Combination of Synovial Fluid IL-4 and Polymorphonuclear Cell Percentage Improves the Diagnostic Accuracy of Chronic Periprosthetic Joint Infection

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Research Article

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Abstract

**Background:** Synovial fluid biomarkers have been confirmed with promising diagnostic value for chronic periprosthetic joint infection (PJI), even there was still no “gold standard”. Interleukin-4 (IL-4) and polymorphonuclear cells (neutrophil) count in synovial fluid play a crucial role in mediating local inflammation of bacterial infections and therefore could be valuable biomarkers for PJI.

**Methods:** The purpose of this study was to investigate the diagnostic capacity of synovial fluid IL4 (SF-IL4) and polymorphonuclear cell percentage(SF-PMN%) for chronic PJI. According to the 2013 Musculoskeletal Infections Society(MSIS 2013) criteria, chronic PJI is defined as occurred more than 6 weeks after the primary arthroplasty. A total of 110 patients who scheduled to undergo revision arthroplasty from January 2019 to October 2020 were enrolled. 11 patients were eliminated by exclusion criteria. 43 of 99 patients were classified as infected and 56 as not infected. In all patients, SF-IL4 and SF-PMN% were measured in synovial fluid, serum CRP, ESR levels were measured preoperatively. The area under the curve(AUC) for each biomarker was analyzed, the diagnostic value and optimal cutoff values were calculated.

**Results:** The demographic data was not statistically different. The SF-IL4 and SF-PMN% showed a great diagnostic accuracy of chronic PJI from aseptic failure patients with AUC of 0.97(95% confidence interval (CI), 0.92-0.99) and 0.89(95%CI, 0.82-0.95) separately, which was higher than the serum ESR (0.72), and serum CRP (0.83). We set 1.7 pg/mL and 75% as the optimal cut-off values of SF-IL4 and SF-PMN% individually. Combination of SF-IL4 and SF-PMN% improved the diagnostic ability for chronic PJI with a specificity of 97.0%, and 96.0% accuracy.

**Conclusion:** Synovial fluid IL-4 was a valuable biomarker for chronic PJI detection. Combination of SF-IL4 and SF-PMN% provided higher specificity and accuracy when met the cut-off values of 1.7 pg/mL and 75% simultaneously.

Introduction

PJI is a catastrophic complication after joint replacement surgery. Even with a lower incidence rate of about 0.3-1.7% of total knee arthroplasty(TKA) and 0.8-1.9% of total hip arthroplasty (THA)[1], it has become the most common cause of revision for failed TKA and the third most common reason for revision THA [2, 3]. The cost of treatment of a PJI is 3 to 4 times higher than the primary surgery[4, 5]. The preoperative distinction between PJI and aseptic failure determines antibiotic therapies and surgical strategies. It remains a challenge as there still has no “gold standard” test available[6].

The diagnostic standards for PJI have been refined over the past decades[7-9]. Serum C-reaction protein(CRP) and Erythrocyte sedimentation rate (ESR) as classic tests with high sensitivity but specificity limit their diagnostic accuracy[10-12]. In recent years, the use of synovial fluid biomarkers to diagnose PJI showed promising results, because of the low cost, ease of interpretation, and high accuracy[13, 14]. Neutrophils as the first cells to produce a defensive response to bacterial infections, with high sensitivity
and specificity for PJI detection[15]. SF-PMN% has been the basic indicators of synovial fluid analysis but the cut-off value is still controversial [14, 16]. Therefore more valuable biomarkers to detect chronic PJI is needed.

IL-4 is involved in acute and chronic bacterial defense inflammatory responses but the diagnostic value for chronic PJI is unrevealed. IL-4 promoting immunoglobulin isotype switching and regulating the function of macrophages mainly via the Stat6 pathway[17]. Serum IL-4 level is upregulated in bacterial infection-induced systemic inflammatory response syndrome (SIRS), and the level of IL-4 is related to infection-related death[18]. Serum IL-4 could be used as immunological markers for diagnosing active tuberculosis and-monitoring antituberculosis therapy efficacy [19]. Local administration or expression of IL-4 enhanced pulmonary clearance of Pseudomonas aeruginosa in vivo and decreased mortality following infection[20]. And in joint aspiration, IL-4 was firstly secreted by synovial mast cells and then by T helper 2(Th2) cells. Previous studies have demonstrated the level of IL-4 elevated in bacterial infected synovial fluid [21, 22], thus we hope synovial fluid IL-4 may be used as a useful biomarker for chronic PJI.

Therefore, the purpose of this study was to (1) explore and set an optimal cut-off value of serum CRP, ESR, SF-IL4, and SF-PMN% for chronic PJI-diagnosis; (2) improve the diagnostic efficiency of chronic PJI through combining SF-IL4 with other biomarkers.

**Patients And Methods**

This prospective study protocol was approved by the institutional ethics board of the First Affiliated Hospital of Chongqing Medical University. Informed consent was obtained from every patient. Patients who underwent revision TKA or THA between January 2019 and October 2020 were enrolled in this study. Patients were divided into chronic PJI group and aseptic group based on the 2013 Musculoskeletal Infections Society (MSIS)(Table 1)[8]. The chronic PJI was defined as PJI symptoms occurred more than 6 weeks after the primary implantation[23, 24]. The aseptic failures including aseptic loosening, wear, instability, dislocation, adverse local tissue reactions, and metal allergic reactions[25]. To rule out interference with other possible preconditions associated with elevated inflammatory factors, the exclusion criteria were as follows:(1)other organs infectious diseases, including pneumonia, urinary tract infection; (2)active rheumatoid arthritis, gouty arthritis, as well as (3)malignant tumors.

Demographic data(age, gender, preoperative diagnosis (PJI or aseptic; hip or knee), and the survivial time of primary implatation were collected. Before revision surgery, 3 milliliters of peripheral venous blood was taken to test serum ESR and CRP. Three to five milliliters of synovial fluid was taken for analyzing SF-IL4, SF-PMN%, and culture(48 hours routine culture, and prolonged culture for 14 days). Then, at least 3 intraoperative tissues were cultured for 48 hours and 14 days. All biochemical assays were performed at the biochemistry laboratory of the biology technical platform in our institution.

**Statistical Analysis**


Data were analyzed using the SPSS 26.0 (IBM Corporation, Texas). Continuous data of non-normal distribution were described as median and inter-quartile range (IQR). Mann-Whitney U test was used to analyze the statistical significance, and Chi-squared test was used to compare the sensitivity and specificity of laboratory tests and categorical data (age, gender, involved joint). P < 0.05 (2-tailed) was considered statistically significant. Receiver operating characteristic (ROC) curves and the area under the curve (AUC) were calculated using MedCalc 19.0.7 (Ostend, Belgium). The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) were estimated for tested markers. The optimal cut-off value for each maker were computed with maximized the Youden index (sensitivity + specificity-1). A higher diagnostic odds ratio (DOR) indicated better discriminatory strength[26].

**Table 1**

The Musculoskeletal Society 2013 criteria for defining periprosthetic joint infection

| Major criteria                                                                 | Minor criteria                                                                 |
|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| 1. A sinus tract communicating with the joint; or                              | 1. Elevated serum C-reactive protein (CRP) AND erythrocyte sedimentation rate(ESR); or |
| 2. Two positive periprosthetic cultures with phenotypical identical organisms. | 2. Elevated synovial fluid white blood cell (WBC) count OR ++ change on leukocyte esterase strip; or |
|                                                                               | 3. Elevated synovial fluid polymorphonuclear neutrophil percentage (PMN%); or   |
|                                                                               | 4. Positive histological analysis of periprosthetic tissue; or                   |
|                                                                               | 5. A single positive culture.                                                   |

**Results**

*Baseline data of all the two groups had no significant differences.*

110 patients initially enrolled, of which 6 patients were excluded due to "dry aspiration", 4 cases with active rheumatoid arthritis, and 1 patient as acute PJI. Finally, a total of 99 patients were included in the present study, with 43 (43.4 %) as chronic PJI and 56 (56.6 %) were the aseptic failure. The baseline characteristics of the two groups were similar and shown in **Table 2**. There had no statistically significant difference in the demographics data of the two groups (P>0.05).

**Table 2** The demographic data for the study population
| Characteristic          | Septic (N=43) | Aseptic (N=56) | P value |
|------------------------|---------------|----------------|---------|
| Age (year)             | 70.58±5.26    | 68.98±6.05     | 0.17*   |
| Gender                 |               |                |         |
| Male                   | 2251.2%       | 2748.2%        | 0.77*   |
| Female                 | 2148.8%       | 2951.8%        |         |
| Joint type             |               |                |         |
| Hip                    | 1739.5%       | 3155.4%        | 0.12*   |
| Knee                   | 2660.5%       | 2544.6%        |         |
| BMI (Kg/m²)            | 22.74±3.91    | 23.21±4.66     | 0.59 #  |
| Survival time of implatation (month) | 67.91±29.06 | 76.82±21.55 | 0.08# |

* chi-square test, # independent student’s T-test

**Synovial fluid IL-4 had higher diagnose power than serum ESR and CRP**

As shown in Table 3, the median value of serum ESR was 35.00mm/h in the chronic PJI group, which was higher than that in the aseptic group of 22.0 mm/h (P=0.001). Similarly, in the chronic PJI group, the serum CRP ranged from 5.80 to 91.20 mg/L, with a median value of 21.4 mg/L, which was higher than 6.75 mg/L of the aseptic group (P<0.0001). Results showed that the median level of SF-IL4 in the chronic PJI group is higher than that in the aseptic group (3.30 vs. 1.10 pg/ml, P<0.0001). Finally, the median SF-PMN% was higher in PJI patients (87.58%) than in the aseptic group (56.95%), with statistical significance (P<0.001).

**Table 3** Analysis the character of single marker in chronic PJI and aseptic failure group
### Table 1

| Marker     | Chronic PJI (N=43) | Aseptic (N=56) | P-value |
|------------|--------------------|----------------|---------|
| **ESR (mm/hr)** | Range 7.20~120.00  | Range 2.00~58.00 |        |
|            | Median 35.00       | Median 22.00    |         |
|            | P25, P75 22.00;50.00 | P25, P75 17.50;32.00 |     |
|            | Mean±SD 42.10±26.23 | Mean±SD 24.38±12.80 | 0.001# |
|            | Range 5.80~91.20   | Range 1.25~28.00 |         |
| **CRP (mg/L)** | Median 21.40       | Median 6.75     |        |
|            | P25, P75 13.20;33.40 | P25, P75 3.29;16.00 |    |
|            | Mean±SD 27.31±20.02 | Mean±SD 9.81±7.75 | <0.001# |
|            | Range 1.20~14.10   | Range 0.09~2.88 |         |
| **SF-IL4 (pg/mL)** | Median 3.30        | Median 1.10     |        |
|            | P25, P75 2.20;9.7  | P25, P75 0.55;1.28 |     |
|            | Mean±SD 5.57±4.37  | Mean±SD 1.00±0.53 | <0.001# |
|            | Range 60.32~96.65  | Range 23~89.20  |         |
| **SF-PMN%** | Median 87.58       | Median 56.95    |        |
|            | P25, P75 83.50,90.50 | P25, P75 53.40,56.95 |  |
|            | Mean±SD 86.15±7.31 | Mean±SD 59.30±15.53 | <0.001# |

ESR, Erythrocyte sedimentation rate; CRP, C-reaction protein; SF-IL4, Synovial fluid Interleukin 4; SF-PMN%, Synovial fluid polymorphonuclear cell neutrophil percentage

SD: standard deviation; # Mann-Whitney U test

The ROC curves were used to measure the discriminatory strength of those indicators (Figure 1a-d). The AUC of SF-IL4 was 0.97 (95% confidence interval, 95%CI, 0.92-0.99) is higher than serum ESR 0.72 (95%CI, 0.62-0.84) (P=0.0004), serum CRP 0.83 (95%CI, 0.74-0.90) (P<0.0001), and SF-PMN% 0.89 (95%CI, 0.82-0.95) (P=0.053) (Figure 1e). The sensitivity, specificity, PPV, NPV, +LR, -LR, and DOR of those markers were as Table 4 shown. The optimal cut-off value for SF-IL4 of 1.7pg/mL, with sensitivity of 93.02% (95% CI, 80.9% - 98.5%), specificity of 94.64% (95% CI, 85.1%-98.9%), and with a high PPV, NPV, DOR of 93.0%, 94.6% and 248 individually. When the cut-off value for serum ESR was set as 34mm/hr, with a poor sensitivity of 58.14% (95%CI, 42.1%-73.0%) and moderate specificity of 83.93% (95%CI, 71.7%-92.4%). When 18mg/L was the cut-off value for serum CRP, with sensitivity about 62.79% (95%CI, 46.7%-77.0%) and specificity about 87.50% (95%CI, 75.9%-94.8%). And those values for SF-PMN% were 95.35% (95%CI, 84.2%-99.4%) and 78.57% (95%CI, 65.6%-88.4%) with the cutoff value of 75%.
### Table 4
The AUC, Cut-off level, Sensitivity, Specificity, PPV, NPV, +LR, -LR, and DOR of each single marker

| Test | CRP (mg/L) | ESR (mm/hr) | CRP (mg/L) | ESR (mm/hr) | SF-IL4 (pg/mL) | SF-PMN% |
|------|------------|-------------|------------|-------------|----------------|----------|
| AUC (95%CI) | 0.83 (0.74-0.90) | 0.72 (0.62-0.84) | 0.97 (0.92-0.99) | 0.89 (0.82-0.95) |
| Cutoff level | 10 | 30 | 18 | 34 | 1.7 | 75% |
| Sensitivity (95%CI) | 81.4 | 67.4 | 62.79 (46.7-77.0) | 58.14 (42.1-73.0) | 93.02 (80.9-98.5) | 95.35 (84.2-99.4) |
| Specificity (95%CI) | 58.9 | 62.6 | 87.50 (75.9-94.8) | 83.93 (71.7-92.4) | 94.64 (85.1-98.9) | 78.57 (65.6-88.4) |
| PPV | - | - | 79.4 (65.0-88.9) | 73.5 (59.2-84.2) | 93.0 (81.6-97.6) | 77.4 (67.3-85.0) |
| NPV | - | - | 75.4 (67.0-82.10) | 72.3 (64.3-79.1) | 94.6 (85.6-98.1) | 95.7 (85.0-98.8) |
| +LR | - | - | 5.02 (2.40-10.40) | 3.62 (1.9-6.9) | 17.36 (5.8-52.4) | 4.45 (2.7-7.4) |
| -LR | - | - | 0.43 (0.3-0.6) | 0.50 (0.3-0.7) | 0.07 (0.02-0.2) | 0.06 (0.02-0.2) |
| DOR | - | - | 11.67 | 7.24 | 248.00 | 74.17 |
| Accuracy | 58.6 | 50.5 | 72.7 | 68.7 | 92.9 | 84.8 |

ESR, Erythrocyte sedimentation rate; CRP, C-reaction protein; SF-IL4, Synovial fluid Interleukin 4; SF-PMN%, Synovial fluid polymorphonuclear cell neutrophil percentage; PPV, Positive Predictive Value; NPV, Negative Predictive Value; +LR, Positive Likelihood Ratio; -LR, Negative Likelihood Ratio; DOR, Diagnostic Odds Ratio;

**Combination SF-IL4 with SF-PMN% improved diagnostic ability of chronic PJI**

Next, we combined SF-IL4 with other biomarkers. As results are shown in Table 5, when met the cut-off of SF-IL4 and SF-PMN% at the same time, which can maximize the specificity to 97% and accuracy to 96%, but decreased the sensitivity to 91% for chronic PJI diagnosis.

### Table 5
The Sensitivity, Specificity, PPV, NPV, and Accuracy of Combination the Different Markers
| Combination          | SF-IL4>1.7 + CRP>18 | SF-IL4>1.7+ SF-PMN%>75% | CRP>18+SF-IL4>1.7+ SF-PMN%>75% |
|----------------------|---------------------|-------------------------|---------------------------------|
| Sensitivity          | 0.88                | 0.91                    | 0.53                            |
| Specificity          | 0.98                | 0.97                    | 0.98                            |
| PPV                  | 0.96                | 0.94                    | 0.95                            |
| NPV                  | 0.75                | 0.92                    | 0.73                            |
| Accuracy             | 80.1%               | 96%                     | 78.8%                           |

CRP, C-reaction protein; SF-IL4, Synovial fluid Interleukin 4; SF-PMN%, Synovial fluid polymorphonuclear cell neutrophil percentage; PPV, Positive Predictive Value; NPV, Negative Predictive Value.

**Discussion**

Periprosthetic joint infection (PJI) is still a catastrophic complication of arthroplasty. Chronic PJI patients have poorer function score, lower quality of life, and significantly increased risk of short-term death[27, 28]. The diagnosis of chronic PJI relies on clinical symptoms, physical examination, biomarkers examination, and radiological examination. As chronic PJI belongs to encapsulated and low-grade infections, it usually caused less extensive systemic inflammation reactions and sometimes has negative laboratory test results[29]. Therefore, the diagnosis of chronic PJI keep challenging and there still has no “gold standard”[30].

Synovial fluid interleukins play an important role in implant-associated infection. TNF, IL-1, and IL-6 as pro-inflammatory cytokines are essential for initiating an inflammatory response to infection[31]. In the present study, IL-4, as an anti-inflammatory cytokine that participates in chronic infection and immune regulation process[32]. IL-4 regulates the ratio of Th1/Th2 lymphocyte subtypes in chronic infectious diseases[17], which inhibit the development of biofilms in chronic infections of Staphylococcus aureus, and may promote the infection cleared spontaneously[33]. IL-4 increases the transformation of macrophage phenotype into M2 type, which inhibits osteoclast differentiation[34, 35], and promotes the differentiation of B cells and plasma cells and produces antibodies, participates in humoral immunity, and exerts anti-infection function[36, 37].

Similarly, synovial fluid IL-4 showed promising predictive value for PJI. Gollwitzer et al. reported that synovial fluid IL-4 has 93% sensitivity and 85% specificity in PJI, which is higher than other serum markers and synovial fluid cytokines like IL-1β and IL-6. However, their study only enrolled the patients infected by Staphylococcus aureus, which is more virulent. So their cut-off value is 7.79pg/ml, which is much higher than our 1.7pg/ml [6]. Fröschen et al. reported combining synovial fluid IL-2, IL-4, IL-5, IL6, IL-12, and GM-CSF can achieve 100% sensitivity and 88.9% specificity, but not universal and expensive[38]. Consistent with previous studies, our present study showed the median level of SF-IL4 in chronic PJI group was 3.30pg/ml. When we set the cutoff value as 1.7 pg/mL, SF-IL4 with the highest sensitivity of
93.02 (95% CI, 80.9%-98.5%), specificity of 94.64% (95% CI, 85.1%-98.9%), and diagnostic accuracy of 94.6% (95% CI, 85.1%-98.9%) compared with serum ESR, CRP, and SF-PMN%.

Synovial leukocyte analysis as the basis of the synovial fluid test but the thresholds have not been unified in chronic PJI, as the results may be affected by many factors, especially the use of antibiotics before the joint aspiration [39–42]. Synovial fluid PMN% more than 80% has been recommended for diagnosis of chronic PJI (> 6 weeks after surgery) in 2013 MSIS consensus [8]. Zahar et al. reported when the cut-off of PMN% was 66.1%, the sensitivity and specificity were 80.6% and 83.3% for chronic PJI [43]. Higuera et al. revealed the sensitivity, specificity of chronic hip PJI were 92.1%, 85.8%, respectively, used 80% as the cut-off value [16]. In the present study, when the optimal cutoff value of synovial fluid PMN% was 75%, the AUC of diagnosing chronic PJI was 0.89 (95% CI, 0.82–0.95), with higher sensitivity, and specificity of 95.35% (95% CI, 84.2%-99.4%) and 78.57% (95% CI, 65.6%-88.4%), respectively.

In our study, when we diagnosed PJI according to the 2013 MSIS consensus recommend CRP cut-off value of 10 mg/L, the sensitivity and specificity were 81.4 % and 58.9 %, respectively, and the diagnostic accuracy was only 58.6 %. When the cutoff value of ESR is 30mm/hr, with only 67.4% sensitivity and 62.6% specificity, and the accuracy is 50.5%. There is unacceptably low sensitivity and a high number of false negatives. When we set the cut-off values of CRP and ESR as 18mg/L and 34mm/hr, respectively, the detective accuracy for chronic PJI improved to 72.7 % and 68.7 %, individually.

As above showed that there is no single test could provide 100% accuracy for PJI diagnosis. And a combination of different indicators, with different sensitivity and specificity, should be used to confirm or rule out the infection when the presence of high clinical suspicion [44–47]. We found that when the SF-IL4 is greater than 1.7 pg/ml and the SF-PMN% more than 75%, the specificity improved to 97%, and 96% accuracy for chronic PJI diagnosis. However, the combined diagnosis brought high specificity but reduced diagnostic sensitivity, which is a problem that clinicians need to weigh, which may lead to missed diagnosis in some patients.

Regarding the limitations of our research, the first one is that we did not adopt the latest 2018 ICM modified PJI diagnostic criteria, which added new markers like serum D-Dimer and explored a scoring system. Which was validated with higher sensitivity of 97.7% and specificity of 99.5% [48]. At the same time, the application of D-dimer for PJI is still controversial [49]. Besides, we excluded patients diagnosed with active inflammatory arthritis at the time of admission, including rheumatoid arthritis, ankylosing spondylitis, and gouty arthritis. As these patients usually have higher serum ESR, CRP, and synovial fluid WBC counts and PMN%, this will affect the accuracy of our calculation results [50]. But excluding these special populations will limit the clinical application of our research results, and the sample size is limited, and if large-sample multi-center research can be executed may produce more reliable results.

**Conclusion**

When we set the cutoff value as 1.7 pg/mL, synovial fluid IL-4 with a higher sensitivity of 93.02, and highest specificity of 94.64% compared with serum ESR, CRP, and SF-PMN%. Combined measurement of
SF-IL4 and SF-PMN% improved the specificity to 97%, and with 96% diagnostic accuracy for chronic PJI, however, at present, the cut-off value of SF-IL4 for chronic PJI detection is not yet consensual, requiring more research data to support our conclusion further.

**Abbreviations**

PJI, Periprosthetic Joint Infection; ESR, Erythrocyte sedimentation rate; CRP, C-reaction protein; SF-IL4, Synovial fluid Interleukin 4; SF-PMN%, Synovial fluid polymorphonuclear cell neutrophil percentage; PPV, Positive Predictive Value; NPV, Negative Predictive Value; +LR, Positive Likelihood Ratio; -LR, Negative Likelihood Ratio; DOR, Diagnostic Odds Ratio; ROC, receiver operating characteristic; AUC, area under the curve.

**Declarations**

**Ethics approval and consent to participate:** This prospective study protocol was approved by the institutional ethics board of the First Affiliated Hospital of Chongqing Medical University (Ethics approved number: 20187101).

**Consent for publication:** Not applicable

**Availability of data and materials:** The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

**Competing interests:** The authors declare that they have no competing interests.

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**Authors' contributions:**

Ning Hu and Wei Huang conceived and designed the study.

Jiaxing Huang, Jiawei Wang, Bo Zhu analyzed and interpreted the data.

Jiaxing Huang, drafted the article, Ning Hu and Wei Huang critically revised the paper.

All of the authors approved the final submitted version.

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Figures
Figure 1

The ROC curve of ESR, CRP, SF-IL4, and SF-PMN% (a-d), and the comparsion of those four markers(e).

ROC, receiver operating characteristic; ESR, Erythrocyte sedimentation rate; CRP, C-reaction protein; SF-IL4, Synovial fluid Interleukin 4; SF-PMN%, Synovial fluid polymorphonuclear cell neutrophil percentage