells/nL, 35.00 to 82.67; group B, 18.53 cells/nL, 1.40 to 58.87; p=0.03), and monocyte cell counts (group A, 2.88 cells/nL, 2.10 to 16.14; group B, 1.86 cells/nL, 0.57 to 4.25; p=0.05).

No statistical difference were found in serum CRP (group A, 86.90mg/L, 50.00 to 256.20; group B, 49.10mg/L, 11.8 to 130.22; p=0.07), WBC counts (group A, 8.86 cells/nL, 5.73 to 12.03; group B, 8.15 cells/nL, 6.53 to 10.81; p=0.70), synovial percentage of monocytes (group A, 10.56%, 4.96 to 14.44; group B, 11.80%, 5.53 to 38.98; p=0.12), and percentage of PMNs (group A, 89.43%, 85.55 to 95.04; group B, 86.67%, 59.90 to 93.64; p=0.09). (Figure 3)

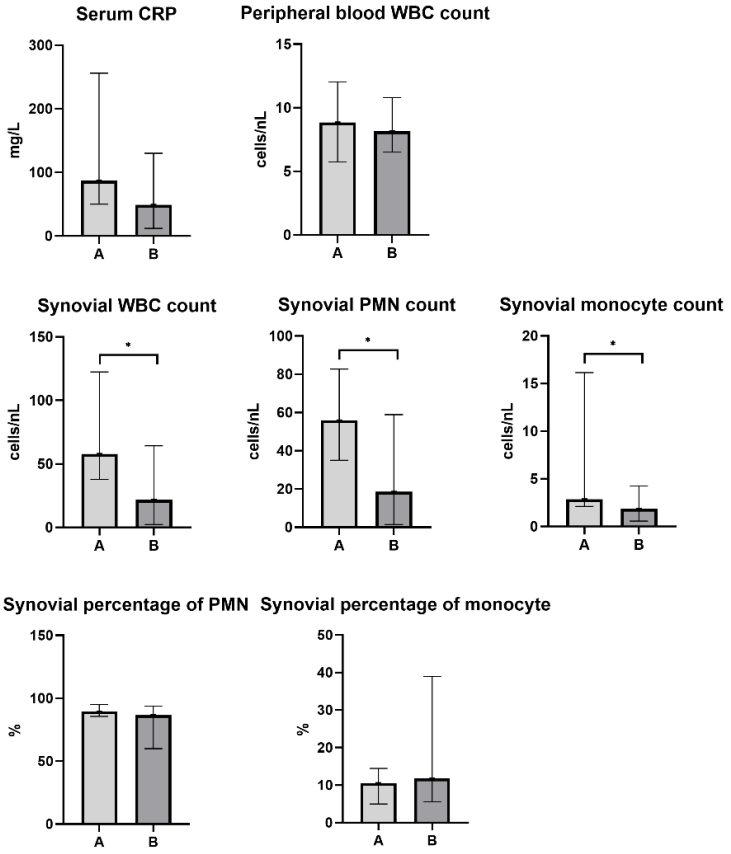

Figure 3: Laboratory test values between PJI with RA (A) and without RA (B). Data are presented as median and interquartile range. (figure self-created)

3.4.2 Subgroup with acute PJI (A1 vs B1)

In patients with RA versus non-RA PJI patients, no significant differences were found in serum CRP (group A1, 88.02mg/L, 86.91 to 256.22; group B1, 129.45mg/L, 72.03 to 244.22; p=0.92), WBC counts (group A1, 9.13 cells/nL, 6.17 to 12.03; group B1, 9.93 cells/nL, 7.22 to 14.22; p=0.31), synovial WBC cell counts (group A1, 60.75 cells/nL, 54.72 to 118.06; group B1, 48.92 cells/nL, 33.58 to 197.55; p=0.54), monocyte cell counts (group A1, 6.69 cells/nL, 2.21 to 11.43; group B1, 3.97 cells/nL, 2.05 to 13.85; p=0.94), PMN cell counts (group A1: 55.89 cells/nL, 48.41 to 86.94; group B1, 48.24 cells/nL, 31.32 to 160.92; p=0.74), synovial percentage of monocytes (group A1, 10.56%, 4.49 to 12.12; group B1, 8.81%, 5.31 to 16.24; p=0.70), and percentage of PMNs (group A1, 89.43%, 87.88 to 95.51; group B1, 91.19%, 83.77 to 94.69; p=0.63). (Figure 4)

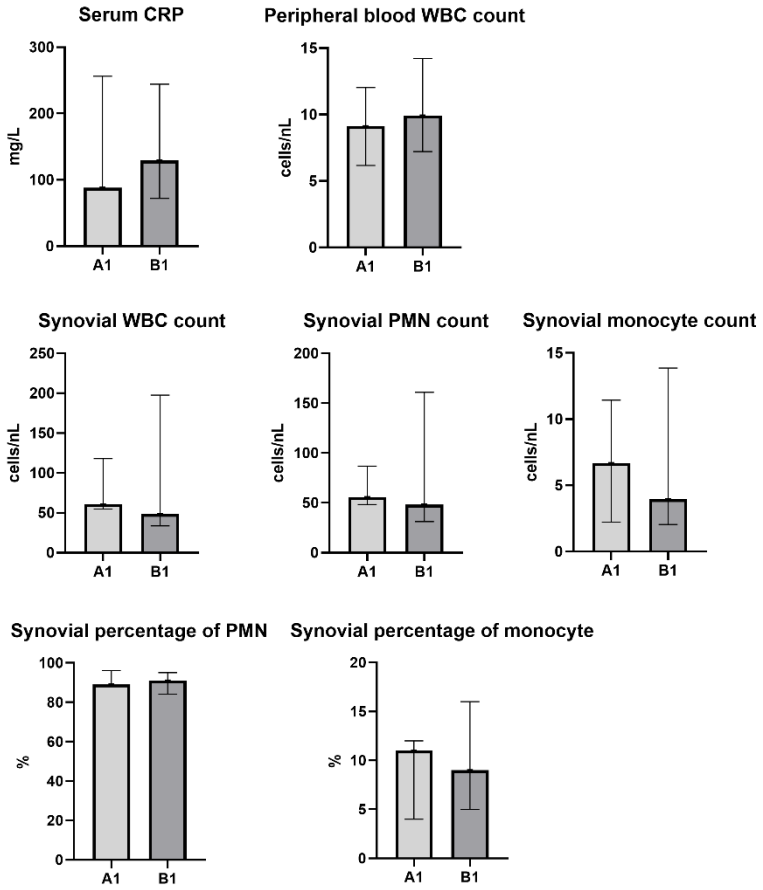

Figure 4: Different laboratory test values among acute PJI with RA (A) and without RA (B). Data are presented as median and interquartile range. (figure self-created)

3.4.3 Subgroup with chronic PJI (A2 vs B2)

For patients diagnosed with chronic PJI, serum CRP (group A2, 43.25mg/L, 25.02 to 145.04; group B2, 18.83mg/L, 6.45 to 47.15; p=0.05), synovial WBCs (group A2, 34.69 cells/nL, 23.06 to 103.17; group B2, 8.33 cells/nL, 0.85 to 23.37; p=0.03), PMNs (group A2: 33.36 cells/nL, 20.48 to 70.75; group B2, 6.13 cells/nL, 0.43 to 16.68; p=0.02), and monocyte cell counts (group A2, 2.27 cells/nL, 1.16 to 13.52; group B2, 0.79 cells/nL, 0.33 to 2.28; p=0.04) were significantly elevated in group A2 (RA PJI patients) compared to non-RA patients.

However, no difference was observed in peripheral WBC counts (group A2, 6.86 cells/nL, 5.16 to 10.81; group B2, 7.45 cells/nL, 6.25 to 8.39; p=0.75), synovial percentage of monocytes (group A2, 10.35%, 5.28 to 14.62; group B2, 23.03%, 7.85 to 42.74; p=0.13), and percentage of PMNs (group A2, 89.65%, 85.38 to 94.72; group B2, 76.59%, 54.71 to 91.48; p=0.10). (Figure 5)

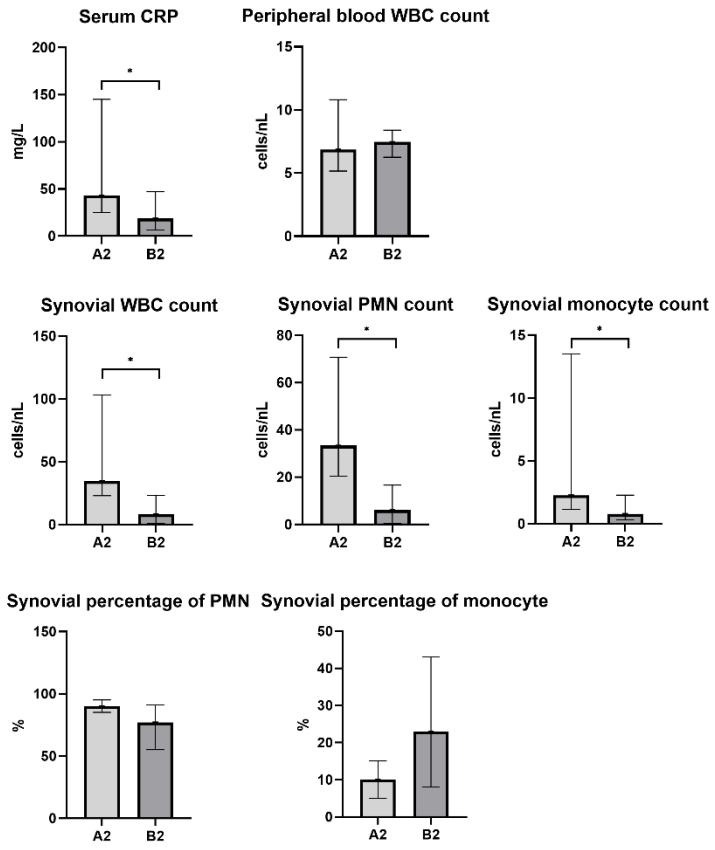

Figure 5: Different laboratory test values among chronic PJI with RA (A) and without RA (B). Data are presented as median and interquartile range. (figure self-created)

3.5 Diagnostic value of laboratory tests

ROC analyses were performed for all the laboratory markers. AUC of synovial WBC cell count (0.72), PMN cell count (0.70), PMN percentage (0.71), and monocyte percentage (0.70) showed fair diagnostic power. Other markers were found to have only poor to no discriminative power. (Figure 6)

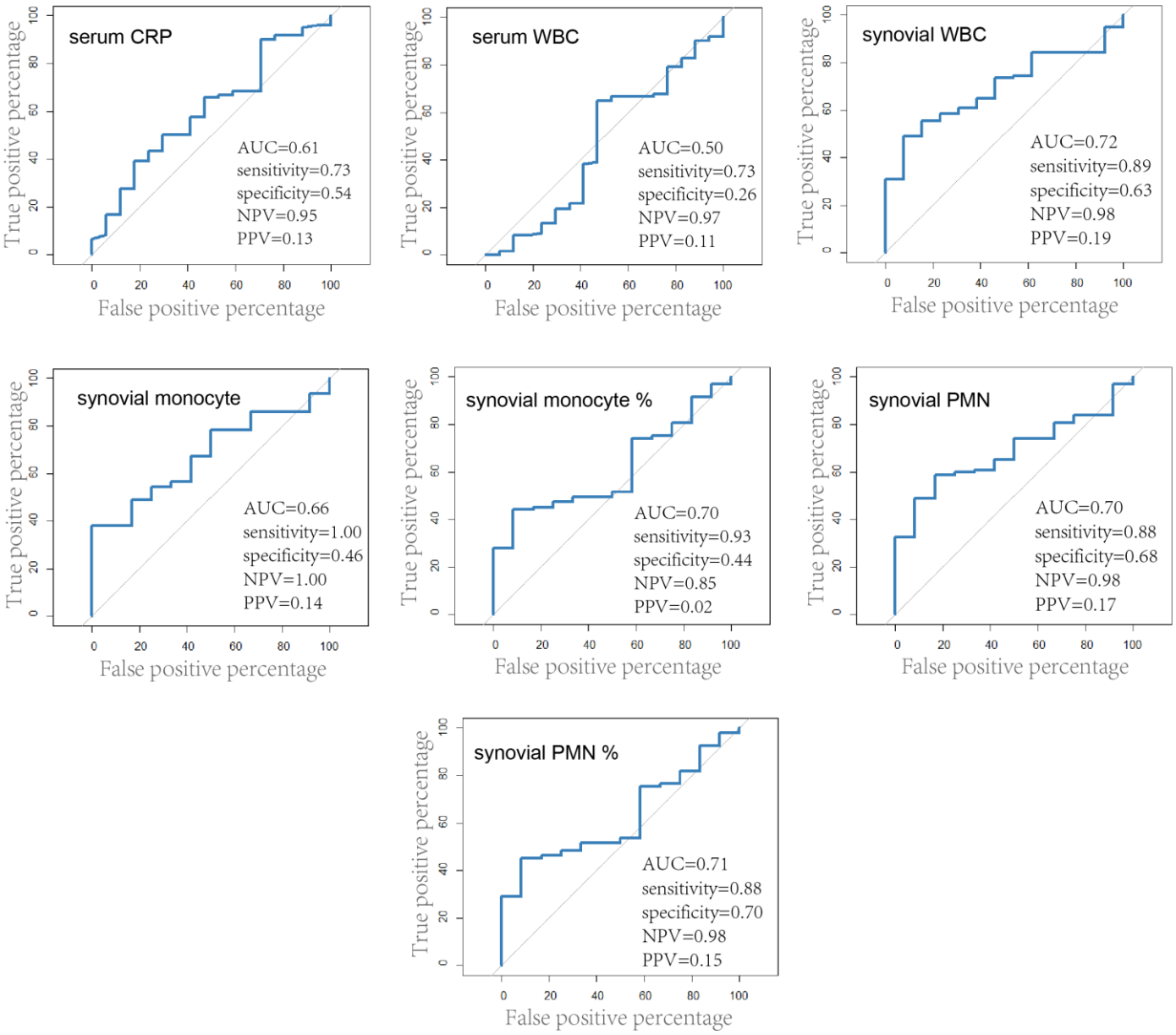

Figure 6: Diagnostic performance of laboratory markers for patients with PJI and RA. Related values (AUC, sensitivity, specificity, NPV, PPV) are shown in ROC plots. (figure modified from [1])

In acute PJI, cut-off values were 107.65 mg/L for serum CRP, 43.18 cells/nL for synovial WBC cell count, and 89.93% for synovial PMN%. However, performance of all markers showed poor to no diagnostic value. (Figure 7)

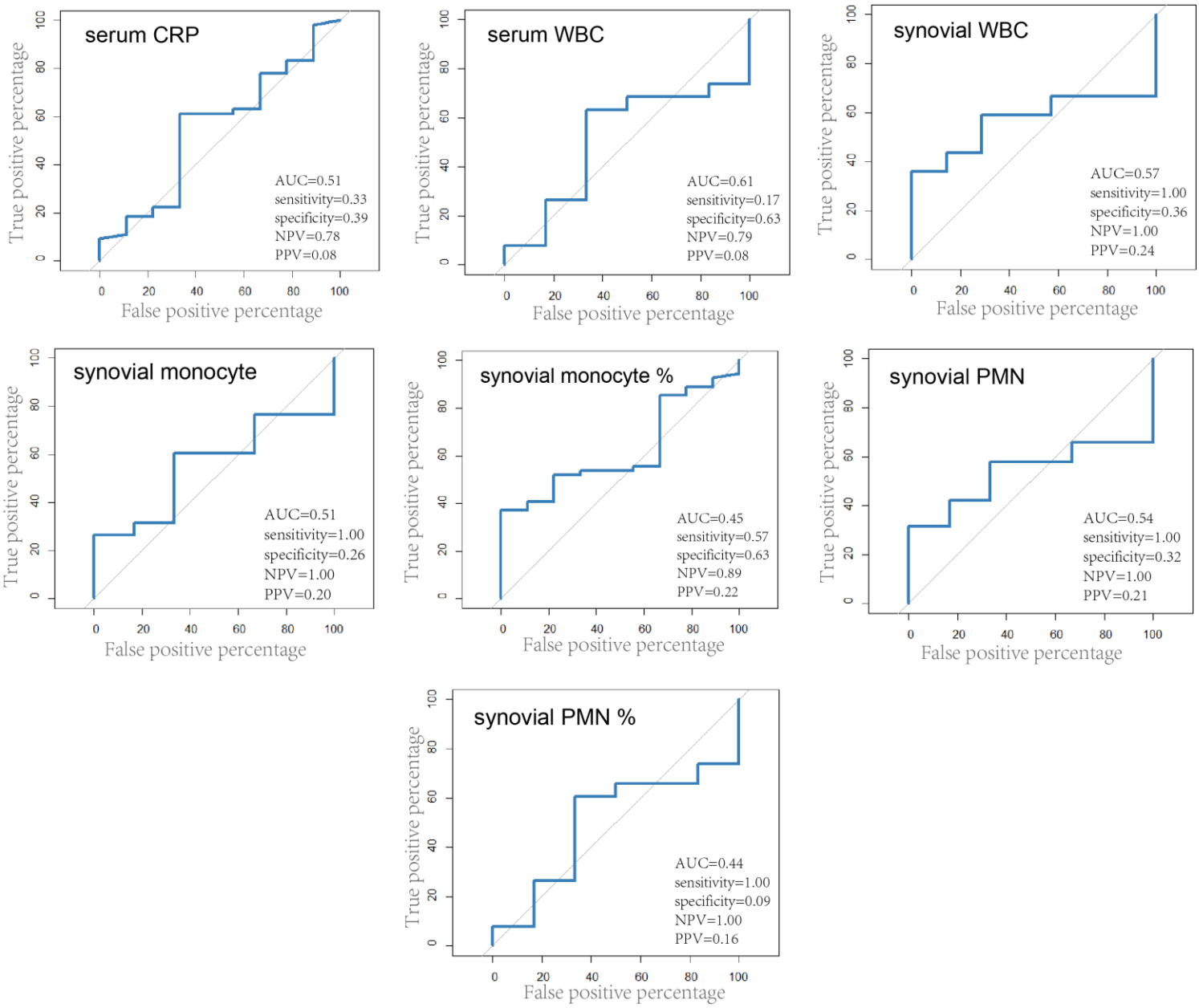

Figure 7: Diagnostic performance of laboratory markers for patients with acute PJI and RA. Related values (AUC, sensitivity, specificity, NPV, PPV) are shown in ROC plots. (figure modified from [1])

Conversely, AUC in patients with chronic PJI indicated fair diagnostic accuracy for serum CRP (0.71), synovial WBC count (0.78), synovial monocyte cell count (0.75), synovial percentage of PMN cell count (0.71), and good diagnostic value for synovial PMN cell count (0.80). Calculated cut-off values were 29.05 mg/L for serum CRP, 19.48 cells/nL for synovial WBC cell count, and 85.30% for synovial PMN%. Sensitivity for these markers ranged from 70 to 90%, with a specificity between 50 to 80%. (Figure 8)

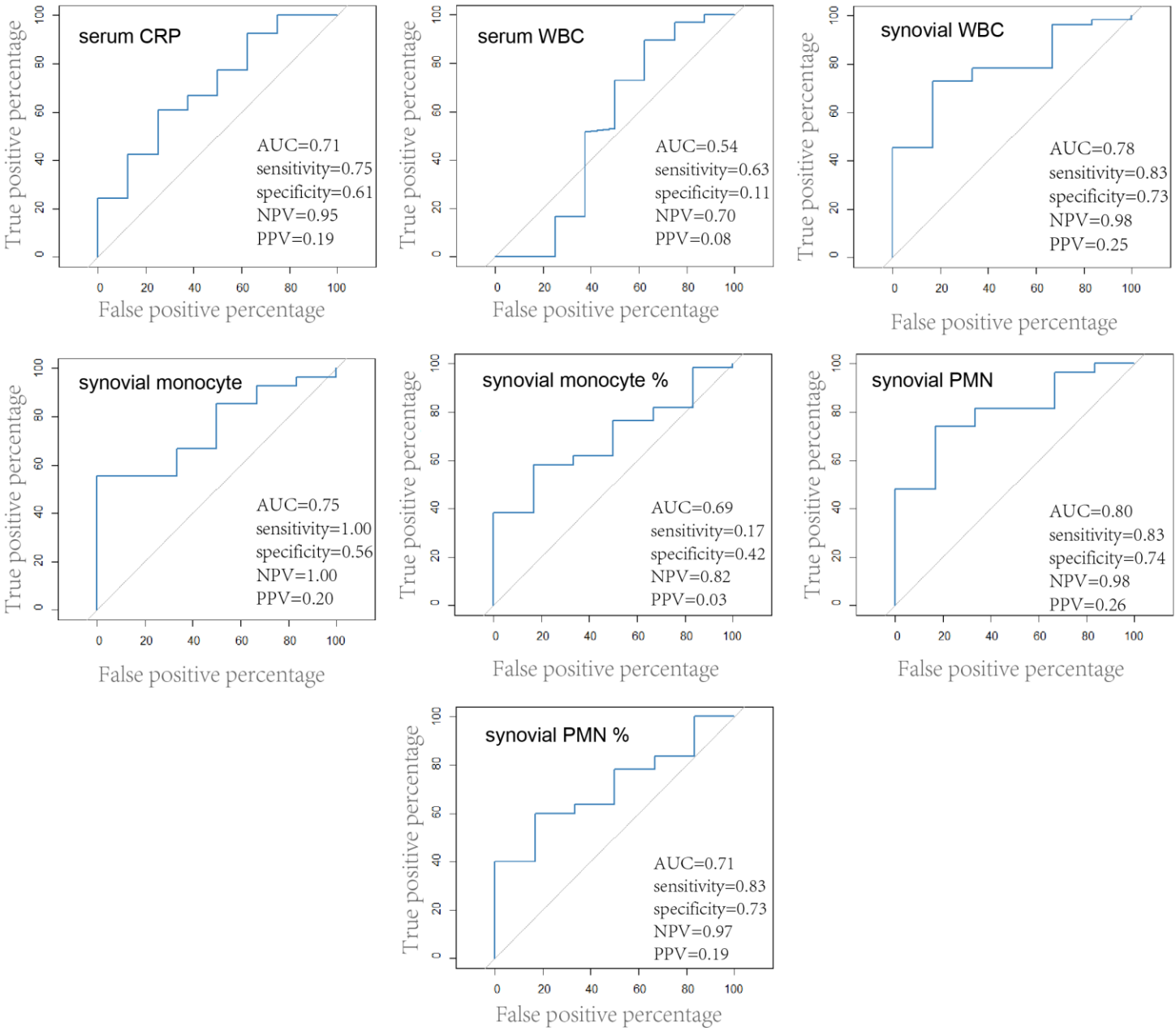

Figure 8: Diagnostic performance of laboratory markers for patients with chronic PJI and RA. Related values (AUC, sensitivity, specificity, NPV, PPV) are shown in ROC plots. (figure modified from [1])

3.6 Survival analysis after revision surgery

During the first nine years of follow-up, patients with RA had a significantly elevated prosthesis failure risk (47.06%) due to aseptic loosening or recurrent PJI, compared to patients without RA (21.48%, p=0.03). In group A, all patients with prosthesis failure were diagnosed with recurrent PJI, while in group B, 19.23% of the patients suffered from aseptic loosening and recurrent PJI was diagnosed in the remaining 80.77%. None of our patients were confronted with component malalignment, bone stem fracture or other reasons for revision.

Additionally, we found prosthesis survival time to be negatively impacted by RA. The median survival time of revision prosthesis was significantly reduced among patients with RA (median value: 1.00 year, IQR 1.00 to 3.00) compared to those without RA (median value: 2.00 year, IQR 1.75 to 4.00; p=0.05). (Figure 9)

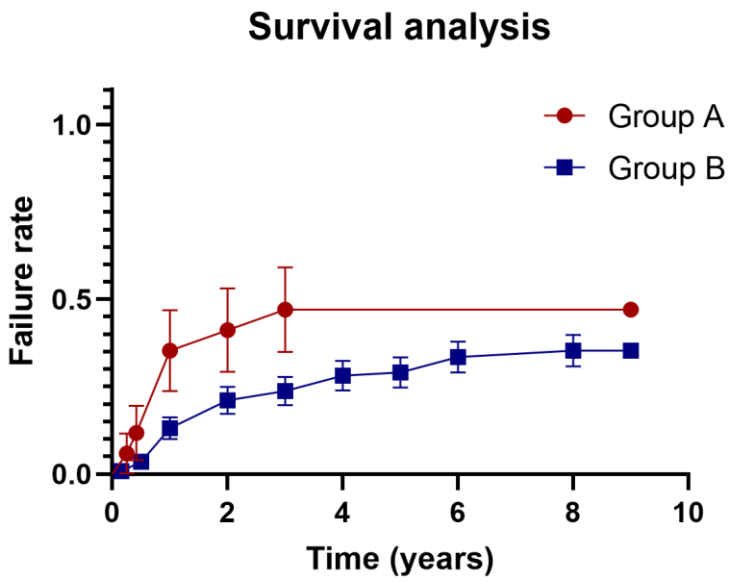

Figure 9: Survival analysis of patients with PJI and RA compared to PJI patients without RA during a nine-year follow-up period. (figure modified from [1])

4. Discussion

4.1 Short summary

This retrospective clinical study analyzed the clinical and paraclinical data of patients diagnosed with PJI and with or without RA. Besides investigating demographic characteristics, histological classifications, pathogen types, and laboratory test results, we performed prosthesis survivorship analysis. Additionally, the differential diagnostic power of commonly used laboratory markers was evaluated.

In this study, patients with or without RA had similar clinical characteristics. Both patient populations A and B presented with similar histological result, with most of them classified as Krenn and Morawietz type II or III. *Staphylococcus aureus* and *Staphylococcus epidermidis* were the most common causative organisms for both groups. Several laboratory tests (serum CRP, synovial WBC, monocyte and PMN counts) were significantly upregulated in patients with chronic PJI and RA compared to without RA. However, in patients with acute PJI and RA, none of the markers were found to be significantly different from those with acute PJI only. AUC analysis showed synovial WBC cell count, PMN cell count, PMN percentage, and monocyte percentage to have a good diagnostic accuracy for differentiating patients with PJI and RA from patients without RA. In chronic PJI, fair to good diagnostic power was found for serum CRP, synovial WBC count, synovial monocyte cell count, synovial percentage of PMN cell count, and synovial PMN cell count, while none of the markers had good capability of differentiating RA from non-RA patients in acute PJI. Long-term prosthesis survival analysis found patients with rheumatoid diseases to have a significantly elevated risk of prosthesis failure due to either aseptic loosening or recurrent PJI.

4.2 Current diagnostics value for PJI

Suspected PJI in patients that present themselves with joint pain and swelling after primary arthroplasty surgery remains a diagnostic challenge for attending orthopedic surgeons. Currently, clinicians rely on clinical features as well as laboratory tests of peripheral blood and synovial fluid to distinguish PJI. However, in patients with RA, diagnostic accuracy of commonly employed markers is limited by similar presentation in clinical and laboratory features. In particular, elevation of inflammatory markers may be caused by either high activity of septic or aseptic, autoimmune-dependent inflammation.

Administration of immunosuppressants commonly prescribed for RA limits the reactivity of the immune system. Biologic agents are linked to an increased infection risk, which can subsequently affect expression of inflammatory markers [29]. In case of PJI, local upregulation and increased secretion of proinflammatory cytokines can be observed in the affected knee joint [34]. These cytokines help eliminate pathogens, but can also activate resting T and B cells, potentially triggering recurrence of RA [31].

Rapid diagnosis is crucial to determine if surgical intervention and antibiotic treatment is necessary, especially in acute cases to avoid uncontrollable local infection or potentially lethal sepsis. However, accurate and timely diagnosis is complicated in cases with pre-existing RA. Commonly utilized tests react to both septic and autoimmune inflammation. In the current MSIS and EBJIS guidelines there is still paucity of knowledge on recommended reference values to differentiate PJI in patients with a medical history of RA. However, the severe impact of both falsely treating or not treating PJI makes it mandatory to investigate potential cut-off values for positive inflammatory serum and synovial markers in this patient population. Traditionally employed markers are especially of interest as they are widespread and easy to carry out. In our study, patients with both acute and chronic PJI were enrolled. Culture negative PJI cases were excluded to ensure all involved cases to be true-positive.

In consistence with previous studies, laboratory markers in the chronic group showed fair to good diagnostic accuracy: Cipriano et al. reported excellent differential capability for CRP, ESR, synovial fluid WBCs, and PMN % in both inflammatory and non-inflammatory arthritis in patients diagnosed with chronic PJI. Of the investigated markers, synovial fluid WBC count displayed highest AUC for predicting PJI in patients with inflammatory arthritis, while synovial PMN% had a higher predicting accuracy among non-inflammatory arthritis. However, the diagnostic threshold in patients with either inflammatory or non-inflammatory arthritis was comparable and similar to values currently employed in clinics [27], implying that changes in these markers were mostly due to septic inflammation surrounding the prosthesis rather than auto-inflammation. In our study, chronic PJI subgroup analysis revealed synovial fluid PMN and total WBC cell count as the best two differential tests to differentiate RA from non-RA, with a relatively high AUC (0.80 and 0.78 respectively). In contrast to what Cipriano et al. reported, we found these markers with valuable diagnostic potential for RA. Additionally, George et al. reported that CRP and ESR showed good specificity and moderate sensitivity to detect persistent infection after first stage revision surgery in patients with inflammatory arthritis [35]. Shohat et al.

found no significant changes in laboratory inflammation markers in patients with inflammatory arthritis undergoing revision surgery due to chronic PJI [36]. In accordance with our results, Qin et al. recently analyzed test results from chronic PJI and non-operated RA patients and reported fair diagnostic potential for CRP and ESR, and good accuracy for synovial PMN% [37]. Compared to previously published results [27, 35], the cut-off value for synovial WBC count was approximately 5- to 6-fold higher in our study suggesting significant inflammatory upregulation. However, in acute PJI, there were no statistically significant differences in any of the analyzed markers. Additionally, the diagnostic accuracy was poor for all parameters. In these patients, septic inflammation may profoundly elevate these inflammatory markers masking the effect of RA [38]. Despite being diagnosed with RA, elevation of these inflammatory markers seems to be more PJI- and not RA-dependent [15, 37]. Consistently with previous studies, our data also suggested a relatively higher sensitivity and NPV, but lower specificity and PPV in acute PJI. Recent work also indicated that novel diagnostic markers such as alpha-defensin have been shown to have excellent discriminative value for non-PJI inflammatory joint cases from PJI [21], while there was no significant difference for patients with inflammatory arthritis undergoing PJI revision surgery compared to patients without inflammatory arthritis [36].

Microbiological analysis is indispensable for diagnosis of PJI and to determine adequate antibacterial treatment alike. In concordance with previously published data [39], *Staphylococcus aureus* and *Staphylococcus epidermidis* were found as causative pathogens in the majority of cases. In recent years, NGS became more accessible for several clinical applications, however is still not a widespread technology. This innovative technique is highly promising for the diagnosis of PJI in general and in patients with RA in particular. First investigations with culture-negative PJI demonstrated a high sensitivity (80-95%), specificity (70-100%) at reduced costs [40].

4.3 Prosthesis survivorship analysis

Progressive bone erosion and an increased risk for infection are the two main reasons for prosthesis failure after TKA in patients with RA. In RA, a variety of proinflammatory cells accumulate in the affected joint and release cytokines that promote inflammation. This inflammatory process can subsequently alter the trabecular structure of the subchondral bone and lower the bone mineral density in patients with RA [41, 42]. The

inflammatory process in these patients has been found to correlate to osteolytic processes that increase the risk of aseptic prosthesis loosening [43].
RA has been identified as an independent factor for tibial component loosening after cemented TKA [44]. Böhler et al. found that radiological prosthesis loosening was evident in around ten percent of all non-RA osteoarthritis patients, compared to over 40% of all RA patients in a ten-year follow-up study. However, the rate of revision due to aseptic loosening was significantly higher in RA (8.2%) than OA (1.1%) [43]. PJI-dependent prosthesis revision surgery was performed in 7.0% of all RA and in 1.8% of all non-RA OA cases [45]. Similar, our data demonstrates that RA negatively impacts the survivorship of revision prostheses. However, in contrast to previous reports, we found a markedly higher revision prostheses failure risk in patients with RA (RA, 47.06%; non-RA, 21.48%). In addition to the use of antirheumatic drugs that reduce immune activity, RA itself can be an independent risk factor for infection by impairing the innate and adaptive immune reaction [28]. After primary knee arthroplasty, patients with RA had an approximately 2-fold long-term risk for deep wound infections and revision surgery due to PJI (odds ratio = 1.89) [46].

4.4 Limitations

Several factors have been identified as limitations of this study. This investigation was a retrospective study that was conducted in a single treatment center with a limited but heterogenous cohort size. Second, patients with RA and PJI but with negative microbiology culture were excluded in this study as with current diagnostic tools, PJI can neither be confirmed nor ruled out in these patients potentially leading to either over- or underestimation of the observed differences. Finally, a potential impact of RA and PJI treatments prior to hospital admission were not analyzed in this study, as well as the choice of antibiotics was not tested for as an independent variable due to the limited population size.

4.5 Future perspectives and applications

Despite increased research activity in the field, diagnosing PJI in patients with RA remains highly challenging. In cases with diagnosed RA-specific autoantibodies, these may be taken into account to identify the disease activity level. Novel laboratory tests designed

for the diagnosis of PJI may bring additional merit but have to be further investigated for their effectiveness in cases with RA. Besides RA, a number of other inflammatory arthritis diseases, i.e. ankylosing spondylitis and psoriatic arthritis, exist that provide similar challenges to attending orthopedic surgeons. The cut-off values reported in this study potentially can be used as a reference for these diseases. However, for a more detailed understanding of the pathomechanisms involved, future research is warranted in patients affected by these pathologies. Additionally, novel laboratory tests may provide tools to predict prosthesis survival in affected patients.

5. Conclusions

In this study, we investigated the influence of RA on laboratory tests on serum and synovial fluid in patients with suspected PJI, and their capability to distinguish PJI in RA versus non-RA patients. Using the currently established diagnostic criteria, serological and synovial markers are markedly enhanced in RA patients with chronic PJI indicating increased immunological activity in the affected knee. In acute PJI, these markers have limited effectiveness in patients with rheumatoid arthritis. Reduced survivorship after revision surgery in RA patients highlights the need for improved diagnostics and therapeutic approaches in these patients.

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Statutory Declaration

“I, Yi Ren, by personally signing this document in lieu of an oath, hereby affirm that I prepared the submitted dissertation on the topic *Periprosthetic joint infections in patients with rheumatoid arthritis – a diagnostic challenge (Periprothetische Gelenkinfektionen bei Patienten mit rheumatoider Arthritis – eine diagnostische Herausforderung)*, independently and without the support of third parties, and that I used no other sources and aids than those stated.

All parts which are based on the publications or presentations of other authors, either in letter or in spirit, are specified as such in accordance with the citing guidelines. The sections on methodology (in particular regarding practical work and statistical processing) and results (in particular regarding figures, charts and tables) are exclusively my responsibility.

Furthermore, I declare that I have correctly marked all of the data, the analyses, and the conclusions generated from data obtained in collaboration with other persons, and that I have correctly marked my own contribution and the contributions of other persons (cf. declaration of contribution). I have correctly marked all texts or parts of texts that were generated in collaboration with other persons.

My contributions to any publications to this dissertation correspond to those stated in the below joint declaration made together with the supervisor. All publications created within the scope of the dissertation comply with the guidelines of the ICMJE (International Committee of Medical Journal Editors; http://www.icmje.org) on authorship. In addition, I declare that I shall comply with the regulations of Charité – Universitätsmedizin Berlin on ensuring good scientific practice.

I declare that I have not yet submitted this dissertation in identical or similar form to another Faculty. The significance of this statutory declaration and the consequences of a false statutory declaration under criminal law (Sections 156, 161 of the German Criminal Code) are known to me.”

Date Signature

Declaration of your own contribution to the publication(s)

Yi Ren contributed the following to the below listed publication:

Ren Y, Biedermann L, Gwinner C, Perka C, Kienzle A. Serum and Synovial Markers in Patients with Rheumatoid Arthritis and Periprosthetic Joint Infection. *J Pers Med*. 2022; 12(5): 810
Contribution: I retrieved most part of data from clinical database of our hospital, and did all statistical analysis. All tables and figures were created based on my data and statistical analysis. Together with co-authors, I drafted the manuscript, all authors contributed to its completion and revision.

_____

Signature, date and stamp of first supervising university professor / lecturer

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Serum and Synovial Markers in Patients with Rheumatoid Arthritis and Periprosthetic Joint Infection

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Abstract: Current diagnostic standards for PJI rely on inflammatory markers that are typically elevated in autoimmune diseases, thus making the diagnosis of PJI in patients with rheumatoid arthritis and joint replacement particularly complicated. There is a paucity of data on differentiating PJI from rheumatoid arthritis in patients with previous arthroplasty. In this study, we retrospectively analyzed the cases of 17 patients with rheumatoid arthritis and 121 patients without rheumatoid disease who underwent surgical intervention due to microbiology-positive PJI of the hip or knee joint. We assessed clinical patient characteristics, laboratory parameters, and prosthesis survival rates in patients with and without rheumatoid arthritis and acute or chronic PJI. ROC analysis was conducted for the analyzed parameters. In patients with chronic PJI, peripheral blood CRP ($p = 0.05$, AUC = 0.71), synovial WBC count ($p = 0.02$, AUC = 0.78), synovial monocyte cell count ($p = 0.04$, AUC = 0.75), and synovial PMN cell count ($p = 0.02$, AUC = 0.80) were significantly elevated in patients with rheumatoid arthritis showing acceptable to excellent discrimination. All analyzed parameters showed no significant differences and poor discrimination for patients with acute PJI. Median prosthesis survival time was significantly shorter in patients with rheumatoid arthritis ($p = 0.05$). In conclusion, routinely used laboratory markers have limited utility in distinguishing acute PJI in rheumatoid patients. In cases with suspected chronic PJI but low levels of serum CRP and synovial cell markers, physicians should consider the possibility of activated autoimmune arthritis.

Keywords: periprosthetic joint infection; rheumatoid arthritis; arthroplasty; total knee replacement; total hip replacement

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1. Introduction

PJI is a major complication following joint replacement occurring in 1–5% of patients with primary arthroplasties [1,2]. Depending on the duration of symptoms, PJI is classified as acute or chronic. While the exact cutoff value is of ongoing debate, acute PJI is commonly defined as an infection with symptom duration ≤ 4 weeks [3,4]. In chronic PJI, symptoms have been present for > 4 weeks and may be the result of a low-virulence organism [5]. In both cases, adequate surgical treatment of PJI is mandatory to achieve a successful, infection-free outcome [6,7]. While treatment with debridement and implant retention can be an effective therapy for acute PJI, one- or two-stage exchange surgery may be required in chronic PJI [8]. In any of these cases, treatment is an enormous burden for patients [9]. In addition to surgical intervention, exchange arthroplasty can significantly impact joint function, cause pain, and has an increased risk of prosthesis failure [10–12].

Attending physicians are often challenged by the need to accurately diagnose PJI within a short time frame to be able to decide upon the necessary treatment strategy. Despite significant progress in recent years, no agreed-upon gold standard for the diagnosis of PJI exists [13]. Besides clinical presentation, diagnosis usually relies upon laboratory

diagnostics using peripheral blood as well as synovial fluid. The markers routinely used are WBC count and serum CRP, as well as synovial WBC count and PMN cell percentage [14,15]. Depending on national, regional, or hospital-specific guidelines and standards, additional testing for leukocyte esterase, alpha-defensin, D-dimer, erythrocyte sedimentation rate, and synovial CRP may be performed. Additionally, microbiological culture is essential but not feasible in an acute setting due to culture time [16]. In some cases, microbiological culture may be negative despite the presence of PJI [17,18].

While both the 2018 Definition of Periprosthetic Hip and Knee Infection by Parvizi et al. and the EBJIS definition of PJI are reliable clinical guidelines for most affected patients, the criteria listed may not be feasible for all patients [14,15]. In particular, diagnosis of both acute and chronic PJI is complicated in patients with rheumatoid arthritis where aseptic joint inflammation causes similar clinical and laboratory presentation. Qin et al. recently demonstrated that commonly used laboratory markers of non-operated rheumatoid arthritis patients do not differ significantly to those of patients with chronic PJI [19]. Patients with active rheumatoid arthritis of the operated joint are always scored to be likely affected by PJI. There is a paucity of data on differentiating PJI from rheumatoid arthritis in patients with previous knee or hip arthroplasty. While PJI cannot be ruled out with current diagnostic standards, a more detailed understanding of the relevant serum and synovial marker levels is necessary to personalize diagnostics and avoid unnecessary surgical intervention.

In this study, we retrospectively analyzed the cases of 17 patients with rheumatoid arthritis and 121 patients with no diagnosed rheumatoid disease who underwent surgical intervention due to microbiology-positive PJI of the hip or knee joint. This is the first study to evaluate differences in serum and synovial fluid markers in patients affected by this pathology.

2. Materials and Methods

2.1. Patients

This study was approved by the Charité University hospital ethics board (EA2/083/19) and was completed in accordance with the Declaration of Helsinki.

All patients receiving total knee or hip replacement exchange surgery due to acute or chronic PJI between 2013 and 2021 at the Charité university hospital in Berlin, Germany were retrospectively analyzed in this study. Patients were treated in a specialized department using a centralized and interdisciplinary treatment approach. In total, we analyzed patient files of 138 patients.

Inclusion criteria were a previously implanted knee or hip replacement and diagnosed PJI. As rheumatoid arthritis and PJI share clinical and paraclinical features, PJI was defined according to modified EBJIS criteria [20]: microbiological growth in synovial fluid, two or more tissue samples (for highly virulent organisms or in patients being treated with antibiotics, one positive sample confirmed infection), or sonication fluid (>50 CFU/mL) and at least one of the following criteria: (1) prevalence of a sinus tract or purulence around a component; (2) >2000 leukocytes/µL or >70% granulocytes in the synovial fluid; or (3) histology of intra-operatively acquired tissue Krenn and Morawietz type II or type III [21]. Acute PJI was defined as an infection within 4 weeks after primary arthroplasty surgery or acute onset of PJI-related symptoms less than 4 weeks before diagnosis and treatment of PJI. Symptom onset >4 weeks was classified as chronic PJI.

Rheumatoid arthritis was diagnosed prior to occurrence of PJI by a board-certified rheumatologist according to the ACR/EULAR Classification Criteria [22]. All patients were actively treated by a rheumatologist.

Patients who met one or more of the following criteria were excluded from this study: (1) culture-negative patients meeting EBJIS criteria for PJI; or (2) primary knee or hip joint infection without prosthesis. There were no further exclusions.

The enrolled patient population was divided into two groups based on whether patients diagnosed with rheumatoid disease (group A) or not (group B). Both groups

were subdivided into acute and chronic cases: A1, acute cases with immune disorders; A2, chronic cases with immune disorders; B1, acute cases without immune disorders; B2, chronic cases without immune disorders.

Besides clinical and paraclinical examination, we assessed demographic data including age, BMI, ASA score, the number of prior surgeries on the affected knee or hip, pathological classification of tissue specimens, and laboratory results.

2.2. Statistical Analysis

All data were collected and recorded in Microsoft® Excel® 2016 (version 2111 Build 16.0.14701.20240, Microsoft, Redmond, WA USA). Continuous data were presented as median and IQR and analyzed using Student's t test or Mann–Whitney U test where applicable. Data between two groups were compared using chi-square test. Optimal cut-off values were determined using the Youden index (J) method (maximal value of "sensitivity + specificity-1") [23]. Based on cut-offs, sensitivity and specificity were defined and NPV, PPV, ROC, and AUC determined. Survival analysis was presented through Kaplan–Meier survival curves. All statistical analyses and plots were analyzed using R software (version: 3.6.3. R Development Core Team, Vienna, Austria).

3. Results

3.1. Patient Characteristics

Patient characteristics are outlined in Table 1. In total, 138 patients were enrolled in this study: 17 patients with rheumatoid arthritis and PJI (group A) and 121 patients without rheumatoid arthritis and PJI (group B). Of the patients included in our analysis, 76 were male (group A: 12; group B: 64) and 62 were female (group A: 5; group B: 57). Average patient age was 72.94 ± 7.10 years in group A and 69.07 ± 10.83. Mean BMI was 29.83 ± 6.97 for group A and 30.59 ± 5.82 for group B. Most patients had an ASA score of 2 (17.65% group A; 56.20% group B) or 3 (70.59% group A; 36.36% group B). Acute PJI occurred in 9 (52.94%; group A) and 54 (44.63%; group B) patients, and chronic PJI in 8 (47.06%; group A) and 67 (55.37%; group B) patients. Most patients had more than one revision surgery prior to PJI (70.59% in group A; 61.98% in group B). No significant differences for any of the analyzed parameters were found.

Table 1. Patient Characteristics.

	Group A (Rheumatoid Arthritis Patients)	Group B (without Rheumatoid Arthritis Patients)	*p* Value
Sex			
Male [# (%)]	12 (70.59%)	64 (52.89%)	0.17
Female [# (%)]	5 (29.41%)	57 (47.11%)	
BMI [kg/m^2]	29.83 ± 6.97	30.59 ± 5.82	0.69
Age [years]	72.94 ± 7.10	69.07 ± 10.83	0.06
PJI onset			
Acute [# (%)]	9 (52.94%)	54 (44.63%)	0.52
Chronic [# (%)]	8 (47.06%)	67 (55.37%)	
ASA score			
1 [# (%)]	0 (0.00%)	2 (1.65%)	0.06
2 [# (%)]	3 (17.65%)	68 (56.20%)	
3 [# (%)]	12 (70.59%)	44 (36.36%)	
4 [# (%)]	1 (5.88%)	4 (3.31%)	
5 [# (%)]	0 (0.00%)	1 (0.83%)	
Number of prior revision surgeries			
One [# (%)]	5 (29.41%)	46 (38.02%)	0.49
More than one [# (%)]	12 (70.59%)	75 (61.98%)	

#, number of patients.

3.2. Pathology and Microbiology

Pathology results indicated an infection (Krenn and Morawietz score of 2 or 3) in 88.24% of the patients with rheumatoid arthritis (group A) and in 77.69% of the patients without rheumatoid arthritis (group B; $p = 0.32$). Of these, 66.67% (group A) and 55.32% (group B) had a low-grade infection and 33.33% (group A) and 44.68% (group B) had a high-grade infection ($p = 0.41$). The remaining patients had a Krenn and Morawietz score of 1 or 4: 11.76% in group A and 22.31% in group B. In none of the patients analyzed was a sinus tract prevalent.

For all patients, synovial fluid samples were analyzed for pathogens (Table 2). In both groups, *Staphylococcus aureus* (47.06% in group A, 33.06% in group B) followed by *Staphylococcus epidermidis* (35.29% in group A, 19.83% in group B) had the highest incidence rate.

Table 2. Pre- and perioperative pathogens.

Pathogen	Group A (Rheumatoid Arthritis Patients)	Group B (without Rheumatoid Arthritis Patients)
Staphylococcus aureus	8 (47.06%)	40 (33.06%)
Staphylococcus epidermidis	6 (35.29%)	24 (19.83%)
Cutibacterium acnes	-	12 (9.91%)
Enterococcus faecalis	1 (5.88%)	10 (8.26%)
Streptococcus anginosus	1 (5.88%)	2 (1.65%)
Streptococcus dysgalactiae	1 (5.88%)	8 (6.61%)
Escherichia coli	-	7 (5.79%)
Staphylococcus hominis	-	8 (6.61%)
Candida albicans	-	1 (0.83%)
Candida parapsilosis	-	2 (1.65%)
Cutibacterium avidum	-	1 (0.83%)
Staphylococcus capitis	-	2 (1.65%)
Streptococcus agalactiae	-	1 (0.83%)
Streptococcus mitis	-	1 (0.83%)
Streptococcus pyogenes	-	1 (0.83%)
Streptococcus pneumoniae	-	1 (0.83%)

3.3. Laboratory

Peripheral blood CRP concentration and WBC numbers as well as synovial fluid cell counts were analyzed for all patients. For acute PJI, no significant difference between patients with (group A1) and without rheumatoid arthritis (group B1) were found (Table 3): Median CRP was 88.00 and 129.45 mg/L ($p = 0.92$), WBC count 9.13 and 9.93 cells/nL ($p = 0.30$), synovial WBC 60.75 and 48.92 cells/nL ($p = 0.54$), and synovial PMN cell count 55.89 and 48.24 cells/nL ($p = 0.74$), respectively. All parameters analyzed showed high variability.

In patients with chronic PJI, peripheral blood CRP (group A2: 43.25 versus B2: 18.80 mg/L; $p = 0.05$), synovial WBC count (group A2: 34.68 versus B2: 8.33 cells/nL; $p = 0.02$), synovial monocyte cell count (group A2: 2.27 versus B2: 0.79 cells/nL; $p = 0.04$), and synovial PMN cell count (group A2: 33.36 versus B2: 6.13 cells/nL; $p = 0.02$) were significantly elevated in patients with rheumatoid arthritis (Table 3). In contrast, peripheral blood WBC count did not differ significantly (group A2: 6.86 versus B2: 7.45 cells/nL; $p = 0.75$).

ROC analysis was conducted for the analyzed parameters: AUC, best cut-off values, sensitivity, specificity, and NPV and PPV are listed in Table 4. All analyzed parameters showed poor discrimination for patients with acute PJI. Conversely, in patients with chronic PJI serum CRP levels (AUC = 0.71), synovial WBC count (AUC = 0.78), synovial monocyte cell count (AUC = 0.75), and synovial percentage of PMN cell count (AUC = 0.71) showed acceptable discrimination and synovial PMN cell count (AUC = 0.80) showed excellent discrimination (Figure 1). While for any of these parameters, sensitivity and NPV was

above 75% and 95%, respectively, specificity and PPV only ranged from 55% to 74% and 18% to 26%, respectively.

Table 3. Laboratory results before prosthesis explantation.

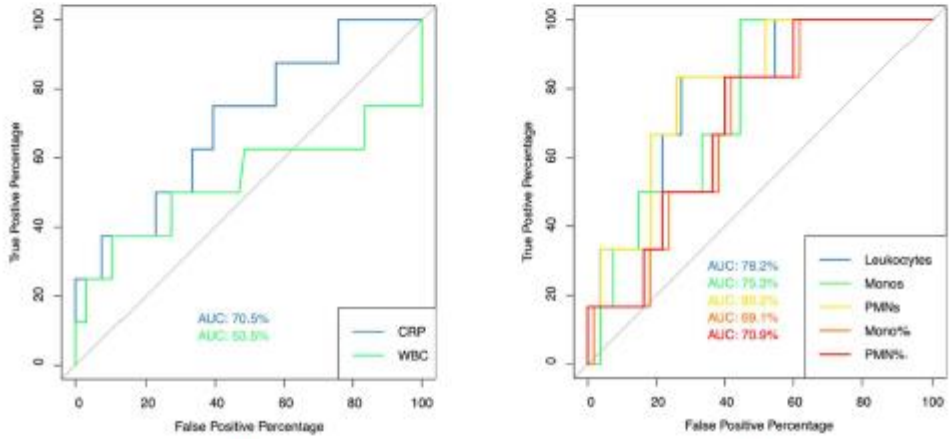
	Group A1 (Rheumatoid Arthritis Patients; *n* = 9)		Group B1 (without Rheumatoid Arthritis Patients; *n* = 54)			
	Median	**IQR**	**Median**	**IQR**	**W**	***p* Value**
Acute PJI						
Serum CRP [mg/L]	88.00	86.90–256.20	129.45	72.03–244.22	237	0.92
Peripheral blood WBC count [cells/nL]	9.13	6.17–12.03	9.93	7.22–14.22	190	0.30
Synovial WBC count [cells/nL]	60.75	54.72–118.06	48.92	33.58–197.56	178	0.54
Synovial monocyte cell count [cells/nL]	6.69	2.21–11.43	3.97	2.05–13.85	136	0.93
Synovial PMN cell count [cells/nL]	55.89	48.41–86.94	48.24	31.30–160.93	144	0.74
Synovial percentage of monocytes [%]	0.11	0.04–0.12	0.09	0.05–0.16	120	0.69
Synovial percentage of PMN cells [%]	0.89	0.88–0.96	0.91	0.84–0.95	149	0.62
	Group A2 (Rheumatoid Arthritis Patients; *n* = 8)		**Group B2 (without Rheumatoid Arthritis Patients; *n* = 67)**			
	Median	**IQR**	**Median**	**IQR**	**W**	***p* Value**
Chronic PJI						
Serum CRP [mg/L]	43.25	25.02–145.00	18.80	6.45–47.15	372	0.05
Peripheral blood WBC count [cells/nL]	6.86	5.16–10.81	7.45	6.25–8.39	245	0.75
Synovial WBC count [cells/nL]	34.68	23.06–103.17	8.33	0.86–23.37	258	0.02
Synovial monocyte cell count [cells/nL]	2.27	1.16–13.5	0.79	0.33–2.28	244	0.04
Synovial PMN cell count [cells/nL]	33.36	20.48–70.75	6.13	0.43–16.68	260	0.02
Synovial percentage of monocytes [%]	0.10	0.05–0.15	0.23	0.08–0.43	102	0.13
Synovial percentage of PMN cells [%]	0.90	0.85–0.95	0.77	0.55–0.91	234	0.09

Table 4. Diagnostic value analysis.

	Cut-Off	**Sensitivity**	**Specificity**	**NPV**	**PPV**	**AUC**	**AUC CI**
Acute PJI							
Serum CRP [mg/L]	107.65	33.30%	38.90%	77.80%	8.30%	0.51	0.31–0.70
Peripheral Blood WBC count [cells/nL]	13.36	16.80%	63.00%	79.10%	8.40%	0.61	0.43–0.78
Synovial WBC count [cells/nL]	43.18	100%	35.90%	100%	24.20%	0.57	0.41–0.73
Synovial monocyte cell count [cells/nL]	2.06	100%	26.30%	100%	20.00%	0.51	0.30–0.71
Synovial PMN cell count [cells/nL]	37.79	100%	31.60%	100%	21.20%	0.54	0.37–0.70
Synovial percentage of monocytes [%]	10.07	57.10%	63.20%	88.90%	22.20%	0.45	0.20–0.69
Synovial percentage of PMN cells [%]	0.90	100%	9.30%	100%	15.60%	0.44	0.20–0.69

Table 4. *Cont.*

	Cut-Off	Sensitivity	Specificity	NPV	PPV	AUC	AUC CI
Chronic PJI							
Serum CRP [mg/L]	29.05	75.00%	60.60%	95.20%	18.80%	0.71	0.50–0.90
Peripheral Blood WBC count [cells/nL]	5.495	62.50%	10.60%	70.00%	7.80%	0.54	0.23–0.83
Synovial WBC count [cells/nL]	19.48	83.30%	72.70%	97.60%	25.00%	0.78	0.61–0.95
Synovial monocyte cell count [cells/nL]	0.83	100%	55.60%	100%	20.00%	0.75	0.58–0.92
Synovial PMN cell count [cells/nL]	16.18	83.30%	74.10%	97.60%	26.30%	0.80	0.63–0.96
Synovial percentage of monocytes [%]	14.70	16.70%	41.80%	82.10%	3.00%	0.69	0.50–0.87
Synovial percentage of PMN cells [%]	85.30	83.30%	73.00%	97.10%	18.50%	0.71	0.52–0.90



(a) (b)

Figure 1. AUC Analysis. (**a**) AUC analysis for serum CRP (blue line) and peripheral blood WBC count (green line) in patients with chronic PJI; (**b**) AUC analysis for synovial fluid WBC count (blue line), monocyte cell count (green line), PMN cell count (yellow line), synovial percentage of monocytes (orange line), and percentage of PMN cell count (red line).

3.4. Prosthesis Survival

Risk for prosthesis failure due to recurrent PJI or aseptic loosening (Figure 2) was significantly elevated in patients with rheumatoid arthritis (prosthesis survival rate in group A: 78.07% versus group B: 52.94%; $p = 0.03$). Additionally, median prosthesis survival times were significantly shorter in group A (median: 1 year, IQR: 1.00–3.00 years) compared to group B (median: 2 years, IQR: 1.75–4.00 years; $p = 0.05$).

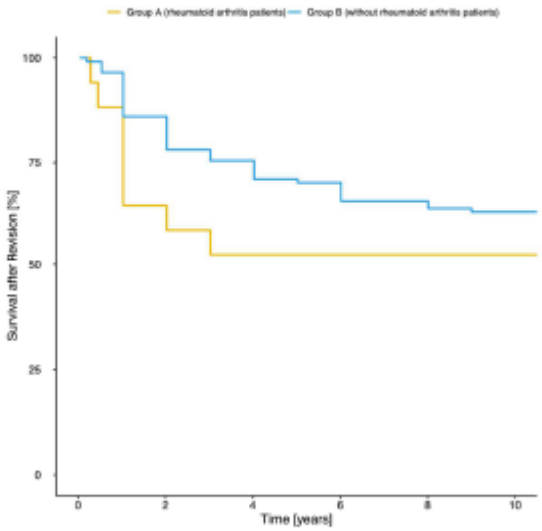


Figure 2. Prosthesis survival rate. Diagnosed recurrent PJI or aseptic loosening was classified as prosthesis failure. After 9 years, 47.06% of patients with rheumatoid arthritis (blue line) and 21.93% of patients without rheumatoid arthritis (yellow line) had suffered from prosthesis failure.

4. Discussion

In this study, we analyzed differences in clinical patient characteristics, laboratory parameters, and prosthesis survival rates in patients with and without rheumatoid arthritis and acute or chronic PJI. Additionally, we retrospectively evaluated the capability of laboratory markers to distinguish these patient groups. Long-term revision arthroplasty failure rate was significantly elevated in patients with rheumatoid arthritis and PJI compared to patients without autoimmune disease.

In both acute and chronic PJI, attending physicians are challenged to accurately confirm diagnosis in patients that are presenting with clinical features of PJI. Similar clinical and laboratory features of aseptic joint inflammation in patients with rheumatoid arthritis and arthroplasty significantly complicate the diagnosis of PJI. All patients with symptoms of active autoimmune arthritis after primary arthroplasty are classified as PJI-likely cases [14,15]. Inherently, investigations are limited to positive cases as PJI-negative cases in patients with active rheumatoid arthritis do not exist per definition. Commonly, diagnosis relies upon peripheral blood WBC count and serum CRP, as well as synovial WBC count and PMN cell percentage [13–15]. Establishing the diagnosis is challenging as guidelines were derived from PJI patients without rheumatoid arthritis [24]. Previous research reported the risk of infection in patients with rheumatoid arthritis to be significantly increased [7,25], potentially due to anti-rheumatic immunosuppressive therapy [26]. However, Trikha et al. found rheumatoid arthritis not to be an independent risk-factor for PJI in a murine model [27], suggesting PJI may be falsely diagnosed in some patients. Thus, in our study, only culture-positive patients were included to avoid analysis of false-positive cases.

To initiate treatment and avoid short- and long-term complications such as sepsis, recurrent PJI or aseptic loosening, a diagnosis is often needed in a short time frame. While microbiological culture is essential, it is not feasible in an acute setting due to culture time [16] and may be negative despite the presence of PJI [17,18]. In our study, we did not find good discriminatory power for peripheral blood WBC counts, serum CRP, synovial WBC count, synovial PNM cell count, synovial percentage of PNM cells, or synovial percentage of monocytes in acute PJI. While discriminatory power for these parameters

was good to excellent in chronic PJI, specificity and PPV were only between 55% and 74% and 18% and 26%, respectively. Novel diagnostic serum and synovial markers such as alpha-defensin, soluble tumor necrosis factor receptor, and B-cell activating factor, as well as technologies such as next-generation sequencing, promise to improve current standards [18,28,29] and could especially benefit rheumatoid arthritis patients.

Due to the immediate severe impact on patients' life quality and to avoid unnecessary surgery, particular consideration must be given to false-positive diagnoses [30,31]. Rheumatoid arthritis patients are especially at risk as improvement of quality of life has been found to be poorer compared to patients with osteoarthritis after primary total joint replacement [32]. In our study, we found prosthesis failure rates after revision arthroplasty to be significantly elevated in patients with rheumatoid arthritis, further stressing the need for a more personalized diagnostic and therapeutic approach in these patients. Similarly, prosthesis survival rates after revision arthroplasty have been found to be significantly decreased in non-rheumatoid arthritis patients [11,12,33].

Limitations of the current study include the heterogeneity of the analyzed population, the retrospective study design, the analyzed rheumatoid arthritis cohort size, and the exclusion of potentially PJI-positive but culture-negative cases with potential subsequent statistical bias.

In conclusion, the current guidelines and routinely used laboratory markers have limited utility in distinguishing acute PJI in rheumatoid patients. In cases with suspected chronic PJI but low levels of serum CRP and synovial cell markers, physicians should consider the possibility of activated autoimmune arthritis. The observed elevated prosthesis failure rate in these patients stresses the need for novel diagnostic markers and a more personalized diagnostic and therapeutic approach for affected patients.

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Abbreviations

American Society of Anesthesiologists, ASA; area under curve, AUC; body mass index, BMI; C-reaction protein, CRP; interquartile range, IQR; negative predictive values, NPV; periprosthetic joint infection, PJI; polymorphonuclear, PMN; positive predictive values, PPV; receiver operating curve, ROC; white blood cell, WBC.

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Curriculum Vitae

My curriculum vitae does not appear in the electronic version of my paper for reasons of data protection.

Publication list

1: **Ren Y**, Biedermann L, Gwinner C, Perka C, Kienzle A. Serum and Synovial Markers in Patients with Rheumatoid Arthritis and Periprosthetic Joint Infection. *J Pers Med*. 2022; 12(5): 810. IF: 3.508

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