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INFECTION

Improved diagnosis of chronic hip and knee prosthetic joint infection using combined serum and synovial IL-6 tests

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Aims

This study aimed to explore whether serum combined with synovial interleukin-6 (IL-6) measurement can improve the accuracy of prosthetic joint infection (PJI) diagnosis, and to establish the cut-off values of IL-6 in serum and synovial fluid in detecting chronic PJI.

Methods

Patients scheduled to have a revision surgery for indications of chronic infection of knee and hip arthroplasties or aseptic loosening of an implant were prospectively screened before being enrolled into this study. The Musculoskeletal Infection Society (MSIS) definition of PJI was used for the classification of cases as aseptic or infected. Serum CRP, ESR, IL-6, and percentage of polymorphonuclear neutrophils (PMN%) and IL-6 in synovial fluid were analyzed. Statistical tests were performed to compare these biomarkers in the two groups, and receiver operating characteristic (ROC) curves and area under the curve (AUC) were analyzed for each biomarker.

Results

A total of 93 patients were enrolled. There was no difference in demographic data between both groups. Synovial fluid IL-6, with a threshold of 1,855.36 pg/ml, demonstrated a mean sensitivity of 94.59% (95% confidence interval (CI) 81.8% to 99.3%) and a mean specificity of 92.86% (95% CI 82.7 to 98.0) for detecting chronic PJI. Then 6.7 pg/ml was determined to be the optimal threshold value of serum IL-6 for the diagnosis of chronic PJI, with a mean sensitivity of 97.30% (95% CI 85.8% to 99.9%) and a mean specificity of 76.79% (95% CI 63.6% to 87.0%). The combination of synovial IL-6 and serum IL-6 led to improved accuracy of 96.77% in diagnosing chronic PJI.

Conclusion

The present study identified that a combination of IL-6 in serum and synovial IL-6 has the potential for further improvement of the diagnosis of PJI.

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Keywords: Prosthetic joint infection, Diagnosis, Interleukin-6, CRP, ESR

Article focus

- Exploring whether serum interleukin-6 (IL-6) combined with synovial IL-6 measurement can improve the accuracy of prosthetic joint infection (PJI) diagnosis.
- Establish the cut-off values for diagnosing chronic PJI based on serum and synovial IL-6.

Key messages

- Synovial fluid IL-6 has a high diagnostic accuracy (93.55%) for the diagnosis of chronic PJI, and the cut-off values of synovial fluid and serum IL-6 were 1,855.36 pg/ml and 6.7 pg/ml, respectively.

Strengths and limitations

- This is the first study to demonstrate that combination of synovial fluid and serum IL-6 improved diagnosis of chronic PJI.
- This was a single-centre study with potential uncontrolled selection biases among subgroups.

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- This study excluded patients with aseptic inflammatory arthritis, such as rheumatoid arthritis, so we concluded that the scope of application would be limited.

Introduction

Although prevention is the most effective strategy, establishing an accurate and timely prosthetic joint infection (PJI) diagnosis remains critical for a successful treatment.[1,2] Over the last decade, several work groups have convened to generate a standardized definition and diagnostic approach to suspected PJI.[3-6] However, discrimination between infected and aseptic failed total joint replacements can be difficult in some cases, because there is no 'gold standard' diagnostic test or protocol to accurately diagnose infection in a timely fashion.[7]

Diagnosis and treatment of PJI is very complex, challenging, and often delayed. Many novel serum and synovial biomarkers, such as CD14, TREM-1, and TLR2, have shown potential in the diagnosis of PJI.[8] However, marker detection techniques are not readily available in many hospitals, and conflicts exist between different studies, making the test results difficult to interpret. It is interesting to note these cytokines are upstream of the inflammatory pathway, and will eventually trigger the expression of the cytokine interleukin-6 (IL-6) under septic conditions.[9] IL-6 is a pleiotropic cytokine produced by a variety of cells including monocytes and macrophages to stimulate the immune response, and is one of the most important fever and acute response mediators. It can be strongly up-regulated during septic inflammation.[10] One previous study has revealed the significance of both serum and synovial IL-6 in distinguishing between infected and aseptic failed total joint replacements.[11] However, studies that describe the benefits of IL-6 tests were heterogeneous in their study designs, and their clinical applicability was limited because of small sample sizes, with poorly defined diagnostic threshold in differentiation between acute and chronic PJI. Also, the assays are not readily available in some laboratories.

In this study, we sought to: 1) explore whether serum IL-6 combined with synovial IL-6 measurement can improve the accuracy of PJI diagnosis; and 2) establish the cut-off values for diagnosing chronic PJI based on serum and synovial IL-6.

Methods

From January 2018 to August 2019, we prospectively enrolled patients who were scheduled to have a revision surgery for indications of chronic infection of knee and hip arthroplasties or aseptic loosening of an implant. The patients were divided into two groups, 'aseptic revision' and 'infection', based on the 2013 Musculoskeletal Infection Society (MSIS) criteria for the diagnosis of PJI.[12] Aseptic revision cases were defined as cases undergoing single-stage revision for a diagnosis other than infection (loosening, wear, instability, malalignment, adverse local tissue reactions, or other aseptic causes).[12] A postoperative infection was considered 'chronic' when PJI symptoms occurred for more than six weeks after implantation.[13,14] This study was approved by the institutional ethics board and patients signed an informed consent form prior to their enrolment in the study.

Table I. Demographic data for the study population. Variables are expressed as means (SDs) or absolute numbers and percentages.

Characteristic	Aseptic revision (n = 56)	Infection (n = 37)	p-value
Mean age, yrs (SD)	72.15 (6.54)	74.57 (6.01)	0.079*
Mean weight, kg (SD)	60.32 (12.79)	60.02 (11.14)	0.909*
Mean height, cm (SD)	161.21 (7.87)	161.70 (8.12)	0.773*
Mean BMI, kg/m^2 (SD)	23.22 (4.66)	22.99 (4.12)	0.811*
Sex, n (%)			0.513†
Male	33 (58.93)	25 (67.57)	
Female	23 (41.07)	12 (32.42)	
Joint type, n (%)			0.403†
Knee	25 (44.64)	20 (54.05)	
Hip	31 (55.36)	17 (49.95)	
Mean timeframe, yrs (SD)	9.61 (2.31)	2.64 (0.96)	< 0.001*‡

*Independent-samples *t*-test.
†Fisher's exact test.
‡Statistically significant.
BMI, body mass index

To rule out interference with other inflammatory markers, patients with the following conditions were excluded: inflammatory arthritis such as rheumatoid arthritis and gout; infectious disease such as pneumonia and urinary tract infection; malignancy; and patients with recent antibiotic use (less than two weeks).

We included a total of 93 patients into our prospective cohort study (there were originally 101 cases, but eight cases were excluded because of 'dry tap'), among which 37 patients met MSIS criteria for chronic PJI. The patients' demographics and details were shown in Table I. We recorded the patients' following baseline data: age, sex, body mass index (BMI), the involved joint, and time since prosthesis implantation. Blood samples were taken from the cubital vein on admission and analyzed for serum IL-6, ESR, and CRP. Synovial fluid was obtained before revision surgery for synovial fluid IL-6 (SF IL-6), percentage of polymorphonuclear neutrophils (PMN%) analysis, synovial white blood cell count, and cultures. During the revision arthroplasty, we obtained at least three tissue samples from the patients for microbiological culture. Those tissue samples were cultured for 24 to 48 hours (standard culture) and 14 days (prolonged culture). Biochemical assays were performed at the biochemistry laboratory of the biology technical platform. All those samples including blood, synovial fluid, and tissue were separated into two groups: group I, patients with PJI diagnosed by MSIS criteria; and group II, patients with aseptic loosening of prothesis.

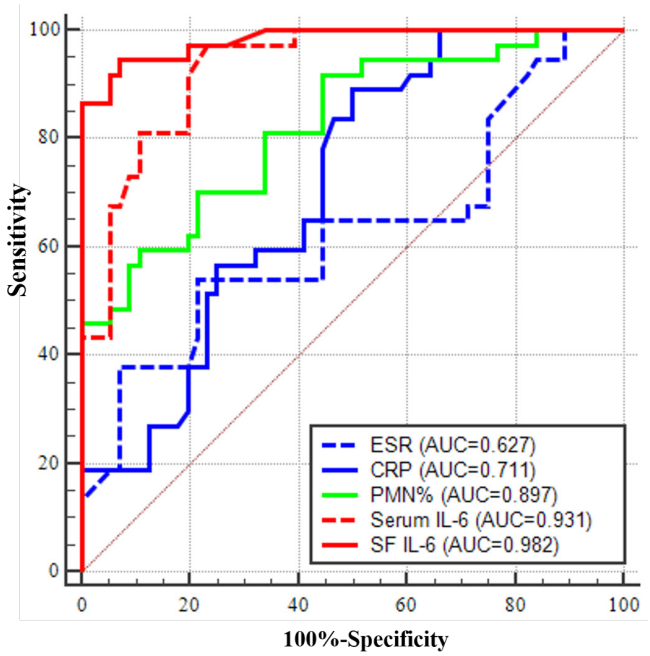

Fig. 1

Receiver operating characteristic curves (ROCs). ROCs with the corresponding area under the curve (AUC) of various inflammatory markers. IL-6, interleukin-6; PMN%, percentage of polymorphonuclear neutrophils; SF, synovial fluid.

Sample determination. Synovial fluid (1 ml to 2 ml) and serum samples were obtained soon after admission. The samples were centrifuged at 2,000 rpm for ten minutes within two hours after collection to remove all cellular and particulate content. The levels of IL-6 in the synovial fluid and serum were determined by using the IMMUNOLITE 1000 Immunoassay System (SIEMENS Healthcare, Erlangen, Germany). The CRP was tested using a particle-enhanced turbidimetric immunoassay with a HITACHI 7600 Series Automatic Biochemical Analyzer (Hitachi, Tokyo, Japan) and diagnostic kit (DiaSys Diagnostic Systems GmbH, Shanghai, China).

Statistical analysis. The data are presented as medians and interquartile ranges (IQRs). The results of the diagnostic tests were compared between the groups using an independent-samples *t*-test. Receiver operating characteristic (ROC) curves were created for IL-6 and PMN% in the synovial fluid and serum; CRP and ESR were used to establish optimal cut-off values as a diagnostic of PJI determined using Youden's J statistic. They also allowed the calculation of sensitivity, specificity, and area under the curve (AUC) with MedCalc 13.2.2 Software (MedCalc Software bv, Ostend, Belgium). The SPSS software version 24.0 for Windows (IBM, Armonk, New York, USA) was used for statistical analysis. A p-value less than 0.05 was considered statistically significant.

Results

We included a total of 93 patients into our prospective cohort study (there were originally 101 cases, but eight cases were excluded because of 'dry tap'), among which 37 patients met MSIS criteria for chronic PJI. The patients' demographics and details are shown in Table I. Although uneven in number, there were no differences regarding age (p = 0.079, independent-samples *t*-test), sex (p = 0.513, Fisher's exact test), or joint distribution (p = 0.403, Fisher's exact test) between the two groups. Mean time since prosthesis implantation was 9.61 years (SD 2.313) in the group with aseptic revision and 2.64 years (SD 0.965) in the group with infection (p < 0.01, independent-samples *t*-test). The rate of positive cultures for PJI in the cohort was 89.2% (33 of 37).

IL-6 in the synovial fluid and serum, as well as synovial PMN% and serum CRP and ESR levels, were significantly higher in the infection group compared to the aseptic revision group. The mean concentration of IL-6 in the synovial fluid for the infection group was 3,637 pg/ml and was significantly higher (p < 0.001, Mann-Whitney U test) than the aseptic revision group with a mean concentration of 307.15 pg/ml. The mean serum IL-6 concentration was 11.4 pg/ml in the infection group compared with 3.2 pg/ml in the aseptic revision group (p < 0.001, Mann-Whitney U test). The median (IQR) level of SF PMN% was 89.21% (72.51% to 91.65%) in the infection group compared with 55.71% (50.66% to 67.91%) in the aseptic revision group (p < 0.001, Mann-Whitney U test. The median serum ESR and CRP levels were 35 mm/hr and 19 mg/l, respectively, in the PJI group, and were also significantly higher than the aseptic revision group with 21 mm/hr (p = 0.038, Mann-Whitney U test) and 13.18 mg/l (p < 0.001, Mann-Whitney U test) for ESR and CRP, respectively.

Synovial fluid IL-6 and PMN% discriminated good differentiation between groups of infection and aseptic revision with AUC of 0.982 (95% CI 0.929 to 0.998) and 0.938 (95% CI 0.832 to 0.987), respectively. The AUCs of serum IL-6, ESR, and CRP were 0.931 (95% CI 0.858 to 0.973), 0.627 (95% CI 0.521 to 0.725), and 0.711 (95% CI 0.608 to 0.801), respectively (Figure 1).

As shown in Table II, the CRP level (10 mg/l) demonstrated a mean sensitivity of 94.59% (95% CI 81.8% to 99.3%) and a mean specificity of 35.71% (95% CI 81.8% to 49.6%). The ESR level (30 mm/h) demonstrated a mean sensitivity of 54.05% (95% CI 36.9% to 70.5%) and a mean specificity of 58.93% (95% CI 45.0% to 71.9%). The optimal serum IL-6 cut-off value was calculated at 6.7 pg/ml, with sensitivity, specificity, and negative predictive value (NPV) of 97.30% (95% CI 85.8% to 99.9%), 76.79% (95% CI 63.6% to 87.0%), and 97.7%, respectively. The SF PMN% at level of 70.03% demonstrated a mean sensitivity of 89.19% (95% CI 74.6% to 97.0%) and a mean specificity of 89.19% (95% CI 71.7% to 92.4%) for detecting chronic PJI. The optimal cut-off value of SF IL-6 with maximal sensitivity (94.59%) and specificity (92.86%) to discriminate aseptic failure from infection was 1,855.36 pg/ml, which produced an AUC of 0.982 (95% CI 0.929 to 0.998).

Table II. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of inflammatory markers.

Parameter	ESR	CRP	Serum IL-6	SF PMN%	SF IL-6	Serum IL-6 + SF IL-6
AUC (95% CI)	0.627 (0.521 to 0.725)	0.711 (0.608 to 0.801)	0.931 (0.858 to 0.973)	0.897 (0.816 to 0.950)	0.982 (0.929 to 0.998)	N/A
Cut-off level	30 mm/hr	10 mg/l	6.70 pg/ml	70.03%	1,855.36 pg/ml	Serum IL-6 > 6.70 pg/ml + SF IL-6 > 1,855.36 pg/ml
Sensitivity, % (95% CI)	54.05 (36.9 to 70.5)	94.59 (81.8 to 99.3)	97.30 (85.8 to 99.9)	89.19 (74.6 to 97.0)	94.59 (81.8 to 99.3)	91.89 (76.9 to 97.9)
Specificity, % (95% CI)	58.93 (45.0 to 71.9)	35.71 (81.8 to 49.6)	76.79 (63.6 to 87.0)	83.93 (71.7 to 92.4)	92.86 (82.7 to 98.0)	100 (92.0 to 100)
PPV, %	46.50	49.30	73.50	78.6	89.70	100
NPV, %	67.40	90.90	97.70	92.2	96.30	94.92
Accuracy, %	56.99	59.14	84.95	86.0	93.55	96.77

AUC, area under the curve; CI, confidence interval; IL-6, interleukin-6; N/A, not applicable; NPV, negative predictive value; PMN%, percentage of polymorphonuclear cells; PPV, positive predictive value; SF, synovial fluid.

The accuracy of diagnosis for combination of serum IL-6 and SF IL-6 was 96.77%, higher than using the SF IL-6 or serum IL-6 alone (Table II).

Discussion

Chronic encapsulated infections, low-grade infections, or infections with a fistula may result in less intense systemic reactions and are sometimes associated with normal laboratory markers.[15,16] The accurate diagnosis of chronic PJI is challenging, as the clinical symptoms often resemble those of aseptic loosening, with non-specific pain and swelling of the joint often similar to that of aseptic failure.[17,18] However, establishing an accurate and timely diagnosis of PJI is a key step toward implementing an effective treatment, as different protocols and surgical interventions are associated with survival of implants, as well as medical costs.[19] The aim of this study was to define the diagnostic utility of combined synovial fluid and serum IL-6 levels as a potential screening marker for chronic PJI. The results of this study suggest that the combination of the two biomarkers improves sensitivity and specificity in differentiating between chronic PJI and aseptic failure, and with better diagnostic accuracy than using each biomarker alone.

In recent years, many studies have made efforts to improve the diagnostic accuracy of PJI, such as laboratory test of inflammatory biomarkers, sonication of implants, molecular techniques, and analysis of circulating cytokines.[20-23] Some novel detection methods have greatly improved the accuracy of PJI diagnosis. Pathogens causing PJI in culture-negative samples of synovial fluid could be identified by 16S ribosomal DNA (rDNA) test and next-generation sequencing;[24,25] however, interpreting the test results is challenging, and the cost-effectiveness and operability of those techniques in most hospitals must be considered. Efforts to identify more accurate markers of PJI have been put into targeting synovial fluid. Because serum markers may be confounded by a concomitant acute or chronic inflammatory state from other organs and systems, assessments of local markers in the affected joints have casted some light on the diagnosis of PJI.[26] Deirmengian et al[27] identified several fluid biomarkers, including IL-1β, IL-1, IL-6, IL-8, granulocyte colony-stimulating factor (G-CSF), tumour necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), α-defensin, and β-defensin, and suggested that synovial fluid IL-1 and IL-6 levels exhibited ideal sensitivity, specificity, and accuracy for diagnosing PJI. The cytokine IL-6 is a small signalling glycoprotein (molecular weight: 21 KD to 30 KD; 212 amino acids with variable glycosylation sites) first identified and characterized as an important signalling molecule in the immune system, which plays a critical role especially in the induction of CRP and fibrinogen synthesis in the liver during the course of bacterial infection.[28,29]

In this study, we measured serum and synovial fluid IL-6 levels in a case-controlled study of 93 participants to explore the value of combined IL-6 levels in both serum and synovial fluid in differentiating between PJI and aseptic loosening, and found that the integration has high accuracy in identifying PJI (84.95% vs 93.55%). In recent years, several studies showed that synovial α-defensin was more sensitive and specific for diagnosis of hip and knee PJI and outperformed other serum and synovial fluid biomarkers. A sensitivity of 100% and a specificity of 95% for hip and knee PJI were demonstrated in a study performed by Bingham et al.[30] However, this test is not readily available in many hospitals and is expensive (USD $760 per test).[31] Our test results showed that the combined quantification of serum and synovial fluid IL-6 level is probably also a promising and more economical (USD $20.27 per test) solution that would help with the PJI diagnosis.

A prospective, case-controlled study suggested that serum IL-6 was a valuable and even more accurate marker than either the ESR or CRP levels for the detection of PJI.[32] As reported in a previous meta-analysis that assessed the findings of three studies, the pooled sensitivity and specificity of serum IL-6 were 0.97 and 0.91, respectively, for PJI detection.[33] A systematic review carried out in 2018, exploring the diagnostic accuracy of serum, synovial, and tissue testing for chronic PJI, demonstrated that serum IL-6 had the appropriate diagnostic value with a sensitivity of 0.875, despite the excellent specificity (0.971) of synovial IL-6.[34] In this study, the AUC for IL-6 was 0.931 (95% CI 0.858 to 0.973), and showed excellent sensitivity of 0.973. The consistency of these results once again confirmed that IL-6 is one of the best serum biomarkers for chronic PJI detection, and serum IL-6 assessment should be included as a regular test for patients with prosthetic failure.

Most recently, Gollwitzer et al[35] assessed the diagnostic efficacy of synovial fluid IL-6 analysis in identifying staphylococcal hip and knee PJI using cytometric bead arrays, and it was found that synovial fluid IL-6 analysis improved diagnostic accuracy. Xie et al[36] also indicated synovial fluid IL-6 level assay had higher diagnostic value than serum IL-6 level for detecting PJI, with an AUC of 0.96, a sensitivity of 91%, and a specificity of 90% using a cut-off value of 2,300 pg/ml. These results were similar to what we have found in our current study, which showed that SF IL-6 had a mean sensitivity of 94.59% (95% CI 81.8% to 99.3%), a specificity of 92.86% (95% CI 82.7% to 98.0%), and an AUC of 0.982 (95% CI 0.929 to0.998) at the cut-off value of 1,855.36 pg/ml in differentiating chronic PJI from prosthesis aseptic loosening. However, there are differences between our findings and those of other centres. In a prospectively controlled study, Wimmer et al[37] performed QuickLine IL-6 lateral flow immunoassay on 26 included patients and indicated IL-6 concentrations > 10,000 pg/ml in synovial fluid for predicting a PJI. Similarly, Lenski et al[38] analyzed synovial fluid IL-6 in 31 PJI patients, proved that the optimal threshold for the diagnosis of PJI by SF IL-6 was 30,750 pg/ml, and deduced that when SF IL-6 < 10,000 pg/ml, the possibility of diagnosis of PJI could be excluded. The cut-off value for synovial IL-6 to detect PJI varies greatly between our studies, for a number of possible reasons. First, the included population is very different, and patients with chronic PJI have less obvious symptoms and a mild inflammatory response. Second, timing of sampling is important. The cytokines are under neuroendocrine control and thus have a diurnal rhythm, and the release of IL-6 peaks early in the morning.[39] In our study, specimens were collected early in the morning. Third, proper sample handling and storage are critical for reliable measurement of circulating cytokines. A delay of sample processing containing cellular components will lead to overexpression of IL-6, and cytokine binding to or release from their soluble receptors can result in an under- or overestimation during spiking assays.[40] In this study we kept our samples at room temperature, and the samples were centrifuged within one hour and tested within two hours.

The disadvantages of serum tests are that they are nonspecific and several biomarkers may increase in response to inflammatory reactions associated with other systems or organs such as the urinary tract or lungs. Because of that, a synovial fluid test for infection appears to be more appealing. Our controlled study used a combination of IL-6 in serum and synovial fluid to improve the diagnostic accuracy of chronic PJI and, to our knowledge, this is the first study to define the synovial fluid IL-6 threshold for chronic PJI.

The limitations of this study deserve to be mentioned. Firstly, there is no gold standard for the diagnosis of PJI following total joint replacements. We used the 2013 MSIS criteria for chronic PJI as the diagnostic standard because of its wide acceptability, and some of the patients who were grouped into the aseptic revision group might have had undetected chronic PJI. But this is a challenging situation that perhaps all studies evaluating a diagnostic test for PJI infection would face. Secondly, the sample size of our study was small for a study investigating arthroplasties. But since this is a preliminary test that showed promising results, a larger prospective multicentre study can be carried out to further validate the test results. Finally, patients with recent antibiotic use were excluded from this study for the elimination of confounding factors. However, this could create a precondition of the test which is different from real-world practice, thus limiting the generalizability of this study's results.

In conclusion, diagnosis of infection in patients undergoing revision total joint replacement remains a challenge due to the low virulence of the most common infecting organisms. This study demonstrates the potential clinical benefit of performing combined synovial fluid and serum IL-6 assays preoperatively for distinguishing chronic PJI from aseptic loosening, and the cut-off values of synovial fluid and serum IL-6 were 1,855.36 pg/ml and 6.7 pg/ml, respectively. During this study the conjoint use of serum and synovial fluid IL-6 (both above cut-off value) appears to have outstripped some current standards of testing, and further validation of the results is critical to the clinical application.

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