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Original Article

Early diagnosis of septic arthritis using synovial fluid presepsin: A preliminary study☆

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ABSTRACT

Therapeutic outcomes for septic arthritis vary greatly depending on the span of time between disease-onset and surgery. The most important factor is making an early and definitive diagnosis; however, some cases may be difficult to diagnose. We investigated presepsin, a biomarker of sepsis, to determine whether or not presepsin in synovial fluid would be useful for the diagnosis of septic arthritis. We selected 18 patients with septic arthritis including periprosthetic joint infections (SA group) and 28 patients with osteoarthritis (OA group). We measured the concentrations of synovial fluid presepsin, blood presepsin and procalcitonin (PCT) in the two groups. We compared the sensitivities and specificities of synovial fluid presepsin, blood presepsin and PCT. Synovial fluid and blood presepsin and blood PCT were all significantly higher in the SA group. Synovial fluid presepsin exhibited both 100% sensitivity and 100% specificity in the SA group, which were higher rates than those for blood presepsin and PCT. We found that synovial fluid presepsin is markedly elevated in case of septic arthritis, and therefore, it has potential as a new biomarker of septic arthritis.

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1. Introduction

Delay in the treatment of septic arthritis allows cartilage damage to progress, resulting in irreversible functional impairments. Thus, the timing of treatment has a major influence on prognosis [1]. And if treatment for periprosthetic joint infection (PJI) is started at an early stage, it may be possible to save the implants [2]. Therefore, early diagnosis is the most important factor for functional prognosis in patients with septic arthritis including PJI. Generally, the primary evidence used to make the diagnosis of septic arthritis consists of local abnormalities in the affected joint, such as swelling, local heat, redness, and sinus tract; elevated white blood cell (WBC) count, elevated C-reactive protein (CRP) levels, and prolonged erythrocyte sedimentation rates (ESRs) on blood tests; and imaging findings. However, the presence of local abnormalities such as swelling and heat may not be diagnostically useful in patients with osteoarthritis or rheumatoid arthritis because these findings are relatively common in such patients. Elevated WBC and CRP are also common in patients with rheumatoid arthritis and those who have recently undergone surgery. Moreover, specific signs of joint infection such as osteolysis are not often apparent on X-ray imaging or magnetic resonance imaging (MRI) in the early stages of the disease process. If the synovial fluid can be easily collected such as the knee joint, then synovial fluid tests can be performed. Synovial fluid testing includes cell and neutrophil count and the identification of crystals are helpful in differentiating septic arthritis from osteoarthritis and crystal arthritis [3,4]. However, there are no clear cutoff values for these tests. Synovial fluid culture is also useful, but false negatives and false positives can both occur [5,6], and it takes several days for the results to be known. Currently, there is no gold standard method for the early diagnosis of septic arthritis, and the definitive diagnosis of septic arthritis or PJI is more difficult to reach.

The soluble CD14 subtype (presepsin) is generated as a product from CD14 when bacteria are phagocytosed by monocytes [7]. Yaegashi et al. reported that the concentration of presepsin in the blood increases significantly in sepsis, and that it is a useful biomarker for making an early diagnosis and evaluating disease

☆ All authors meet the ICMJE authorship criteria.

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severity [8]. They found that presepsin was not elevated in the blood of patients with systemic inflammatory response syndrome in the absence of infection. They reported that presepsin was highly specific for infection. Marazzi et al. found that blood presepsin levels were significantly higher in patients with PJI than in those with aseptic loosening, which may be useful for the diagnosis [9]. However, we hypothesized that the concentration of presepsin in the synovial fluid would increase in septic arthritis, and that the sensitively and specificity of synovial fluid might be higher than that of blood presepsin because bacteria are phagocytosed within the synovial fluid.

Our objectives in this study were to examine whether or not the concentration of presepsin in the synovial fluid increased in patients with septic arthritis including PJI. Moreover, we investigated whether synovial fluid presepsin is useful for early diagnosis of septic arthritis.

2. Materials and methods

2.1. Study design

This was a prospective study of 46 joints in 46 patients diagnosed with septic arthritis including PJI, or osteoarthritis from 2015. They comprised 18 men and 28 women with a mean age of 71.5 ± 9.3 years (range 48–90 years). We divided the group into two subgroups comprising 18 joints with septic arthritis (SA group, including 8 with PJI) and 28 joints with osteoarthritis (OA group). The mean age was 75.0 ± 8.6 years in the SA group and 69.3 ± 9.2 years in the OA group. It was significantly higher in the SA group (p value < 0.05). Five patients in the SA group were taking oral antibiotics before the synovial fluid was collected. The SA group comprised 11 knees, 1 hip, 1 shoulder, and there were 3 cases of prosthetic knee infection and 2 cases of prosthetic hip infection. All joints in the OA group were knee joints.

2.2. Diagnosis of septic arthritis and osteoarthritis

The diagnosis of septic arthritis was made according to Newman's diagnostic criteria for septic arthritis [10], and that of PJI was made according to the Musculoskeletal Infection Society (MSIS) criteria in 2011 [11]. And synovial fluid cultures were positive in all patients of infection. Osteoarthritis was diagnosed if the synovial fluid culture and the tests for crystals in the synovial fluid were both negative, and two senior doctors agreed with the diagnosis.

2.3. Collection and measurement of blood and synovial fluid

All patients had blood collection and arthrocentesis performed at the initial visit. Procalcitonin (PCT) levels in blood were measured the same day. The synovial fluid crystal tests and synovial fluid cultures were performed at the central laboratory of our hospital. The blood and synovial fluid samples were immediately centrifuged at 3000 rpm for 15 min, 4 °C and the supernatants were frozen and stored at −80 °C until testing. The concentrations of presepsin in the blood and synovial fluid were measured using a Pathfast® immunoanalyzer presepsin kit (Mitsubishi Chemical Corporation, Tokyo, Japan). Blood and synovial fluid presepsin and blood PCT results were compared between the SA and OA groups.

2.4. Ethical statement

This study was approved by the institutional Review Board at Yamaguchi University Hospital. We informed all patients about the study and obtained their consent.

2.5. Statistical analysis

All data were analysed using StatFlex ver.6 (Artech Co.,Ltd., Osaka, Japan). The continuous variables were presented as mean ± SD. For the statistical analysis, Student's t-test was used to compare the two groups, with $p < 0.05$ regarded as significant. To compare the utility of the test results, receiver operating characteristic (ROC) curves were produced for blood and synovial fluid presepsin, and blood PCT. And the areas under the curve (AUC) were determined. The sensitivity and specificity of presepsin and PCT were calculated by assigning cutoff values using the Youden index which is equal to sensitivity plus specificity1 [12].

3. Results

The mean synovial fluid presepsin level was 2430.4 ± 1169.8 pg/ml in the SA group and 704.6 ± 207.7 pg/ml in the OA group. The mean synovial fluid presepsin level was significantly higher in the SA group (Fig. 1). The mean blood presepsin was 529.4 ± 470.8 pg/ml in the SA group and 136.4 ± 52.4 pg/ml in the OA group, which was also significantly higher in the SA group (Fig. 2). The mean blood PCT was 0.16 ± 0.17 ng/ml in the SA group and 0.03 ± 0.01 ng/ml in the OA group, and the results were significantly higher in the SA group (Fig. 3). The AUCs for synovial fluid presepsin and blood presepsin were 1.0 and 0.86, respectively (Figs. 4 and 5). The AUC for the blood PCT was 0.88 (Fig. 6). With a cutoff value of 1099.0 pg/ml, the synovial fluid presepsin was found to be 100% sensitivity and 100% specificity. With a cutoff value of 162.6 pg/ml, the blood presepsin was 77.8% sensitivity and 75.0% specificity. With a cutoff value of 0.039 ng/ml, the blood PCT was 94.4% sensitivity and 53.6% specificity. The causative organisms were *Methicillin-susceptible Staphylococcus aureus*: 8 cases, *Methicillin-resistant Staphylococcus aureus*: 3 cases, *Streptococcus species*; 4 cases, *Escherichia coli*; 2 cases and *Corynebacterium straitum*; 1 case in septic arthritis. There was not significant difference of presepsin levels among these causative organisms (data not shown).

4. Discussion

Septic arthritis is a relatively rare condition. Previous studies reported that the incidence was 2–6 cases per 100,000 people per year [13–15]. However, once it does develop, the articular cartilage becomes damaged. Delayed and inadequate treatment can lead to irreversible functional impairment and fatal condition [1].

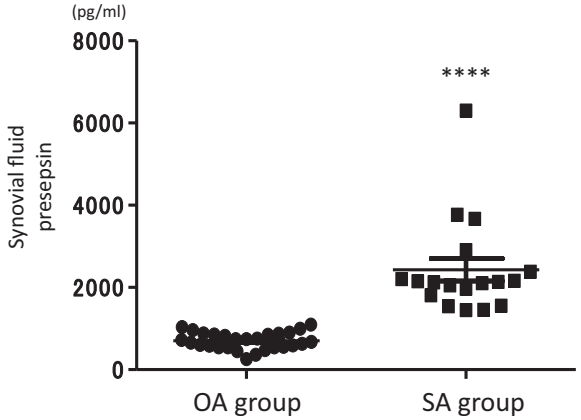

Fig. 1. A comparison of the concentrations of synovial fluid presepsin between the two groups. Synovial fluid presepsin levels in the septic arthritis (SA) group were significantly higher than those in the osteoarthritis (OA) group (****p < 0.0001).

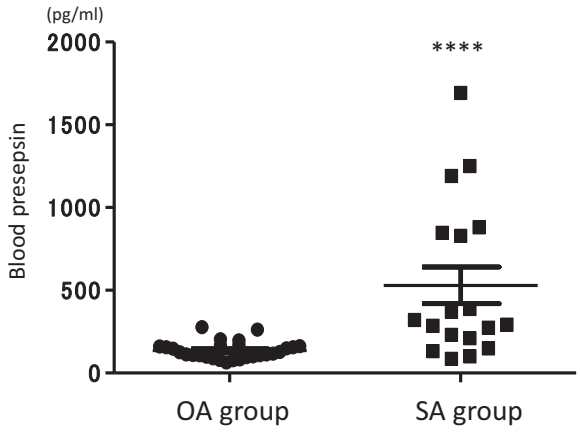

Fig. 2. A comparison of the concentrations of blood presepsin between the two groups. Blood presepsin levels in the septic arthritis (SA) group were significantly higher than those in the osteoarthritis (OA) group (****$p < 0.0001$).

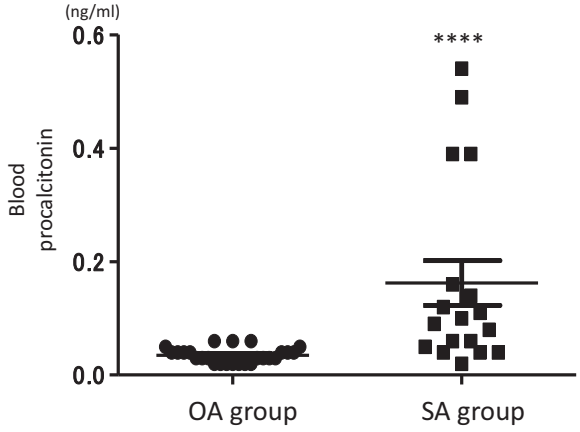

Fig. 3. A comparison of the concentrations of blood procalcitonin between the two groups. Blood procalcitonin levels in the septic arthritis (SA) group were significantly higher in the osteoarthritis (OA) group (****$p < 0.0001$).

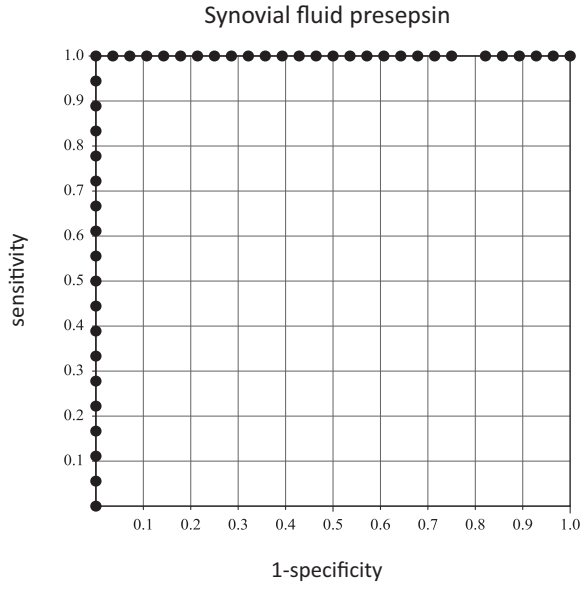

Fig. 4. Receiver operating curve for synovial fluid presepsin is shown. The area under the curve is 1.0.

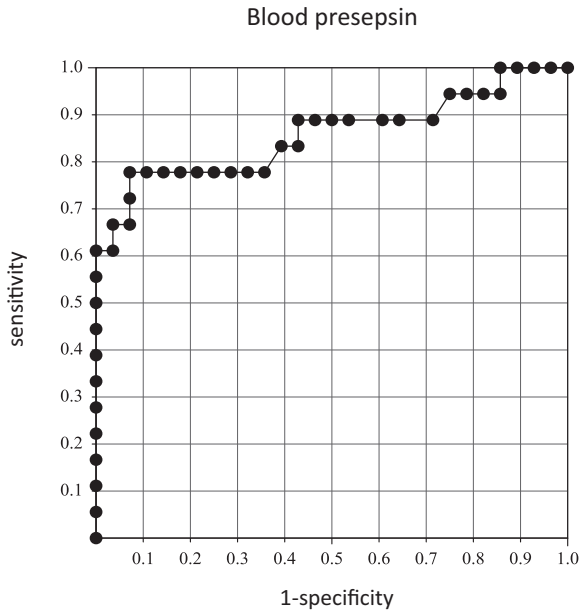

Fig. 5. Receiver operating curve for blood presepsin is shown. The area under the curve is 0.86.

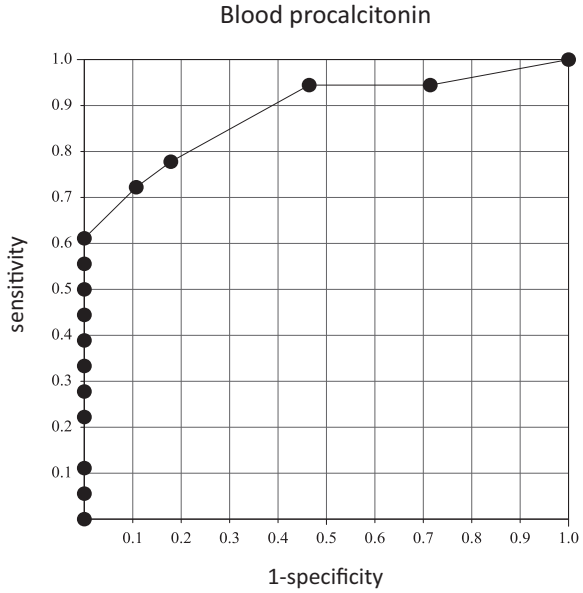

Fig. 6. Receiver operating curve for blood procalcitonin is shown. The area under the curve is 0.88.

Regarding PJI, Gravin et al. found that patients who underwent surgery soon after disease onset had better implant preservation rates [2]. Therefore, the consensus is that the surgery should be performed as soon as possible once a definitive diagnosis of septic arthritis including PJI is made. However, in some cases it is difficult to reach the early diagnosis required to make the decision to perform treatment expeditiously.

Local signs are the first point of reference for septic arthritis. The presence or absence of local pain, swelling, heat, redness, and sinus tracts are helpful in the diagnosis of septic arthritis. The presence of sinus tracts in particular is strongly suggestive of infection and is included in the MSIS diagnostic criteria for PJI. However, other local signs are not highly specific. Carpenter et al. reported in their

review article that in patients with septic arthritis, swelling, heat and redness were 45.0–92.0%, 18.0–92.0% and 13.0–64.0% sensitivity respectively [16]. As swollen signs are also not unusual in cases of osteoarthritis, rheumatoid arthritis, and crystal arthritis, it is often difficult to definitively diagnose septic arthritis. Other test results suggestive of septic arthritis include elevations of WBC and CRP, and a prolonged ESR in the blood, as well as an increased cell count and increased neutrophil fraction in the synovial fluid. These are also among the MSIS diagnostic criteria for PJI [11]. However, their sensitivities and specificities are not high. Previous study reported that blood WBC count was 75% sensitivity and 55% specificity [3], ESR was 66% sensitivity and 48% specificity [17], and CRP was 87% sensitivity and 39% specificity [18]. And synovial fluid WBC count of $<50 \times 10^9$/L was 56% sensitivity and 90% specificity [16]. Microbiological culture is one of the most important examinations for diagnosis. Synovial fluid and blood culture are important role for definitive therapy of septic arthritis. Gram stain of synovial fluid is also helpful for empiric antibiotic selection. Therefore, Microbiological culture is essential for treatment of septic arthritis. However, synovial fluid culture has a reported sensitivity of 67% [19]. Moreover, it is disadvantage for early diagnosis that several days are generally required for the result to become known. Therefore, comprehensive examinations are needed to diagnose septic arthritis.

In this study, we compared synovial fluid presepsin concentrations to those in patients with OA. We found that presepsin were notably elevated in the synovial fluid of patients with septic arthritis. To the best of our knowledge, this is the first report to identify presepsin in the synovial fluid and to associate its elevation with septic arthritis. Presepsin is a soluble CD14 subtype that is mainly produced when CD14 is decomposed by monocytes that have phagocytosed bacteria, along with the action of enzymes such as elastase [7]. Yaegashi et al. reported that presepsin in the blood rises markedly in patients with sepsis, and it is regarded as more useful than PCT as a biomarker reflecting disease severity [8]. Unlike PCT or CRP, presepsin is not mediated by inflammatory cytokines, and it is produced in the sites where bacteria are present. Therefore, they described that elevated presepsin is useful because it specifically reflects the presence of infection, even when CRP is elevated for reasons unrelated to infection, such as after trauma. Koakutsu et al. also reported that although blood presepsin concentration rose after spinal surgery, they returned to preoperative levels within 1 week postoperatively [20]. They also suggested that elevated blood presepsin levels at this point are suggestive of surgical site infections. In septic arthritis, Marazzi et al. was reported that a comparison of PJI and aseptic loosening showed that blood presepsin levels were significantly higher in patients with PJI [9]. They also reported that the AUC for blood presepsin was higher than that for blood CRP or interleukin-6 (IL-6), indicating its usefulness as a biomarker of infection. Blood PCT is also reported to be useful for the diagnosis of septic arthritis [18]. Our results in this study also showed that blood presepsin and PCT were significantly higher in the SA group and that the AUCs were higher than the OA group. On the other hand, synovial fluid presepsin was significantly higher in the SA group. Moreover, the AUC for synovial fluid presepsin was 1.0. It was a better result compared to that of blood presepsin or PCT. The sensitivity and specificity of synovial fluid presepsin were both 100% for a cut off value of 1099 pg/dl. This indicates that synovial fluid presepsin is higher diagnostic value than the others. PCT is cytokine-mediated and is produced in the liver and other organs [21]. However, because presepsin is directly produced intraarticularly where bacteria are most numerous in septic arthritis, the infection might more accurately be reflected by synovial fluid presepsin than by blood presepsin and PCT. We suggest that synovial fluid presepsin is a potential new biomarker for septic arthritis including PJI.

For early diagnosis, it is important that the results of tests with high sensitivity and specificity be rapidly available and that the results can be determined quickly. Culture tests are also useful in diagnosing septic arthritis. However, it takes several days for these results to be known. Presepsin can be measured in around 15 min with the Pathfast® kit used in this study. This is a major advantage for early diagnosis.

One limitation of this study was the small number of patients. Further studies with larger numbers of subjects are required. This was a preliminary study that evaluated OA patients as a comparison group. There are no reports on investigating blood and synovial fluid presepsin in rheumatoid arthritis or crystal arthritis compared to septic arthritis. Further studies are required to investigate the value of presepsin in comparison with other conditions that are clinically difficult to distinguish, such as crystal arthritis, rheumatoid arthritis, and aseptic loosening of prosthetic joints.

In conclusion, presepsin was elevated in both the blood and synovial fluid of patients with septic arthritis including PJI compared with those of patients with osteoarthritis. Synovial fluid presepsin exhibited higher sensitivity and specificity than that of blood presepsin and PCT. Synovial fluid presepsin may be a new potential biomarker of septic arthritis and useful for early diagnosis.

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Conflicts of interest

The authors declare no conflicts of interest.

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