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INFECTION

Diagnosis of periprosthetic joint infections in patients who have rheumatoid arthritis

APPLICATION OF ROUTINE SEROLOGICAL AND SYNOVIAL FLUID INDEXES

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Aims

To investigate the optimal thresholds and diagnostic efficacy of commonly used serological and synovial fluid detection indexes for diagnosing periprosthetic joint infection (PJI) in patients who have rheumatoid arthritis (RA).

Methods

The data from 348 patients who had RA or osteoarthritis (OA) and had previously undergone a total knee (TKA) and/or a total hip arthroplasty (THA) (including RA-PJI: 60 cases, RA-non-PJI: 80 cases; OA-PJI: 104 cases, OA-non-PJI: 104 cases) were retrospectively analyzed. A receiver operating characteristic curve was used to determine the optimal thresholds of the CRP, ESR, synovial fluid white blood cell count (WBC), and polymorphonuclear neutrophil percentage (PMN%) for diagnosing RA-PJI and OA-PJI. The diagnostic efficacy was evaluated by comparing the area under the curve (AUC) of each index and applying the results of the combined index diagnostic test.

Results

For PJI prediction, the results of serological and synovial fluid indexes were different between the RA-PJI and OA-PJI groups. The optimal cutoff value of CRP for diagnosing RA-PJI was 12.5 mg/l, ESR was 39 mm/hour, synovial fluid WBC was 3,654/μl, and PMN% was 65.9%; and those of OA-PJI were 8.2 mg/l, 31 mm/hour, 2,673/μl, and 62.0%, respectively. In the RA-PJI group, the specificity (94.4%), positive predictive value (97.1%), and AUC (0.916) of synovial fluid WBC were higher than those of the other indexes. The optimal cutoff values of synovial fluid WBC and PMN% for diagnosing RA-PJI after THA were significantly higher than those of TKA. The specificity and positive predictive value of the combined index were 100%.

Conclusion

Serum inflammatory and synovial fluid indexes can be used for diagnosing RA-PJI, for which synovial fluid WBC is the best detection index. Combining multiple detection indexes can provide a reference basis for the early and accurate diagnosis of RA-PJI.

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Keywords: Periprosthetic joint infection, Rheumatoid arthritis, Serology, Synovial fluid, Diagnosis

Article focus

- Guidelines for the diagnosis of periprosthetic joint infection (PJI) issued by the Musculoskeletal Infection Society (MSIS) defined the diagnostic thresholds of serological and synovial fluid detection indexes commonly used in the clinic. However, it is clear that patients with rheumatoid diseases were not included in the research work of formulating the guidelines.
- We aimed to investigate the optimal thresholds and diagnostic efficacy of commonly used serological and synovial

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fluid detection indexes for diagnosing PJI in patients who have rheumatoid arthritis (RA).

Key messages

- The optimum cutoff values of CRP level, ESR, synovial fluid white blood cell count (WBC), and polymorphonuclear neutrophil percentage (PMN%) for the diagnosis of PJI in patients with RA are all higher than those of patients with osteoarthritis, and their optimal cutoff values can be used as important auxiliary indexes for a clear diagnosis of PJI in patients with RA.
- Compared with other indexes, the synovial fluid WBC has strong predicting power and lower misdiagnosis rate, which could be the best detection index for identifying whether the RA patients have PJI.
- The combined index diagnostic test can improve the specificity and positive predictive value of PJI diagnosis in patients with RA. Combining multiple detection indexes can provide a reference basis for the early and accurate diagnosis of RA-PJI.

Strengths and limitations

- There are currently neither gold-standard nor relevant diagnostic guidelines for PJI diagnosis in RA patients for reference in clinical practice, and there are few relevant studies at home and abroad. However, CRP, ESR, synovial fluid WBC, and PMN% are classical indexes for diagnosing PJI, which are economical and convenient to operate, so it is of great clinical importance to establish the thresholds of these common detection indexes for PJI diagnosis in patients who have RA.
- It was a single-centre retrospective study with a limited sample size and selection bias, and the conclusions need to be further verified by multicentre and large samples.

Introduction

Periprosthetic joint infection (PJI) is one of the most serious complications after total joint replacement (TJR), with an overall incidence of 1% to 2%.[1] TJR can alleviate pain symptoms and improve joint function and quality of life in patients who have advanced rheumatoid arthritis (RA).[2,3] However, due to the immune dysfunction in RA patients and their use of disease-modifying antirheumatic drugs (DMARDs),[4,5] the infection rate after TJR in patients who have RA can be three-times higher than that in patients who have osteoarthritis (OA), with infection rates of 4.2% and 1.4%,[6] respectively. Indeed, RA is considered to be an independent risk factor for PJI.[7]

Guidelines for the diagnosis of PJI issued by the Musculoskeletal Infection Society (MSIS) define the diagnostic thresholds of serum CRP, ESR, synovial fluid white blood cell count (WBC), and polymorphonuclear neutrophil percentage (PMN%).[1] However, it is clear that patients who have rheumatoid diseases were not included in the research work of formulating the guidelines. Especially when RA disease is in active stage, the above inflammatory indexes will be in an abnormal state regardless of infection, due to the inflammatory response of RA patients themselves. Therefore, the application of the conventional PJI diagnostic threshold for patients who have RA can lead to misdiagnosis, leading to incorrect treatment.[8] The current focus of research on the diagnosis of PJI includes markers such as alpha-defensin.[9-11] However, CRP, ESR, synovial fluid WBC, and PMN% are classical indexes for diagnosing PJI, which are economical and convenient to operate, so it is of great clinical importance to establish the thresholds of these common detection indexes for PJI diagnosis in patients who have RA.

We retrospectively analyzed the clinical data of serum inflammation and synovial fluid indexes in patients who have RA and OA who had undergone a total knee (TKA) and/or a total hip arthroplasty (THA). The purpose of this study was to determine the optimal thresholds and diagnostic efficacy of preoperative CRP, ESR, synovial fluid WBC, and PMN% in the diagnosis of postoperative PJI in patients who have RA, and to investigate whether the combined testing of serology and synovial fluid indexes can improve the diagnostic efficacy.

Methods

Study design and inclusion criteria. After obtaining approval from the Institutional Review Board, a total of 442 patients who were admitted to the hospital from 1 January 2006 to 31 December 2021 were retrospectively analyzed. The inclusion criteria included patients who had a definite preoperative diagnosis of RA or OA and had previously undergone a primary TKA or THA. It should be noted that all the infected patients included in our study were chronic PJI cases. Additional inclusion criteria for non-infected patients with RA and OA included a follow-up period of at least one year after a primary TKA or THA, and no occurrence of PJI. Patients were excluded if they had a combination of other inflammatory arthritis diseases, such as pigmented villonodular synovitis, combined malignant neoplasms, combined other local or systemic infections, such as articular tuberculosis, and combined fractures on admission.

Of the 442 cases, two with incomplete medical records, 78 with acute PJI (< 90 days), seven with a malignant neoplasm history, and seven with knee or hip tuberculosis were excluded; the other 348 cases were included in this study. The patients were divided into groups according to the type of disease and whether chronic PJI occurred postoperatively: PJI occurred (RA-PJI: 60 cases; OA-PJI: 104 cases); and no PJI occurred (RA-non-PJI: 80 cases; OA-non-PJI: 104 cases).

The diagnosis of RA-PJI must either meet one of the following two criteria: 1) there is a sinus tract communicating with the prosthesis and 2) a pathogen is isolated by culture from at least two separate tissue or fluid samples obtained from the affected prosthetic joint; or meet two of the following three criteria: 1) presence of purulence in the affected joint, 2) isolation of a microorganism in one culture of periprosthetic tissue or fluid,

Table I. Comparison of general clinical data between infected and noninfected groups in patients with rheumatoid arthritis.

Variable	RA-PJI (n = 60)	RA-non-PJI (n = 80)	Statistical value	
Sex (female/male), n	40/20	68/12	$\chi^2 = 6.535$	p = 0.011*
Median age, yrs (IQR)	66 (57 to 72)	62 (52 to 71)	$Z = -1.508$	p = 0.131†
Joint (knee/hip), n	40/20	56/24	$\chi2 = 0.177$	p = 0.674*
Median BMI, kg/m² (IQR)	23 (20 to 28)	25 (22 to 28)	$Z = -1.467$	p = 0.142†
ASA grade, n (%)			$\chi2 = 5.919$	p = 0.015*
I	0	0		
II	35 (58.33)	62 (77.50)		
III	25 (41.67)	18 (22.50)		
IV	0	0		
V	0	0		
Sinus tract, n (%)	19 (31.67)	N/A	N/A	N/A
Positive for microbiological culture, n (%)	44 (73.33)	N/A	N/A	N/A
Self-prophylactic use of antibiotics before admission, n (%)	22 (36.67)	N/A	N/A	N/A
Use of DMARDs, n (%)	14 (23.33)	13 (16.25)	$\chi2 = 1.105$	p = 0.293*

*Chi-squared test.
†Mann-Whitney U test.
ASA, American Society of Anesthesiologists; DMARDs, disease-modifying anti-rheumatic drugs; IQR, interquartile range; N/A, not applicable; PJI, periprosthetic joint infection; RA, rheumatoid arthritis.

and 3) positive result from pathological examination of periprosthetic tissues. The diagnosis of OA-PJI was based on the MSIS criteria.[1]

Follow-up routine. Patients were followed up at one month, three months, six months, and one year after a primary TKA or THA. After that, they were followed up annually in the outpatient service.

Patients were tested for serum CRP and ESR at the time of follow-up, and if the results were abnormal, patients were evaluated on a case-by-case basis. If the patient had clinical signs of suspected infection, such as joint warmth, redness or swelling, pain, or tenderness, a further arthrocentesis was performed at the outpatient medical office to aspirate synovial fluid and send it for microbiological culture, and white blood cell count/differential. If the synovial fluid results were abnormal, the patient was recommended to be hospitalized for further examination and treatment. The final diagnosis of RA-PJI was based on a combination of preoperative and intraoperative markers comprising synovial fluid cell count/differential, serum markers, microbiological cultures, clinical signs, and tissue pathology.

For patients with abnormal CRP and ESR levels, synovial fluid was aspirated by repeated arthrocentesis for testing. If the results of synovial fluid indexes were normal, the microbiological culture was negative, and in the absence of other reliable evidence of infection, PJI could be provisionally excluded; however, whether RA was active should be evaluated simultaneously. Such patients were judged to be at a lower probability for PJI, but to prevent misdiagnosis leading to serious consequences, they required re-evaluation once a month for three consecutive months. Of course, for some low-virulence bacteria, the patient's synovial fluid WBC and PMN% and CRP may be normal, so we also needed to wait for the results of microbiological cultures, because microbiological culture is also a key element in the diagnosis of PJI,[12] and if the culture results were negative and there was no other reliable evidence of infection, only then could we exclude such patients.

Index detection. Blood collection and arthrocentesis were performed preoperatively or before the use of antibiotics. For the detection of serological indexes, the level of CRP was detected by immune turbidimetry. The normal reference value of CRP is < 8 mg/l. The level of ESR was detected by the Westergren method. The normal reference value of ESR is < 15 mm/hour for males and < 20 mm/hour for females.

For the detection of synovial fluid indexes, knee arthrocentesis was performed preoperatively at the joint line areas of the knee joint under aseptic conditions. When the synovial fluid in the hip joint was detected by ultrasound, a positioning guide probe was used to guide joint aspiration under aseptic conditions. The extracted synovial fluid was transported to the laboratory for testing within one hour. If the results could not be detected by the instruments, then manual counting was performed by using a Neubauer-improved counting chamber. Based on the MSIS criteria, a synovial fluid WBC of greater than 3,000 per µl and a PMN% of greater than 80% were considered to be elevated levels. It should be noted that not all patients performed the synovial fluid tests due to reasons such as an insufficient amount of synovial fluid.

Statistical analysis. The measurement data that did not conform to a normal distribution were analyzed by the Mann-Whitney U test, and categorical data were analyzed by the chi-squared test. Receiver operating characteristic (ROC) curves of CRP, ESR, synovial fluid WBC, and PMN% were established, and the optimal cutoff value was determined by the Youden index. The area under the curve (AUC) was calculated, the AUCs were compared using the DeLong test, and the diagnostic value of each

Table II. Comparison of general clinical data between infected and noninfected groups in patients who have osteoarthritis.

Variable	OA-PJI (n = 104)	OA-non-PJI (n = 104)	Statistical value	
Sex (female/male, n)	58/46	68/36	χ^2 = 2.013	p = 0.156*
Median age, yrs (IQR)	67 (58 to 74)	67 (56 to 74)	*Z* = -0.323	p = 0.747†
Joint (knee/hip, n)	56/48	67/37	χ2 = 2.407	p = 0.121*
Median BMI, kg/m^2 (IQR)	25 (22 to 28)	26 (23 to 29)	*Z* = -1.432	p = 0.152†
ASA grade, n (%)			χ2 = 2.484	p = 0.289*
I	0	0		
II	58 (55.77)	69 (66.35)		
III	45 (43.27)	34 (32.69)		
IV	1 (0.96)	1 (0.96)		
V	0	0		
Sinus tract, n (%)	36 (34.62)	N/A	N/A	N/A
Positive for microbiological culture, n (%)	79 (75.96)	N/A	N/A	N/A
Self-prophylactic use of antibiotics before admission, n (%)	32 (30.77)	N/A	N/A	N/A

*Chi-squared test.
†Mann-Whitney U test.
ASA, American Society of Anesthesiologists; IQR, interquartile range; N/A, not applicable; OA, osteoarthritis; PJI, periprosthetic joint infection.

Table III. Glucocorticoid use in patients who have rheumatoid arthritis.

		History of long-term GC use within 2 yrs of preoperative period		History of long-term GC use but discontinued for > 2 yrs		No history of preoperative GC use; only IV supplemental GC use given perioperatively	No GC use
Group	Cases, n	Perioperative IV GC supplementation	No GC supplementation	Perioperative IV GC supplementation	No GC supplementation		
RA-PJI, n (%)	60	6 (10.00)	2 (3.33)	3 (5.00)	11 (18.33)	22 (36.67)	16 (26.67)
RA-non-PJI, n (%)	80	4 (5.00)	6 (7.50)	5 (6.25)	3 (3.75)	16 (20.00)	46 (57.50)
Statistical value	N/A	χ^2 = 0.648	χ^2 = 0.467	χ^2 = 0.000	χ^2 = 6.563	χ^2 = 4.816	χ^2 = 13.211
	N/A	p = 0.421*	p = 0.494*	p = 1.000*	p = 0.010*	p = 0.028*	p < 0.001*

*Chi-squared test.
GC, glucocorticoid; IV, intravenous; N/A, not applicable; PJI, periprosthetic joint infection; RA, rheumatoid arthritis.

index was evaluated according to the Swets criteria.[13] The diagnostic efficacy was evaluated by the sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio. The four detection indexes were combined and analyzed by binary logistic regression analyses, a ROC curve was established with the prediction probability 'p' as the combined index, and the combined index diagnostic test was performed to analyze its application value. Statistical analyses were performed using SPSS software (Version 21.0; IBM, USA) with statistical significance set at p < 0.05.

Results

General clinical characteristics of patients. In this study, there were more females than males in patients who had RA; this difference between groups was statistically significant (p = 0.011, chi-squared test). Moreover, there was a significant difference between the RA-PJI group and the RA-non-PJI group in terms of American Society of Anesthesiologists (ASA)[14] grade (p = 0.015, chi-squared test). However, there was no significant difference in the use of DMARDs between the two groups (p = 0.293, chi-squared test) (Table I). For patients with OA, there was no significant difference in sex, age, BMI, ASA grade, or the distribution of knee and hip cases between the OA-PJI group and the OA-non-PJI group (sex, p = 0.156, chi-squared test; age, p = 0.747, Mann-Whitney U test; BMI, p = 0.152, Mann-Whitney U test; ASA grade, p = 0.289, chi-squared test; joint, p = 0.121, chi-squared test) (Table II).

Our statistical analysis also showed that there were 19 patients (31.67%) with sinus tract in the RA-PJI group and 36 patients (34.62%) in the OA-PJI group. Overall, 44 patients (73.33%) in the RA-PJI group and 79 patients (75.96%) in the OA-PJI group showed positive microbiological culture results. In addition, there were 22 patients (36.67%) in the RA-PJI group and 32 patients (30.77%) in the OA-PJI group who took antibiotics self-prophylactically before admission.

We also investigated the use of glucocorticoids in patients who have RA. In particular, we noticed that the proportion of patients without any glucocorticoid use in the RA-non-PJI group was significantly higher than that in the RA-PJI group (p < 0.001, chi-squared test). For the

Table IV. Comparison of serum and synovial fluid detection indexes between the RA-PJI and RA-non-PJI groups.

Group	Median CRP, mg/l (IQR)	Median ESR, mm/hr (IQR)	Median synovial fluid WBC/μl (IQR)	Median PMN% (IQR)
RA-PJI	22.50 (14.83 to 48.58)	54.00 (40.50 to 64.75)	7,506 (3,936 to 14,971)	85.00 (73.90 to 95.00)
RA-non-PJI	11.40 (4.96 to 22.20)	38.00 (28.00 to 52.00)	448 (226 to 2,161)	58.00 (34.50 to 69.35)
Statistical value	*Z* = -5.202	*Z* = -4.237	*Z* = -5.054	*Z* = -4.326
	p < 0.001*	p < 0.001*	p < 0.001*	p < 0.001*

Note: The sample size for CRP and ESR in the RA-PJI group was 60 cases, and that for synovial fluid WBC and PMN% was 41 cases; the sample size for CRP and ESR in the RA-non-PJI group was 80 cases, and that for synovial fluid WBC and PMN% was 18 cases.
*Mann-Whitney U test.
IQR, interquartile range; PJI, periprosthetic joint infection; PMN%, polymorphonuclear neutrophil percentage; RA, rheumatoid arthritis; WBC, white blood cell count.

Table V. Comparison of serum and synovial fluid detection indexes between the OA-PJI and OA-non-PJI groups.

Group	Median CRP, mg/l (IQR)	Median ESR, mm/hr (IQR)	Median synovial fluid, WBC/μl (IQR)	Median PMN% (IQR)
OA-PJI	20.40 (10.28 to 31.73)	50.00 (34.00 to 60.00)	9,769 (4,850 to 20,446)	90.00 (79.50 to 95.00)
OA-non-PJI	3.64 (2.12 to 5.07)	16.50 (10.00 to 20.00)	671 (331 to 1,483)	29.00 (21.10 to 44.90)
Statistical value	*Z* = -10.915	*Z* = -10.692	*Z* = -8.944	*Z* = -8.981
	p† < 0.001	p† < 0.001	p† < 0.001	p† < 0.001

Note: The sample size for CRP and ESR in the OA-PJI group was 104 cases, and that for synovial fluid WBC and PMN% was 69 cases; the sample size for CRP and ESR in the OA-non-PJI group was 104 cases, and that for synovial fluid WBC and PMN% was 56 cases.
† Mann-Whitney U test.
IQR, interquartile range; OA, osteoarthritis; PJI, periprosthetic joint infection.

proportion of patients who had no history of preoperative glucocorticoid use, and only used intravenous glucocorticoid supplementation in the perioperative period, the RA-PJI group was significantly higher than the RA-non-PJI group (p = 0.028, chi-squared test). However, for patients with a history of long-term glucocorticoid use within two years of the preoperative period, the proportion of patients who were given intravenous glucocorticoid supplementation in the perioperative period did not differ significantly between the two groups (p = 0.421, chi-squared test) (Table III).

Serum and synovial fluid indexes in patients with PJI. It should be noted that a correlation analysis could not be performed due to the insufficient amount of synovial fluid in some patients. The sample size of synovial fluid in each group was as follows: RA-PJI: 41 cases; RA-non-PJI: 18 cases; OA-PJI: 69 cases; OA-non-PJI: 56 cases.

The mean levels of CRP, ESR, synovial fluid WBC, and PMN% in the RA-PJI group were higher than those in the RA-non-PJI group (CRP, ESR, WBC, PMN%; p < 0.001, Mann-Whitney U test) (Table IV). Similarly, the mean levels of the above indexes in the OA-PJI group were higher than those in the OA-non-PJI group (CRP, ESR, WBC, PMN%; p < 0.001, Mann-Whitney U test) (Table V).

Diagnostic efficacy of serum and synovial fluid indexes for postoperative PJI in patients who have RA. According to the ROC curve analysis, the optimal cutoff value of CRP for diagnosing RA-PJI was 12.5 mg/l, ESR was 39 mm/hour, synovial fluid WBC was 3,654 μl, and PMN% was 65.9% (Figures 1 and 2); and those of OA-PJI were 8.2 mg/l, 31 mm/hour, 2,673/μl, and 62.0% (Figures 3 and 4), respectively.

According to the Swets criteria, the AUC of CRP, ESR, and PMN% in the RA-PJI group was between 0.7 and 0.9, and the diagnostic value was moderate, while the AUC of synovial fluid WBC was between 0.9 and 1, and the diagnostic value was higher. The AUC of each index in the OA-PJI group was between 0.9 and 1, and the diagnostic value was higher. The AUCs of synovial fluid WBC (0.916, 95% CI 0.848 to 0.984; p < 0.001, DeLong test) in the RA-PJI group and PMN% (0.968, 95% CI 0.937 to 0.998; p < 0.001, DeLong test) in the OA-PJI group were the largest, respectively, yielding higher diagnostic accuracy compared with other indexes.

In addition, the sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio of all indexes were different in patients who have RA-PJI and OA-PJI when evaluating diagnostic efficacy (Table VI).

Diagnostic efficacy of serum and synovial fluid indexes for PJI after TKA and THA in patients who have RA. ROC curve analyses were performed for serum and synovial fluid indexes in patients who have PJI after TKA and THA, respectively. The optimal cutoff value of CRP for diagnosing RA-PJI after TKA was 12.5 mg/l, ESR was 47 mm/hour, synovial fluid WBC was 3,661/μl, and PMN% was 66.6%; those of OA-PJI were 8.8 mg/l, 33 mm/hour, 2,520/μl, and 57.5%, respectively. According to the Swets criteria, the AUC of each index in the RA-PJI group was between 0.7 and 0.9, and the diagnostic value was moderate; the

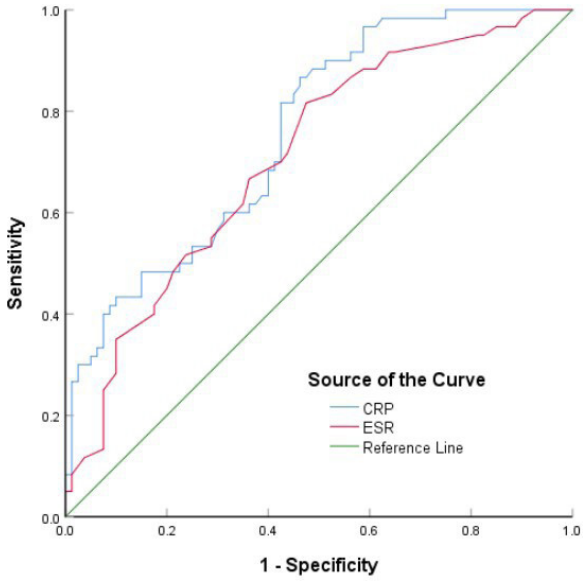

Fig. 1

Receiver operating characteristic curves of CRP and ESR in the diagnosis of periprosthetic joint infection in patients with rheumatoid arthritis.

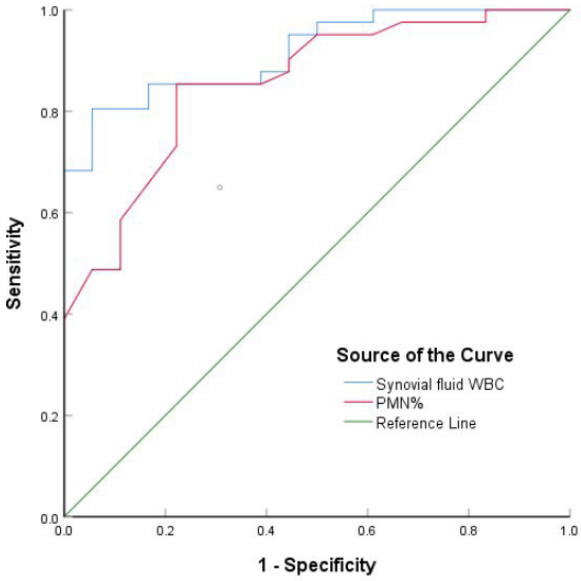

Fig. 2

Receiver operating characteristic curves of synovial fluid white blood cell count (WBC) and polymorphonuclear neutrophil percentage (PMN%) in the diagnosis of periprosthetic joint infection in patients with rheumatoid arthritis.

OA-PJI group was between 0.9 and 1, and the diagnostic value was higher. The AUCs of synovial fluid WBC (0.893, 95% CI 0.803 to 0.983; p < 0.001, DeLong test) in the RA-PJI group and PMN% (0.979, 95% CI 0.954 to 1.000; p < 0.001, DeLong test) in the OA-PJI group were the largest, respectively, yielding higher diagnostic accuracy compared with other indexes.

The optimal cutoff value of CRP for diagnosing RA-PJI after THA was 9.5 mg/l, ESR was 35 mm/hour, synovial fluid WBC was 5,208/μl, and PMN% was 76.8%; and those of OA-PJI were 8.2 mg/l, 23 mm/hour, 2,696/μl, and 66.4%, respectively. According to the Swets criteria, the AUC of CRP and ESR in the RA-PJI group were between 0.7 and 0.9, and the diagnostic value was moderate, while the AUC of synovial fluid WBC and PMN% were between 0.9 and 1, and the diagnostic value was higher; the AUC of each index in the OA-PJI group was between 0.9 and 1, and the diagnostic value was higher. The AUCs of synovial fluid WBC (0.940, 95% CI 0.838 to 1.000; p = 0.002, DeLong test) in the RA-PJI group and PMN% (0.987, 95% CI 0.959 to 1.000; p < 0.001, DeLong test) in the OA-PJI group were the largest, respectively, yielding higher diagnostic accuracy compared with other indexes.

In addition, the sensitivity, specificity, positive predictive value, and negative predictive value of all indexes were different when evaluating diagnostic efficacy in patients who have RA-PJI or OA-PJI after TKA and THA (Table VII).

Application of the combined serum and synovial fluid indexes in the diagnosis of postoperative PJI in patients who have RA. Combined with the four detection indexes of CRP, ESR, synovial fluid WBC, and PMN%, and after binary logistic regression analyses of the above four detection indexes, a ROC curve was established with the prediction probability 'p' as the combined index. The sensitivity of the combined index for diagnosing RA-PJI was 80.5%, the specificity was 100%, the positive predictive value was 100%, the negative predictive value was 69.2%, and the AUC was 0.944 (95% CI 0.892 to 0.997; p < 0.001, DeLong test) (Figure 5). The diagnostic value of the combined index was higher according to the Swets criteria.

We compared the AUC of the combined index with the AUCs of other detection indexes (CRP, ESR, synovial fluid WBC, PMN%). In the RA-PJI group, there was no significant difference between the AUC of synovial fluid WBC and the AUC of the combined index (p = 0.239, DeLong test), but there was a significant statistical difference between the AUCs of CRP, ESR, and PMN% and the AUC of the combined index (CRP: p = 0.004, ESR: p < 0.001, PMN%: p = 0.035; DeLong test). In the OA-PJI group, there was a significant statistical difference between the AUCs of CRP, ESR, synovial fluid WBC, and PMN%, and the AUC of the combined index (CRP: p = 0.002, ESR: p < 0.001, synovial fluid WBC: p = 0.035, PMN%: p = 0.035; DeLong test).

Discussion

Pre-existing rheumatoid disease in patients places them at greater risk of PJI, and makes diagnosis more difficult because the increase in serum inflammation and synovial fluid indexes may reflect the underlying rheumatoid disease, rather than PJI.[15] Therefore, to date, there is no gold standard for diagnosing RA-PJI.[16] However, if the preoperative diagnostic process does not provide sufficient information for a definite diagnosis, it can affect treatment decisions.[17–20] Many studies have confirmed the limited diagnostic efficiency of CRP, ESR, synovial

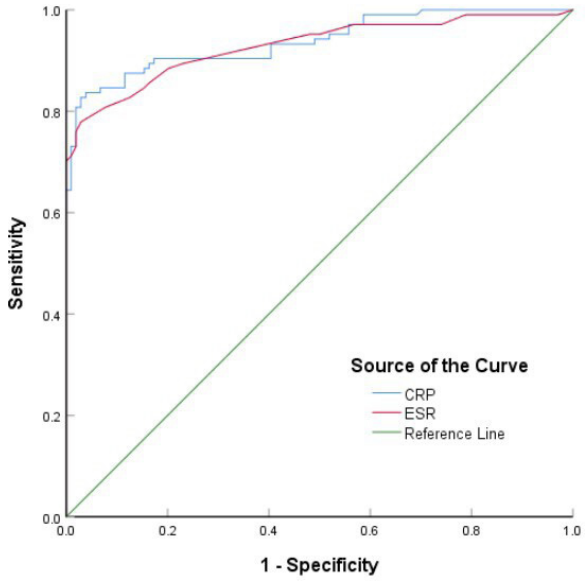

Fig. 3

Receiver operating characteristic curves of CRP and ESR in the diagnosis of periprosthetic joint infection in patients with osteoarthritis.

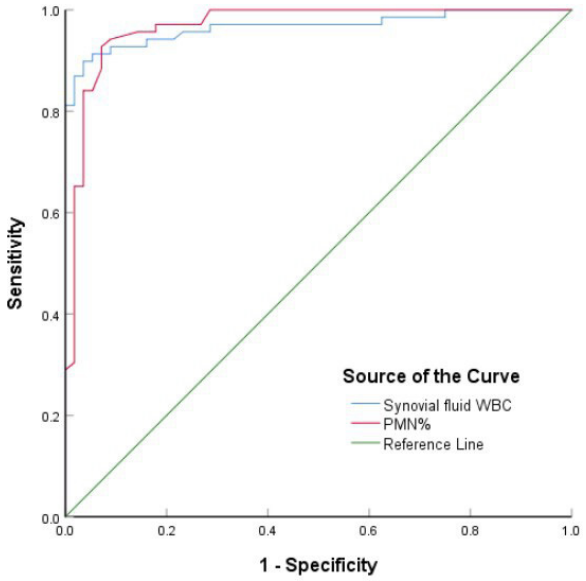

Fig. 4

Receiver operating characteristic curves of synovial fluid white blood cell count (WBC) and polymorphonuclear neutrophil percentage (PMN%) in the diagnosis of periprosthetic joint infection in patients with osteoarthritis.

fluid WBC, or PMN% alone; additionally, because the above indexes are usually not specific for diagnosing RA-PJI, previous studies have not typically analyzed their diagnostic value in this context.[21]

Currently, CRP and ESR are common detection indexes assisting in the diagnosis of PJI in a clinical setting. The results of this study showed that the optimal cutoff values of CRP and ESR for diagnosing RA-PJI were higher than those of OA-PJI, and higher than the diagnostic criteria recommended by MSIS (CRP ≥ 10 mg/l, ESR ≥ 30 mm/hour). We believe that the elevated diagnostic thresholds of CRP and ESR in RA patients are due to the increase in basal levels caused by underlying rheumatoid diseases. A study by Shimada et al,[22] on the correlation between joint involvement and CRP and ESR in 10,720 patients with RA, showed that the more types and greater number of joints involved in RA, the higher the overall level of CRP and ESR.

A study by Cipriano et al[21] reported that the optimal cutoff values and diagnostic values of CRP and ESR for diagnosing inflammatory arthritis PJI were not significantly different from those for noninflammatory arthritis. The reason their results differed from ours is that theirs was a prospective study with a large sample size, and their cases contained not only RA but also other inflammatory arthritis, such as ankylosing spondylitis. However, both their study and ours share the common characteristics of high sensitivity and negative predictive value but low specificity and positive predictive value, which is also in line with the characteristics of CRP and ESR for diagnosing PJI.[23] Through our study, we believe that since baseline levels of CRP and ESR are elevated in patients who have RA, the threshold baseline level for diagnosing RA-PJI should also be raised. Moreover, setting different cutoff values for diagnosing PJI in RA and OA patients would improve the diagnostic value.

Although serum CRP and ESR determinations are currently important detection methods for the diagnosis of suspected PJI in RA patients, these markers are controversial when used alone in a state of combined inflammation; furthermore, their diagnostic efficiency is low, and elevated basal levels may increase the possibility of false positives.[24–26] The American Academy of Orthopaedic Surgeons (AAOS) guidelines for diagnosing PJI recommend that when PJI is suspected, arthrocentesis should be performed to aspirate synovial fluid, and then send it for testing and culture of pathogenic microorganisms.[27] There is aseptic inflammation in RA, which yields a false increase in synovial fluid WBC and PMN%.[28,29] However, synovial fluid is the internal environment in direct contact with the prosthesis, and researchers are paying more attention to whether changes in synovial fluid can better diagnose PJI.[30–33]

The cutoff values with the highest sensitivity and specificity for synovial fluid WBC and differential will facilitate the accurate diagnosis of infection after TJR in RA patients. A study by Ren et al[8] reported that in patients with chronic PJI, the optimal cutoff values of synovial fluid WBC and PMN% were significantly elevated in RA patients, showing acceptable-to-excellent discrimination. The results of this study showed that the optimal cutoff values of synovial fluid WBC and PMN% for diagnosing RA-PJI were higher than those of OA-PJI. The optimal cutoff value of synovial fluid WBC was also higher than the 3,000/μl recommended by MSIS criteria, while the PMN% was lower than the 80% in the diagnostic criteria. We believe that the elevated diagnostic threshold of synovial fluid WBC

Table VI. Efficacy analysis of CRP, ESR, synovial fluid white blood cell count, and polymorphonuclear neutrophil percentage in the diagnosis of RA-PJI and OA-PJI.

Detection index	Group	Optimal cutoff values	Sensitivity, %	Specificity, %	PPV, %	NPV, %	PLR	NLR	AUC (95% CI)	p-value‡ for AUC	Comparison with AUC of the combined index	
											Z value	p-value*
CRP	RA-PJI	12.5 mg/l	86.7	53.7	58.4	84.3	1.87	0.25	0.757 (0.680 to 0.835)	< 0.001	2.868	0.004
CRP	OA-PJI	8.2 mg/l	83.7	96.2	95.6	85.5	22.03	0.17	0.938 (0.905 to 0.971)	< 0.001	3.157	0.002
ESR	RA-PJI	39 mm/hr	81.7	52.5	56.3	79.2	1.72	0.35	0.709 (0.624 to 0.795)	< 0.001	3.726	< 0.001
ESR	OA-PJI	31 mm/hr	77.9	97.1	96.4	81.5	26.86	0.23	0.929 (0.892 to 0.965)	< 0.001	3.666	< 0.001
Synovial fluid WBC	RA-PJI	3,654/μl	80.5	94.4	97.1	68.0	14.38	0.21	0.916 (0.848 to 0.984)	< 0.001	1.177	0.239
Synovial fluid WBC	OA-PJI	2,673/μl	89.9	96.4	96.9	88.5	24.97	0.10	0.966 (0.935 to 0.997)	< 0.001	2.106	0.035
PMN%	RA-PJI	65.9%	85.4	77.8	89.7	70.0	3.85	0.19	0.855 (0.754 to 0.956)	< 0.001	2.111	0.035
PMN%	OA-PJI	62.0%	92.8	92.9	94.1	91.2	13.07	0.08	0.968 (0.937 to 0.998)	< 0.001	2.104	0.035
Combined index	RA-PJI	N/A	80.5	100.0	100.0	69.2	N/A	0.20	0.944 (0.892 to 0.997)	< 0.001	N/A	N/A
Combined index	OA-PJI	N/A	97.1	98.2	98.5	96.5	53.94	0.03	0.996 (0.989 to 1.000)	< 0.001	N/A	N/A

*DeLong test.
AUC, area under the curve; CI, confidence interval; N/A, not applicable; NLR, negative likelihood ratio; NPV, negative predictive value; OA, osteoarthritis; PJI, periprosthetic joint infection; PLR, positive likelihood ratio; PMN%, polymorphonuclear neutrophil percentage; PPV, positive predictive value; RA, rheumatoid arthritis; WBC, white blood cell count.

for diagnosing RA-PJI is caused by increased basal levels of rheumatoid diseases and persistent synovitis after TJR. For PMN% lower than 80%, we considered the following possible reasons: 1) the sample size of the study was small; 2) the synovial fluid was viscous or turbid in some patients, and it was detected after diluting with a diluent ratio; 3) some patients took antibiotics self-prophylactically before admission; 4) the coagulation of synovial fluid may have a greater impact on cell classification in the process of detection; and 5) some studies have shown that in the presence of corrosion reactions at the metal interface of the prosthesis, it will have an impact on the synovial fluid WBC and PMN%.[34,35] However, the reasons listed above are all speculative, rather than definitive; because this is a retrospective study and it spans a long period of time, some of the possible reasons mentioned above cannot be identified. We performed a subgroup analysis by excluding 22 RA-PJI patients and 32 OA-PJI patients who took antibiotics self-prophylactically before admission. The results showed that the optimal cutoff value of PMN% for diagnosing RA-PJI was 65.9%, the sensitivity was 90.9%, the specificity was 77.8%, and the AUC was 0.861 (95% CI 0.745 to 0.978; $p < 0.001$); the optimal cutoff value of PMN% for diagnosing OA-PJI was 57.5%, the sensitivity was 95.9%, the specificity was 91.1%, and the AUC was 0.970 (95% CI 0.939 to 1.000; $p < 0.001$). We found that the optimal cutoff values for PMN% diagnosis of RA-PJI and OA-PJI were still lower than 80% after excluding patients with PJI who took antibiotics self-prophylactically before admission, and we consider that the main reason for this is the small sample size of the study.

In our study, we found that the diagnostic specificity (94.4%), AUC (0.916, 95% CI 0.848 to 0.984), positive predictive value (97.1%), and positive likelihood ratio (14.38) of synovial fluid WBC were all the highest among the parameters studied. Compared with other indexes in the auxiliary diagnosis of RA-PJI, synovial fluid WBC has a strong predictive ability and a low misdiagnosis rate, and it is the best detection index for identifying whether RA patients have PJI preoperatively. Therefore, we recommend that as long as RA patients have highly suspicious symptoms of infection after TJR, regardless of their CRP and ESR levels, arthrocentesis is recommended for further diagnosis, which will help to detect infection as soon as possible and treat it in time. However, arthrocentesis also has some limitations: for example, sometimes it may not be possible to obtain synovial fluid from the patient's articular cavity. In addition, the detection of bloody synovial fluid cannot clearly distinguish between white blood cells and synovial fluid white blood cells,[36] which will affect the final analysis results. It also suggests that arthrocentesis should be performed repeatedly for comparison at different times preoperatively.

Although the commonly used international guidelines and consensuses have proposed reference thresholds for serum and synovial fluid indexes that are helpful for the diagnosis of PJI, there are currently no precise diagnostic reference thresholds for TKA or THA postoperative infections. In our study, according to the different types of

Table VII. Efficacy analysis of CRP, ESR, synovial fluid white blood cell count, and polymorphonuclear neutrophil percentage in the diagnosis of RA-PJI and OA-PJI after total knee arthroplasty and total hip arthroplasty.

Detection index	Group	Optimal cutoff values	Sensitivity, %	Specificity, %	PPV, %	NPV, %	PLR	NLR	AUC (95% CI)	p-value for AUC*
Knee										
CRP	RA-PJI	12.5 mg/l	92.5	51.8	57.8	90.6	1.92	0.14	0.764 (0.671 to 0.857)	< 0.001
CRP	OA-PJI	8.8 mg/l	85.7	98.5	98.0	89.2	57.13	0.15	0.947 (0.905 to 0.990)	< 0.001
ESR	RA-PJI	47 mm/hr	75.0	62.5	58.8	77.8	2.00	0.40	0.726 (0.625 to 0.827)	< 0.001
ESR	OA-PJI	33 mm/hr	83.9	98.5	97.9	88.0	55.93	0.16	0.941 (0.893 to 0.988)	< 0.001
Synovial fluid WBC	RA-PJI	3,661/μl	81.3	92.9	92.9	83.3	11.45	0.20	0.893 (0.803 to 0.983)	< 0.001
Synovial fluid WBC	OA-PJI	2,520/μl	91.1	97.5	97.6	90.7	36.44	0.09	0.974 (0.940 to 1.000)	< 0.001
PMN%	RA-PJI	66.6%	84.4	78.6	79.4	83.3	3.94	0.20	0.873 (0.769 to 0.977)	< 0.001
PMN%	OA-PJI	57.5%	93.3	95.0	95.5	92.7	18.66	0.07	0.979 (0.954 to 1.000)	< 0.001
Hip										
CRP	RA-PJI	9.5 mg/l	95.0	50.0	61.3	92.3	1.90	0.10	0.760 (0.620 to 0.901)	0.003
CRP	OA-PJI	8.2 mg/l	81.3	94.6	95.1	79.5	15.06	0.20	0.933 (0.884 to 0.982)	< 0.001
ESR	RA-PJI	35 mm/hr	85.0	58.3	63.0	82.4	2.40	0.26	0.716 (0.562 to 0.870)	0.015
ESR	OA-PJI	23 mm/hr	87.5	89.2	91.3	84.6	8.10	0.14	0.939 (0.892 to 0.987)	< 0.001
Synovial fluid WBC	RA-PJI	5,208/μl	75.0	100.0	100.0	85.0	N/A	0.25	0.940 (0.838 to 1.000)	0.002
Synovial fluid WBC	OA-PJI	2,696/μl	87.5	100.0	100.0	88.9	N/A	0.13	0.953 (0.886 to 1.000)	< 0.001
PMN%	RA-PJI	76.8%	75.0	100.0	100.0	85.0	N/A	0.25	0.905 (0.770 to 1.000)	0.004
PMN%	OA-PJI	66.4%	95.8	100.0	100.0	96.0	N/A	0.04	0.987 (0.959 to 1.000)	< 0.001

*DeLong test.
AUC, area under the curve; CI, confidence interval; N/A, not applicable; NLR, negative likelihood ratio; NPV, negative predictive value; OA, osteoarthritis; PJI, periprosthetic joint infection; PLR, positive likelihood ratio; PMN%, polymorphonuclear neutrophil percentage; PPV, positive predictive value; RA, rheumatoid arthritis; WBC, white blood cell count.

joints involved after TJR, we analyzed the thresholds of serum and synovial fluid indexes for diagnosing PJI of the hip and knee, respectively. Our results showed that the optimal cutoff values of each index for diagnosing RA-PJI were higher than those of OA-PJI, whether for hip or for knee. Moreover, the sensitivity and negative predictive value of CRP in diagnosing RA-PJI were higher than those of other indexes, but the specificity and positive predictive value were significantly lower, which was also in line with the characteristics of the previously mentioned inflammatory indexes for PJI diagnosis. Meanwhile, we also found that the accuracy of synovial fluid WBC in the diagnosis of RA-PJI was higher than other indexes in both hip and knee, which was also consistent with the results mentioned above. It should be noted that the optimal cutoff values of synovial fluid WBC and PMN% for diagnosing RA-PJI after THA were significantly higher than those of TKA. A study by Zahar et al[37] evaluated the efficacy of synovial fluid WBC and PMN% in diagnosing PJI of the hip and knee, and included RA patients. Their results showed that the optimal cutoff value of synovial fluid WBC for the diagnosis of hip and knee PJI was 2,582/μl, and the PMN% was 66.1%; the optimal cutoff value of synovial fluid WBC for the diagnosis of knee PJI was 1,630/μl, and the PMN% was 60.5%; those of hip PJI were 3,063/μl and 66.1%, respectively. We believe that there are differences in threshold levels between knees and hips: setting different cutoff values would improve the diagnostic value. The currently used international guidelines and diagnostic criteria need further revisions in terms of these parameters.

The results of our study show that the diagnostic efficacy of using any one of the above indexes alone has some limitations. For RA patients, the specificity of the combined index is significantly increased, which reduces the misdiagnosis rate; the increase in positive predictive

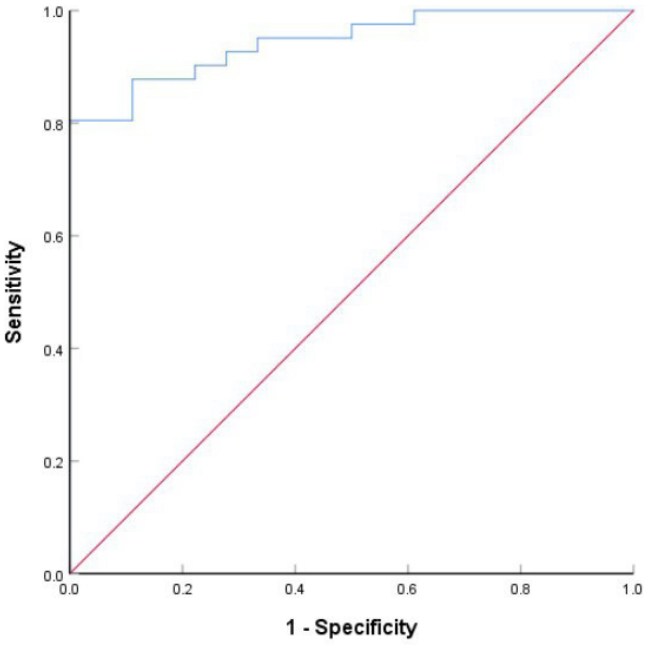

Fig. 5

Receiver operating characteristic curve of the combined index in the diagnosis of periprosthetic joint infection in patients with rheumatoid arthritis.

value is also conducive to diagnosis. The AUC of the combined index was higher than that of a single index, and although the AUC of the synovial fluid WBC was not significantly different from that of the combined index, the other detection indexes still differed significantly from the AUC of the combined index. Therefore, the diagnostic value and accuracy of the combined index were higher overall. We believe that, due to the characteristics of RA patients, misdiagnosis should be avoided. Compared with a single index, the combined index can improve the diagnostic efficacy of RA-PJI.

Regarding the history of glucocorticoid use in RA patients, the long-term use of glucocorticoids can lead to suppression of the body's immune function and reduced defense clearance against pathogenic bacteria; thus, these patients are at higher risk of PJI.[38,39] One study showed that glucocorticoid treatment is a significant risk factor for PJI and death, with a clear dose-response relationship.[40] Due to the use of corticosteroids and DMARDs in RA patients, it may affect the role of serum inflammation and synovial fluid indexes in the diagnosis of PJI, making it impossible to accurately diagnose RA-PJI.[41] However, long-term use of glucocorticoids will suppress adrenal cortical secretion function, resulting in insufficient secretion of the patient's own glucocorticoids.[42] Therefore, out of an abundance of caution, we usually supplement glucocorticoids intravenously in the perioperative period for patients who have discontinued taking glucocorticoids for less than two years. Meanwhile, for other RA patients, we usually further evaluate whether glucocorticoids are used intravenously in the perioperative period based on the results of plasma cortisol detection. The guidelines of the American Association of Hip and Knee Surgeons (AAHKS) recommend continuing the current daily dose of glucocorticoids with the same strength rather than providing stress dosing,[43] to avoid stress doses increasing the risk of infection. However, whether the supplemental use of high-dose glucocorticoids in the perioperative period increases the risk of postoperative infection still needs to be studied.

This investigation had several limitations: 1) it was a single-centre retrospective study with a limited sample size and selection bias, and the conclusions need to be further verified by multicentre and large samples; 2) we observed that patients in the RA group were more often female (although this constitutes a potentially sex-confounding bias, the prevalence of RA in women is known to be higher in general, not only in our study population); 3) not all patients performed the synovial fluid tests, resulting in a small sample size of synovial fluid in our study; 4) patients who took antibiotics self-prophylactically before admission were not excluded, which may have lowered the predictive power of the detection indexes; 5) since it was a retrospective study, the bloody synovial fluid samples in this study were not calculated using the adjusted synovial WBC formula; and 6) the observation index is limited, so it is necessary to further explore the value of other markers, such as interleukin 6 (IL-6), synovial fluid alpha-defensin, and synovial fluid calprotectin,[44–46] for diagnosing RA-PJI in the future.

In conclusion, although we found that synovial fluid WBC is the best detection index for the auxiliary diagnosis of PJI in RA patients, there is no single index that can be used as the diagnostic gold standard. Consequently, we should combine multiple detection indexes on the basis of determining the diagnostic thresholds of the above indexes in order to diagnose PJI accurately in the early stage.

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