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# The Ideal Diagnostic Thresholds for Diagnosing Periprosthetic Joint Infection in Patients with Rheumatoid Arthritis: A Multicenter Study

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## Abstract

**Background**: While patients with rheumatoid arthritis (RA) are known to be at an increased risk of periprosthetic joint infection (PJI), it remains unclear if the optimal threshold for the Musculoskeletal Infection Society (MSIS) minor criteria differs in patients with RA. The purpose of this study was to determine which of the MSIS minor criteria is best in patients with RA and to determine optimal thresholds for the MSIS minor criteria in this patient population.

**Methods**: A retrospective review of 842 patients from 2004 to 2016 was conducted and included 58 RA and 784 non-RA patients. The diagnosis of PJI was based on the revised MSIS criteria. Receiver operating characteristic (ROC) curves were used to evaluate erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and synovial fluid white blood cell (WBC) count and polymorphonuclear neutrophil percentage (PMN%) for diagnosing a PJI with Youden J statistics to determine optimal thresholds.

**Results**: In the RA group, the synovial fluid WBC count area under the curve (AUC) was 94% with a cutoff of 4600 cells/μL, while in the non-RA group, the AUC was 96% with an optimal cutoff of 3100 cells/μL (p=0.49). The threshold value for synovial fluid PMN% was 80% with an AUC of 94% in RA patients and 87% with an AUC of 94% in non-RA patients (p=0.31). The threshold ESR value was 58 mm/hr with an AUC of 84% in RA patients and 52 mm/hr with an AUC of 85% in non-RA patients (p=0.83). The threshold value for CRP was 27 mg/L with an AUC of 77% in RA patients and 21 mg/L with an AUC of 86% in non-RA patients (p=0.31). However, none of the differences in threshold values were statistically significant.

**Conclusion**: While the MSIS minor criteria have standard defined thresholds for the diagnosis of a PJI, not all minor criteria are equivalent and the ideal thresholds for some of the minor criteria may vary based on underlying patient medical comorbidities. In this cohort, synovial fluid WBC count was the best diagnostic test for the diagnosis of a PJI in patients with RA.

**Keywords**: Total Joint Arthroplasty, Periprosthetic Joint Infection, Musculoskeletal Infection Society, Rheumatoid Arthritis

## Introduction

Periprosthetic joint infection (PJI) following a total joint arthroplasty (TJA) is an uncommon but challenging and debilitating complication [1]. PJI can also be difficult to diagnose and treat [2]. Before 2011, there were no generally accepted criteria for the diagnosis of PJI. However, the Musculoskeletal Infection Society (MSIS) assembled a group of experts that ultimately published what was later recognized to be the standard set of criteria used to aide in the diagnosis of PJI [2,3]. These criteria were released in 2011 and updated at the International Consensus Meeting (ICM) in 2013 [3,4]. The MSIS definition of PJI includes two major criteria and six minor criteria; the presence of at least

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one major criterion or four minor criteria is diagnostic of a PJI [3]. The MSIS also put forth recommended threshold values for laboratory tests such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and the synovial fluid white blood cell (WBC) count and polymorphonuclear neutrophil percentage (PMN%). The American Academy of Orthopaedic Surgeons later proposed an algorithmic approach to using the MSIS criteria to accurately diagnose PJI [3]. At the ICM in 2018, an update to the defining criteria for PJI was proposed based on the continued work of Parvizi and colleagues but this definition reached a weak consensus and has not been implemented by the MSIS [5-7].

While the MSIS-recommended thresholds for ESR, CRP, and synovial fluid WBC count and PMN% have been previously validated in a general population [3], there remains a limited understanding if these thresholds are appropriate for patient populations with specific comorbidities, such as rheumatoid arthritis (RA) [8-11]. RA is an autoimmune, chronic inflammatory disease that causes joint destruction and disability with varying degrees of severity [12]. Approximately 1.5 million people in the United States have RA, and 25% of patients with RA are estimated to undergo total joint arthroplasty at some point in their life [13,14]. Patients with RA are known to have an increased risk of PJI and death when compared to patients without RA (i.e. patients with non-inflammatory osteoarthritis) [13,15]. One purported reason for the increased incidence of PJI is the use of immunosuppressive therapies that forms part of the treatment regimen for RA [13]. As many of the diagnostic tests included in the MSIS criteria rely upon a normal immune response, it would not be surprising if these tests performed differently among RA patients compared to controls.

Patients with RA present with atypical features that may impact the reliability of certain screening tools and threshold values used in diagnosing PJI [16,17]. As it remains uncertain if the optimal threshold for the MSIS minor criteria differ in patients with RA compared to a normal patient population, the purpose of this multicenter study was to determine the optimal thresholds for the MSIS minor criteria specifically in patients with RA.

## Methods

After institutional review board approval, a multicenter single institution retrospective review of 1026 patients in our total joint registry who underwent total knee or hip arthroplasty with subsequent suspected PJI from 2004 to 2016 was conducted. Demographic information, history of RA, and surgical procedure were recorded for each patient (Table 1). The diagnosis of PJI was based on the revised MSIS criteria [3]. ESR, CRP, and synovial fluid WBC count and PMN% were also collected. Patients missing any of these diagnostic values in their workup were excluded.

### Statistical analysis

Descriptive statistics for variables among both study groups were calculated. Differences between continuous variables were evaluated using a 2-sample, 2-tailed, Mann–Whitney U test. Differences between categorical variables were evaluated using a $\chi^2$ (Chi-square) analysis or a Fisher's exact test to account for small sample bias. Receiver operating characteristic (ROC) curves were used to evaluate the MSIS minor criteria, including ESR, CRP, and synovial fluid WBC count and PMN% for diagnosing PJI. The area under the curve (AUC), representing accuracy of the diagnostic test, was utilized as the main performance measure. Youden J statistics were used to determine optimal thresholds by maximizing sensitivity and specificity [18]. All data were analyzed using JMP software (version 14.0.0, SAS Institute Inc, Cary, NC, 1989-2007).

**Table 1. Demographics of rheumatoid arthritis (RA) and non-RA cohorts.**

| | RA Group | Non-RA Group |
|---|---|---|
| Total Patients | 58 | 784 |
| Female | 45 (77.6%) | 454 (57.9%) |
| Male | 13 (22.4%) | 330 (42.1%) |
| Median Age (Range) (y) | 62 (39-85) | 68 (30-95) |
| Mean Age (y) | 63.3 | 66.8 |
| Hip Arthroplasty | 37 (63.8%) | 442 (56.4%) |
| Knee Arthroplasty | 21 (36.2%) | 342 (43.6%) |

## Results

Of the 1042 patients, 184 were excluded for an incomplete workup, leaving 842 patients for final analysis. Fifty-eight (7%) patients had the diagnosis of RA while 784 (93%) were in the non-RA group. In the RA group, 18 (31%) patients had a positive PJI workup, while 242 (31%) patients in the non-RA group had a positive PJI workup. The mean age at presentation in the RA group was 63 (range 39-85) years old and the mean age in the non-RA group was 67 (range 30-95) years old. Forty-five (78%) of the RA patients were female, while 454 (58%) of the non-RA patients were female. Thirty-seven (64%) of the RA patients had a total hip arthroplasty (THA), and 442 (56%) of the non-RA patients had a THA (Table 1).

Based on the AUCs, the synovial fluid WBC count demonstrated greater diagnostic accuracy for PJI in both the RA cohort and non-RA cohort (Figures 1A and 1B; Table 2). In the RA cohort, the synovial fluid WBC count AUC was 94% with a cutoff of 4600 cells/μL. With this cutoff, 90% of PJIs were correctly diagnosed. In the non-RA cohort, the synovial fluid WBC count AUC was 96% with an optimal cutoff of 3100 cells/μL. With this cutoff, 94% of PJIs in the non-RA cohort were correctly identified. While the cutoff was higher for the synovial fluid WBC count in the RA cohort, the AUCs were not statistically different (p=0.49). The ideal threshold value for synovial fluid PMN% was 80% with an AUC of 94% in RA patients and 87% with an AUC of 94% in non-RA patients (p=0.31). The ideal threshold ESR value was 58 mm/hr with

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**Table 2. RA group vs. non-RA group Minor Criteria Comparison.**

| | RA Group | | | Non-RA Group | | | |
|---|---|---|---|---|---|---|---|
| | AUC (%) | Best cut-off value | % Correctly Identified Above Cutoff (TP+FN) | AUC (%) | Best cut-off value | % Correctly Identified Above Cutoff (TP+FN) | P-value |
| Synovial Cell Count | 94 | 4600 cells/μL | 90 | 96 | 3100 cells/μL | 94 | 0.49 |
| Neutrophil percentage | 94 | 80% | 88 | 94 | 87% | 90 | 0.31 |
| ESR | 84 | 58 mm/hr | 81 | 85 | 52 mm/hr | 83 | 0.83 |
| CRP | 77 | 27 mg/L | 75 | 86 | 21 mg/L | 87 | 0.31 |

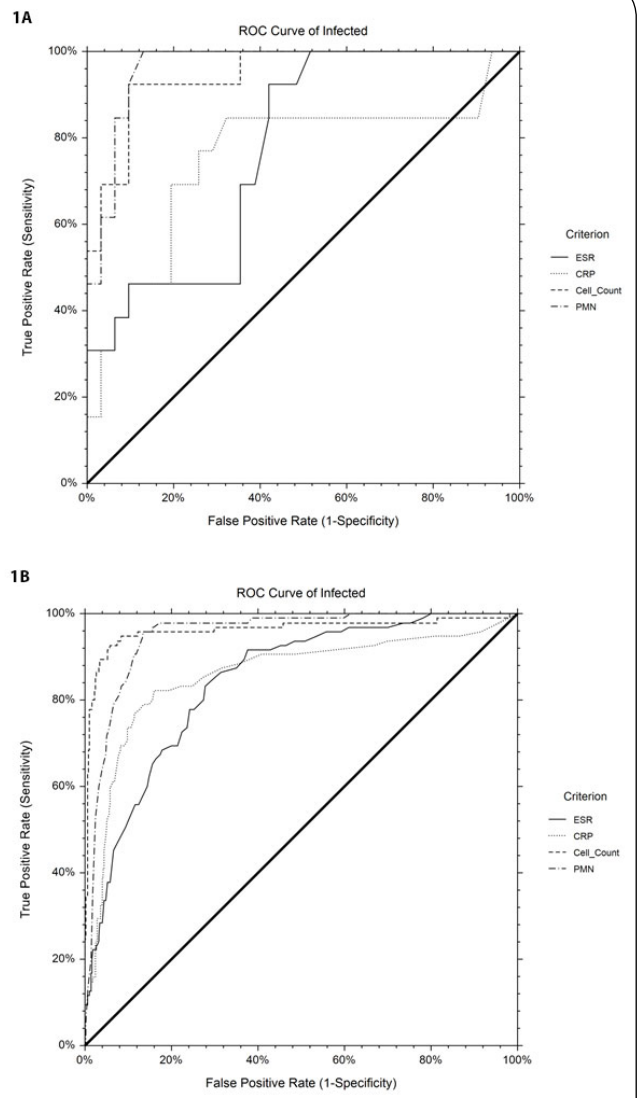


**Figure 1**. Receiver operating characteristic (ROC) curves. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), synovial fluid white blood cell (WBC) count, and synovial fluid polymorphonuclear neutrophil (PMN) percentage for (**A**) RA and (**B**) Non-RA groups.

an AUC of 84% in RA patients and 52 mm/hr with an AUC of 85% in non-RA patients (p=0.83). The threshold value for CRP was 27 mg/L with an AUC of 77% in RA patients and 21 mg/L with an AUC of 86% in non-RA patients (p=0.31). Similar to the synovial fluid WBC count, none of the additional tests demonstrated a statistical difference in thresholds between the RA and non-RA cohorts (**Table 2**).

## Discussion

In this study, synovial fluid WBC count demonstrated to be the best test for determining a PJI diagnosis in patients both with and without RA. However, differences in ROC curves between the two groups were not significantly different for synovial fluid WBC count (p=0.49), synovial fluid PMN% (p=0.31), ESR (p=0.83), or CRP (p=0.31). The findings in the present study corroborate previous research that has suggested synovial fluid WBC counts and PMN% may be the most accurate diagnostic tests in assessing PJI in patients with and without inflammatory arthritis [**11**,**19**]. It is encouraging that the other MSIS minor criteria tested in this study, including ESR and CRP, also seemed to be accurate predictors of PJI in RA patients. However, accuracy can be improved by adjusting the MSIS minor criteria thresholds for RA patients. As determined in this study by the ROC curves (**Figures 1A** and **1B**), the ideal MSIS minor criteria cutoff values for patients in the RA group were a synovial fluid WBC count of 4600 cells/μL, a synovial fluid PMN% of 80%, an ESR of 58 mm/hr, and a CRP of 27 mg/L. While the AUCs did not differ significantly between the RA and non-RA cohorts, there was a trend of higher ideal cutoff values for all minor criteria, except for synovial fluid PMN%, in the RA cohort compared to the non-RA cohort (**Table 2**).

Testing for PJI includes both non-invasive screening with ESR and CRP, and if appropriate, aspiration of synovial fluid [19]. If used correctly, the MSIS criteria are excellent for identifying a PJI. However, the MSIS criteria does not adequately account for unique groups of patients with complicated underlying immunologic comorbidities. For example, patients with RA often present with atypical symptoms due to their condition and polypharmacy. Additionally, immunosuppressive agents may have a substantial effect on generalized MSIS minor criteria lab values [**17**]. The present study provides evidence that when performing PJI diagnostic workups in RA patients, it may be beneficial to adjust the minor MSIS criteria thresholds. Based on our results, the best cutoff values for RA patients for synovial fluid WBC count, ESR and CRP should be higher

than the current MSIS minor criteria threshold values, while the best cutoff value for synovial fluid PMN% should remain equal to the current threshold value.

Successful treatment of patients with RA and PJI depends first on the proper diagnosis. Ensuring the generalizability of MSIS criteria, while adjusting for patient populations with common diseases that could affect the criteria thresholds is essential to improve outcomes for all patients. Despite RA patients having higher complication rates after surgery [17], patients with RA who develop a PJI have similar outcomes to patients without RA when properly identified and treated [20]. Thus, a more thorough understanding of the appropriate cutoff values for PJI diagnosis is important for patients with RA for prompt and effective treatment.

Previous studies have concluded that synovial fluid WBC counts, ESR, and CRP values provide excellent utility in diagnosing PJI in patients without RA but failed to comment on their use in RA patients [14,21]. RA patients suffer from chronic inflammation due to the overproduction of cytokines, such as tumor necrosis factor (TNF)-alpha. This causes an elevation in inflammatory markers, such as ESR and CRP, that are also used to screen for and diagnose PJI [13]. Patients with RA that are chronically immunosuppressed may also have an altered response to a PJI [13]. The use of inaccurate cutoff values could potentially result in unnecessary surgical treatments from overdiagnosis or undiagnosed PJIs. It has become essential to evaluate currently proposed cutoff values for patients with underlying medical conditions, specifically patients with RA, because of the presence of chronic inflammation, immunosuppression, and disease modifying antirheumatic drug use.

Despite the strong relationship that lab values have with diagnosing PJI in RA and non-RA patients, it is important to interpret them with caution. An in-depth clinical history of the patient must be considered in order to make a well-informed decision regarding the diagnosis and treatment of PJI. Additionally, there are other medical comorbidities which may require alterations in the MSIS PJI-defining minor criteria thresholds. Other autoimmune diseases (i.e., psoriasis or ankylosing spondylitis) cause chronic inflammation resulting in elevated markers of inflammation at baseline [22,23]. Furthermore, severe obesity, chronic stress, and substance abuse may create a state of inflammation which could alter the interpretation of the MSIS minor criteria thresholds [24].

This study is not without limitations. Although a cohort of more than 800 patients was included, a limited sample size could limit our results. Additionally, not all patients in our study had a complete laboratory or synovial fluid workup. Thus, data for the MSIS minor criteria remained uncaptured in some patients, resulting in their exclusion from the study. This could have altered the final analysis. However, the number of patients excluded was relatively small and we believe unlikely to have significantly altered the conclusions. Finally, this data was collected from multiple laboratories and thus could potentially lead to minor differences in data collection, processing, or measurement of patient blood and synovial fluid samples. These differences were also small and unlikely to have substantially affected the findings in this study.

## Conclusion

In this retrospective study, the synovial fluid WBC count was the best test for detecting a PJI in patients both with and without RA, while ESR, CRP, and synovial fluid PMN% demonstrated good clinical predictive value in diagnosing PJI in these cohorts. No significant differences in the AUCs were observed between the RA and non-RA cohorts for each of the MSIS minor criteria; however, some ideal thresholds did vary. Additional research in this area is warranted to validate our results and confirm which laboratory testing thresholds are most appropriate for patients with RA.

### Competing interests

The authors declare that they have no competing interests.

### Authors' contributions

| Authors' contributions | JMI | JRP | MLM | AP | CP | JSB |
|---|---|---|---|---|---|---|
| Research concept and design | √ | √ | √ | √ | √ | √ |
| Collection and/or assembly of data | √ | √ | √ | √ | √ | √ |
| Data analysis and interpretation | √ | √ | √ | √ | √ | √ |
| Writing the article | √ | √ | √ | √ | √ | √ |
| Critical revision of the article | √ | √ | √ | √ | √ | √ |
| Final approval of article | √ | √ | √ | √ | √ | √ |
| Statistical analysis | √ | √ | √ | √ | √ | √ |

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