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Do inflammatory markers play a role in the detection of periprosthetic infections?

İnflamatuar belirteçlerin periprostetik enfeksiyonların belirlenmesinde rolü var mıdır?

Duran Topak [1], Ahmet Salan [2], Fatih Doğar [1], Selçuk Nazik [3]

[1] Kahramanmaras Sutcu Imam University, Faculty of Medicine, Department of Orthopaedic and Traumatology, Kahramanmaras, Turkey
[2] Kahramanmaras Sutcu Imam University, Faculty of Medicine, Department of Nukleer Medicine, Kahramanmaras, Turkey
[3] Kahramanmaras Sutcu Imam University, Faculty of Medicine, Department of İnfections Diseases and Clinical Microbiology, Kahramanmaras, Turkey

ORCID ID of the author(s)
DT: 0000-0002-1442-3392
AS: 0000-0002-5022-1851
FD: 0000-0003-3848-1017
SN: 0000-0003-0587-0104

Corresponding author/Sorumlu yazar:
Duran Topak
Address/Adres: Kahramanmaraş Sütçü İmam Üniversitesi, Tıp Fakültesi, Ortopedi ve Travmatoloji Anabilim Dalı, Kahramanmaraş, Türkiye
e-Mail: drdtopak@gmail.com

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Abstract

Aim: Periprosthetic joint infection after total hip or knee arthroplasty is one of the most feared complications. The aim of this study was to evaluate the efficacy of inflammatory biomarkers in identifying periprosthetic joint infection.

Methods: This cross-sectional and bi-centered study included 131 patients, who had suspected prosthesis infection and underwent three-phase bone scintigraphy. Patients were divided into three groups according to the Musculoskeletal Infection Society criteria and scintigraphic study results: Group 1 comprised cases with prosthetic infection, Group 2 included aseptic loosening cases and Group 3 included cases with healthy prostheses.

Results: White blood cell average was 11.5 (3.2) 10^9/L in group 1, 8. (2.1) 10^9/L in group 2 and 7.9 (2.1) 10^9/L in group 3, among which it was significantly higher in Group 1 compared to Groups 2 and 3, (P<0.001, P<0.001), while there was no significant difference between groups 2 and 3 (P=0.753). C reactive protein values (CRP) were 46.6 (50.0) mg/L in group 1, 18.8 (17.5) mg/L in group 2 and 15.3 (17.1) mg/L in group 3, significantly higher in group 1 than the other groups (P<0.001, P<0.001), and similar in Groups 2 and 3 (P=0.876). The mean erythrocyte sedimentation rate values did not differ significantly between the groups.

Conclusion: The use of three-phase bone scintigraphy and inflammatory biomarkers such as C reactive protein and white blood cell have been shown to be effective in predicting prosthetic infection.

Keywords: White blood cell, Biomarker, C-reactive protein, Prosthetic infection

Öz

Amaç: Total kalça veya diz artroplastisi sonrası periprostetik eklem enfeksiyonu en korkulan komplikasyonlardan biridir. Bu çalışmanın amacı, inflamatuar biyobelirteçlerin periprostetik eklem enfeksiyonunun tanımlanmasındaki etkinliğini değerlendirmektir.

Yöntemler: Çalışma kesitsel ve iki merkezli planlandı. Protez enfeksiyonundan şüphelenilen ve üç fazlı kemik sintigrafisi uygulanan 131 hasta dahil edildi. Hastalar Kas İskelet Enfeksiyonları Derneği kriterlerine ve sintigrafik çalışma sonuçlarına göre üç gruba ayrıldı: Grup 1 protez enfeksiyonu olan olgular, Grup 2 aseptik gevşemesi olan olgular, Grup 3 sağlıklı protezleri olan olgulardan oluşmaktadır.

Bulgular: Beyaz küre sayısı ortalaması grup 1'de 11,5 (3,2) 10^9/L, grup 2'de 8,3 (2,1) 10^9/L ve grup 3'de 7,9 (2,1) 10^9/L bulundu. Beyaz küre sayısı değerleri grup 1'de diğer gruplara göre istatistiksel olarak anlamlı derecede yüksek bulundu (P<0,001, P<0,001), grup 2 ve 3 arasında anlamlı fark yoktu (P=0,753). C-reaktif protein değerleri grup 1'de 46,6 (50,0) mg/L, grup 2'de 18,8 (17,5) mg/L ve grup 3'de 15,3 (17,1) mg/L olarak bulundu ve C-reaktif protein değerleri gruplar arasında karşılaştırıldığında istatistiksel olarak anlamlı derecede yüksek bulundu. Grup 1'de diğer gruplara göre (P<0,001, P<0,001) ve grup 2 ile 3 arasında anlamlı fark yoktu (P=0,876). Ortalama eritrosit sedimantasyon hızı değerleri karşılaştırıldığında gruplar arasında anlamlı fark bulunmadı.

Sonuç Üç fazlı kemik sintigrafisi, C-reaktif protein ve beyaz küre sayısı gibi inflamatuar biyobelirteçlerin kullanılmasının, protez enfeksiyonunu öngörmede etkili olduğu gösterilmiştir.

Anahtar kelimeler: Beyaz küre sayısı, Biyobelirteç, C-reaktif protein, Protez enfeksiyonu

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Introduction

The prolongation of life expectancy and increase in living standards of humans have led to a significant increase in orthopedic prosthesis operations in recent years [1]. Joint replacement in cases of hip and knee osteoarthritis is one of the most cost-effective and safe surgical procedures that relieve or improve the pain symptoms of the patients, restore joint function and improve quality of life [2,3].

Periprosthetic joint infection (PJI) is one of the most terrible complications after total hip arthroplasty or total knee arthroplasty, and has a very negative impact on the physical, emotional, social and economic aspects of the patient's life [4,5].

Early diagnosis is a positive factor for preserving prosthesis and joint function. It has been shown that a mix of multiple tests positively improves diagnostic accuracy, as any test or indicator used in the clinic or laboratory does not provide ideal sensitivity and specificity for PJI diagnosis [6].

The aim of this study was to assist early diagnosis and treatment by determining the sensitivity of inflammatory biomarkers in identifying PJI.

Materials and methods

Data from the Kahramanmaras Sutcu Imam University Medical Faculty Hospital and Kahramanmaras Necip Fazıl City Hospital in the same province were used. A hundred thirty-one patients with suspected prosthesis infections who underwent three-phase bone scintigraphy between January 2015 and June 2017 were included in this study, and divided into three groups: The patients with PJI were classified as Group 1, patients with aseptic loosening (AL) were classified as Group 2 and those with healthy prosthesis were classified as Group 3. Kahramanmaras Sutcu Imam University Medical Faculty Clinical Research Ethics Committee approval was received for the study (Session: 2019/2, Date: 06.02.2019, Decision no: 11).

Demographic data, laboratory results and three-phase bone scintigraphy results were recorded using patient files and hospital database. Patients whose examination findings and laboratory results were not available were excluded from the study, even if their three-phase bone scintigraphy could be reached. Three-phase bone scintigraphy was performed to strengthen the diagnosis in patients suspected of prosthesis infection by physical examination and laboratory results. According to these results, joint aspiration was performed.

White blood cells (WBC) (normal range: 3.5-8.9 10^9/L), C-reactive protein (CRP) (normal range:0-5 mg/dL), and erythrocyte sedimentation rate (ESR) (normal range:0-20 mm/h) were used for as inflammatory markers. The white blood cells, CRP and ESR were analyzed using the Beckman coulter LH 750, Beckman coulter image 800 and Thermo linear devices respectively, according to the guidelines of the producer firms.

The diagnosis of PJI was made by evaluating the Musculoskeletal Infection Society (MSIS) criteria (Table 1) and scintigraphy results [7]. In joint aspirations, twice culture positivity was observed in twelve patients. Twenty-seven patients were determined to have periprosthetic infection with minor criteria. Five patients had fistula tract. The inclusion of types of group 1 according to MSIS criteria and typing of reproductive microorganisms are shown in Table 2. Group 1 was formed according to these results. Two-stage revision knee arthroplasty was performed in 26 patients and revision surgery could not be performed in 14 patients due to additional diseases. Four patients refused surgical treatment in Group 1. Eighteen patients in the aseptic loosing group underwent single-stage revision surgery and 16 patients rejected the revision surgery in Group 2.

Table 1: MSIS Workgroup standard definition for PJI

One of the following must be met for diagnosis of PJI

1. There is a sinus tract communicating with the prosthesis
2. A pathogen is isolated by culture from at least two separate tissue or fluid samples obtained from the affected prosthetic joint
3. Four of the following six criteria exist:
   - Elevated ESR and CRP (ESR>30 mm/hour; CRP>10 mg/L)
   - Elevated synovial fluid WBC count (>3000 cells/L)
   - Elevated synovial fluid neutrophil percentage (>65%)
   - Presence of purulence in the affected joint
   - Isolation of a microorganism in one periprosthetic tissue or fluid
   - Greater than five neutrophils per high-power field in five high-power fields observed from histologic analysis of periprosthetic tissue at 9400 magnification.

MSIS: Musculoskeletal Infection Society, PJI: Periprosthetic joint infection, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, WBC: White blood cell

Table 2: Group 1 according to MSIS criteria

		n (%) n=44
A pathogen is isolated by culture from at least two separate tissue or fluid samples obtained from the affected prosthetic joint	MRSE+MRSE: 4 MRSA+MRSA:3 MRSE+ESBL (+)*Escherichia coli*: 2 Gr (+) coccus non-typable: 2 CNS+CNS: 1	12 (27.2)
There is a sinus tract communicating with the prosthesis		5 (11.4)
Minor criteria of MSIS		27 (61.4)
Elevated ESR and CRP (ESR>30 mm/hour; CRP>10 mg/L)	n:24	
Elevated synovial fluid WBC count (>3000 cells/L)	n:21	
Elevated synovial fluid neutrophil percentage (>65%)	n:21	
Presence of purulence in the affected joint	n:26	
Isolation of a microorganism in one periprosthetic tissue or fluid	Gr (+) coccus non-typable: 8 Gr (-) bacilli: 2 MRSE:3 MSSA:2 ESBL (+) *Escherichia coli*: 1 ESBL (+) *Klebsiella pneumoniae*: 1 *Streptococcus agalactiae*:1 *Streptococcus pyogenes*:1	
Greater than five neutrophils per high-power field in five high-power fields observed from histologic analysis of periprosthetic tissue at 400 magnification	-	

MRSE: Methicillin Resistant *Staphylococcus epidermidis*, MRSA: Methicillin Resistant *Staphylococcus aureus*, ESBL: Extended Spectrum Beta-Lactamase, CNS: Coagulase Negative Staphylococcus, MSSA: Methicillin Sensitive *Staphylococcus aureus* MSIS: Musculoskeletal Infection Society

E-Cam double-headed Gamma Camera (Siemens, Erlangen, Germany) was used for the evaluation of three-phase bone scintigraphy, and interpretations in favor of infection were divided into three groups as mild, moderate, and high probability.

Statistical analysis

SPSS 22.0 package program was used for statistical evaluation of the data obtained from the study (SPSS Inc, Chicago, Illinois, USA). Continuous data were summarized as mean, standard deviation while categorical data were summarized in numbers and percentages. Student t test was used to compare continuous variables in independent groups. For comparisons between the groups, chi-square (χ^2) test was used to evaluate two categorical independent groups. The mean values of continuous variables were compared with one-way ANOVA, and post-hoc Tukey test was used to compare the groups. Receiver operating characteristic (ROC) curve was used to evaluate the markers' ability to predict prosthetic infection. *P*-value <0.05 was considered statistically significant.

Results

A total of 131 patients (38.2% (n=50) male) were included in the study, the mean age of which was 64.8 (15) years (min-max: 20-90 years). The groups were similar in terms of age and gender (P values for age and gender, respectively; Group 1-2: 0.369, 0.586, Group 1-3: 0.961, 0.609; Group 2-3: 0.449, 0.330).

The findings of Group 1 according to MSIS criteria were presented in Table 2.

Of the three-phase bone scintigraphies, 49.6% (n=65) were for knee prosthesis and 50.4% (n=66) were for hip prosthesis. More than half (55%) of the prostheses were applied to the right knee and hip while 37.4% (n=49) were applied to the left knee and hip, and 7.6% (n=10) were applied bilaterally.

It was found that 33.6% (n=44) of the three-phase bone scintigraphies performed for various reasons were compatible with infection while 26% (n=34) were compatible with loosening, whereas 40.5% (n=53) were intact.

The degree of infection was evaluated according to the level of radioactive material uptake in perfusion, soft tissue and bone phase. Accordingly, 59% (n=26) of 44 cases were found to be mild, 20.5% (n=9) were moderate and 20.5% (n=9) were high. The laboratory values of all three groups are presented in Table 3.

Cut-Off, sensitivity, specificity, AUC, 95% confidence interval and p values of the ability of inflammatory markers to predict prosthetic infection are presented in Table 4 and the image of the ROC curve is shown in (Figure 1).

Table 3: Laboratory values of cases

	Group 1 (n=44)	Group 2 (n=34)	Group 3 (n=53)	*P*-value 1-2	1-3	2-3
WBC (10^9/L)	11.5 (3.2)	8.3 (2.1)	7.9 (2.1)	<0.001	<0.001	0.753
CRP (mg/L)	46.4 (50.0)	18.8 (17.5)	15.3 (17.1)	0.001	<0.001	0.876
ESR (mm/sa)	36.7 (18.6)	38.7 (23.5)	28.6 (17.9)	0.900	0.111	0.055
NLR	2.8 (1.8)	3.1 (1.7)	2.8 (2.0)	0.756	1.000	0.748
PLR	165.8 (75.6)	185.0 (67.7)	143.0 (66.4)	0.452	0.251	0.019
MPV (fL)	9.9 (1.1)	10.0 (1.0)	10.0 (1.1)	0.886	0.894	0.997

* ANOVA test and posthoc Tukey test were used to compare the groups. Group 1: Prosthesis infection, Group 2: Aseptic loosening, Group 3: Intact Prosthesis, WBC: White Blood Cell, CRP: C-reactive protein, NLR: Neutrophile-to-Lymphocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio, MPV: Mean Platelet Volume, *P*<0.05 value was considered statistically significant

Table 4: Cut-Off, sensitivity, specificity, AUC, 95% confidence interval and p values of ESR, CRP, WBC, MPV, NLO, and PLO for predicting prosthetic infection

	Cut-off	Sensitivity %	Specificity %	AUC	%95 CI	*P*-value
WBC (10^9/L)	8.6	91	61	0.845	77.7-91.4	0,001
CRP (mg/L)	12.2	84.1	55.2	0.777	69.2-86.1	0.001
ESR (mm/sa)	19.5	84.8	34.5	0.589	48.9-68.9	0.097
NLR	2.4	50	36.8	0.457	35.2-56.1	0.419
PLR	138.3	59.1	49.4	0.527	42.2-63.2	0.612
MPV (fL)	10.1	50	55.2	0.492	38.7-59.6	0.878

* ROC curve was used to calculate the values, ANOVA test and posthoc Tukey test were used to compare the groups. Group 1: Prosthesis infection, Group 2: Aseptic loosening, Group 3: Intact Prosthesis, WBC: White Blood Cell, CRP: C-reactive protein, NLR: Neutrophile-to-Lymphocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio, MPV: Mean Platelet Volume, *P*<0.05 value was considered statistically significant

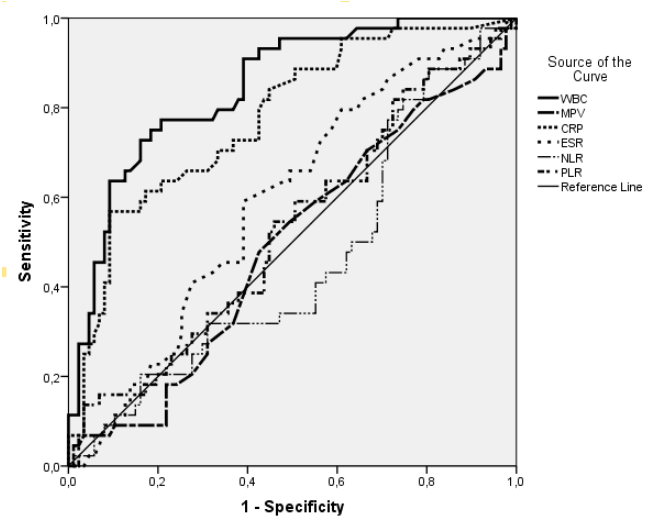

Figure 1: ROC curve of patients with prosthetic infection

Discussion

The number of joint prostheses is increasing due to increased life expectancy, lifestyle changes in the elderly population, and increased expectations such as mobility at an older age. With increasing prosthesis application, the lifetime of prosthesis in the body is prolonged. As a result, the possibility of hematogenous infections and AL increases during its lifetime [8].

Hip and knee arthroplasties are successful elective surgical procedures and have a survival rate of over 95% at 10-year follow-up [9]. Complications may be observed, although not often. Painful orthopedic prosthesis can be caused by intraarticular (infection, instability, AL) or extraarticular (tendinitis, periprosthetic fracture, degenerative joint disease, neurological problems) causes [1,10,11].

Early diagnosis is a positive factor for preserving prosthesis and joint function. Despite its clinical importance, difficulties remain in the emergency diagnosis of orthopedic prosthesis infection, and definitive diagnostic testing is still lacking. Although many serologic markers for PJI have been evaluated in the past including interleukin-6 (IL-6), ESR, and CRP are often used as a screening test since they are more susceptible to infection, faster, cheaper and more cost-effective than other serological biomarkers. Radiological methods also have a limited contribution to the diagnostic evaluation of infection. So, co-evaluation of multiple tests and radiology may reasonably improve diagnostic accuracy [7,12,13].

In the study of Xiong et al. [14] comparing PJI and AL groups, it was found that ESR values were 40.0 and 13.9 mm/h respectively and were significantly higher in the PJI group. In another study, it was found that the cut-off value of the ESR was 41 mm/h and significantly higher in the PJI group compared to the AL group. In the same study, sensitivity for ESR was 63.6%, specificity was 70.2% and AUC:0.719 [15]. In our study, the mean ESR, cut-off value, sensitivity, specificity, and AUC values were very low compared to the literature. This was related to the fact that most of the patients in our study group had chronic infection.

Abnormal CRP increases after primary arthroplasty were evaluated in a retrospective study by Tae Won Kim et al. [16]. While 24% of the cases had CRP elevation associated with

PJI, 56% of the cases had CRP elevation due to non-prosthetic reasons (paralytic ileus, upper respiratory tract infection, deep vein thrombosis, acute renal failure). However, in 20% of cases, the cause could not be determined. When Marcus Lensky et al. [17] retrospectively evaluated a total of 719 patients, they showed that the mean CRP of 67 patients diagnosed with PJI was 10.6 (9.7) mg/dL (sensitivity 91.7%; specificity 15.4% and AUC:0.746). In another study by Alijanipour et al. [18] 84 patients with PJI and 1962 AL cases were compared. When the cut-off value for CRP was 23.5 mg/dL, the sensitivity was 87%, the specificity was 94%, and the AUC value was 0.950. In the study by Leilei Qin et al. [15] it was determined that CRP values were significantly higher in PJI group than AL group. In conclusion, it was emphasized that CRP is a good biomarker in predicting the correct diagnosis. Our results for CRP were similar to the literature.

Clinical studies have shown that CRP and ESR are rarely normal in the presence of infection. Hence, in patients suspected of infection or planned for revision arthroplasty for any reason, these should be screened before surgery [19].

Although the number of white blood cells (WBC) in synovial fluid is one of the minor criteria for the diagnosis of PJI according to MSIS criteria, serum WBC value may be helpful in the diagnosis of infection. While Friedrich et al. [20] were using microbiology and histology data as reference test in the prospective evaluation of 120 patients who underwent total knee or hip revision, they found 21% sensitivity and 94% specificity for serum WBC. Bottner et al. [21] reported that in a prospective study of 78 patients who underwent revision total knee or hip arthroplasty, the sensitivity and specificity for WBC were 70% and 60%, respectively, and these results limit the utility of WBC in the diagnosis of PJI. In another study, they reported that WBC average was 11 (6.4) 10^9/L, cut-off value was 11.5 10^9/L, sensitivity was 92.3% in patients with PJI and had good diagnostic potential (AUC:0.751). As a result of the study, it was found that WBC has diagnostic potential equivalent to CRP [16]. In our study, WBC average was significantly higher in PJI group compared to AL and healthy prosthesis groups.

Limitations

The retrospective design and the fact that some of the cases did not have culture results are the limitations of our study.

Conclusions

The use of three-phase bone scintigraphy and inflammatory markers such as CRP and WBC have been shown to be important in the diagnosis of prosthetic infection.

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