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Diagnostic value of preoperative blood parameters in periprosthetic joint infections

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ABSTRACT

Aim: Diagnosis of periprosthetic joint infection (PJI) is not easy and it is made by presenting of combined findings rather than a single finding. The aim of this study is to investigate the role of blood parameters in diagnosing PJI.

Material and Method: Revisions of total knee replacement and total hip replacement operated by the same surgeon between 2008 and 2018 were included in this study. Preoperative blood parameters of the patients were recorded. 69 primary arthroplasty patients with similar demographic characteristics to the patients were also included as the control group.

Results: 214 arthroplasty patients, 79.0% of whom were female (n=169), were included in this study. The patients were divided into 3 groups; 32.2% were primary arthroplasty, 36.9% were aseptic revision arthroplasty, and 30.8% were septic revision arthroplasty. There was no difference between the three groups in terms of demographic characteristics. In pairwise comparisons, preoperative erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), lymphocyte, and platelet-to-lymphocyte rate (PLR) parameters were found to be significantly different in the septic group when compared to both the aseptic group and the primary arthroplasty group. Further analyzes were performed to evaluate the diagnostic performances of ESR, CRP, lymphocyte, and PLR in PJI relative to aseptic patients by plotting to receive operating characteristic curves.

Conclusion: Lymphocyte, PLR, ESR, and CRP may have diagnostic value in predicting PJI. Therefore, these parameters may be helpful in deciding on revision arthroplasty for PJI.

Keywords: Periprosthetic joint infection, knee arthroplasty, hip arthroplasty, blood parameters, revision arthroplasty

INTRODUCTION

Periprosthetic joint infection (PJI) may develop after total knee arthroplasty and total hip arthroplasty. In the United States, the annual incidence rate of PJI has been shown to increase from 1.99% to 2.18% for hip arthroplasty and from 2.05% to 2.18% for knee arthroplasty from 2001 to 2009 (1) which are the most frequently performed orthopedic surgeries all over the world (2) , continues to be the most challenging and most devastating complication. 60-70 % of PJI occurs in the first two years (3,4). It constitutes a huge economic burden in social and individual health expenditures (5-7). The most common cause of early failure after total knee and hip arthroplasty is PJI (8,9).

Although PJI is the worst dream of orthopedic and traumatology surgeons, there is no gold standard method defined in the literature to make the diagnosis (10). Rather than a single finding for diagnosis; it is important to have clinical, radiological, and laboratory results together. The diagnosis is made by meeting the combined diagnostic criteria used by internal branches (rheumatological diseases), which orthopedic and traumatology surgeons are not very accustomed to. In 2011, the Musculoskeletal Infection Society (MSIS) group defined 2 major and 4 minor criteria Parvizi et al. (11) Later in 2018, Parvizi et al. (12) accepted the presence of two positive cultures or sinus tracts as the major criterion and diagnosis for PJI. Again, Parvizi et al. calculated weights of high serum C-reactive protein (CRP) (>1 mg/dL), D-dimer (>860 ng/mL), and erythrocyte sedimentation rate (ESR) (>30 mm/hour) were 2, 2, and 1 point, respectively. In addition, increased synovial fluid white blood cell count (>3000 cells/μL), alpha-defensin (signal-to-cut ratio >1), leukocyte esterase (++), polymorphonuclear percent (>80%), and synovial CRP (>6, 9 mg/L) scored 3, 3, 3, 2, and 1, respectively. Patients with a total score equal to or greater than 6 were considered infected. However, most of these tests are not easily available and expensive (12,13).

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The aim of this study is to investigate the role of serum biomarkers in the diagnosis of PJI, which are simple, inexpensive, and easily obtained before the operation and do not impose additional time and cost on the patient.

MATERIAL AND METHOD

The study was carried out with the permission of Ankara City Hospital No:1 Clinical Researches Ethics Committee (Date: 28.04.2021, Decision No: E1-21-1783). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Revisions of total knee arthroplasty and total hip arthroplasty operated by the same surgeon between 2008 and 2018 were included in this study. Preoperative blood parameters and demographic characteristics of the patients were recorded. Among the patients who underwent revision arthroplasty in our clinic in the mentioned years, patients who met the infection criteria (14). were included in the septic group (Group 3, n=66) and a 2-stage revision was performed, while patients who did not show any signs of infection were included in the aseptic group (Group 2, n=79) and a one-stage revision was performed. Primary arthroplasty patients with demographic characteristics similar to the septic and aseptic revision arthroplasty groups and operated by the same surgeon were also included in the control group (Group 1, n=69).

Patients with hematological disease, those with infections other than PJI, and those with autoimmune disease were excluded from the study.

Statistical analysis was performed using the SPSS 25.0 for Windows (SPSS, Inc.; Chicago, USA) package program. As for statistical analysis, categorical variables in the descriptive findings section were number, percentage and continuous variables were mean ± standard deviation and median (minimum, largest value). Pearson's chi-square or Fisher's Exact tests were used in the comparison of categorical variables. The conformity of continuous variables to normal distribution was evaluated by analytical (Kolmogorov-Smirnov and Shapiro-Wilks analysis) and visual (histogram and probability graphs) methods. Since the normal distribution could not be determined, the Kruskal-Wallis test was used for comparisons between three independent groups. When a significant difference was detected, the groups were compared in pairs to determine the source of the difference, and the level of significance was determined according to Bonferroni correction. The groups that differed after the Bonferroni correction were accepted as the source of the difference. ESR, CRP, PLR, and Lymphocyte values were evaluated by receiver operating curve (ROC) analysis whether these values predicted PJI. The area under the curve (AUC) and cut-off values, sensitivity, specificity PPV, and NPV of these cut-off values are presented. A value of $p<0.05$ was accepted as statistically significant.

RESULTS

A total of 214 arthroplasty patients, 79.0% of whom were female (n=169), were included in this study. The mean age of the participating patients was 69.25±8.45. Thirty-five (16.4%) of the patients are smokers. Most of the patients were knee arthroplasty (primary or revision) patients (82.7%). Postoperative complications developed in 20 patients (9.3%). A positive culture was obtained in 39 patients (18.2%) (**Table 1**).

Table 1: Demographic characteristics of the patients

N=214		
Gender, n %		
Male	45	21.0
Female	169	79.0
Age Avr±Sd 69,25±8,45, median 70 (min: 39- max 93)		
Smoker, n %		
No	179	83.6
Yes	35	16.4
Side, n %		
Right	112	52.3
Left	101	47.2
Bilateral	1	0.5
Placement, n %		
Knee	177	82.7
Hip	37	17.3
Complication (other), n%		
No	194	90.7
Yes	20	9.3
Reproduction, n %		
No	175	81.8
Yes	39	18.2
Situation, n %		
Normal	69	32.2
Aseptic	79	36.9
Septic	66	30.8

Avr±Sd: Average±Standard deviation

The patients were divided into 3 groups; 32.2% (n=69) were primary arthroplasty (Group 1), 36.9% (n=79) were aseptic revision arthroplasty (Group 2), and 30.8% (n=66) were septic revision arthroplasty (Group 3).

There was no difference between the three groups in terms of demographic characteristics such as gender, side, and smoking (**Table 2**).

Table 2. Comparison of demographic and laboratory results of the groups

N=214	Group 1: Normal (n=69)	Group 2: Aseptic (n=79)	Grup 3: Septic (n=66)	p Value
Gender, n (%)				0.075*
Male	10 (23.8)	13 (31.0)	19 (45.2)	
Female	59 (34.3)	66 (38.4)	44 (27.3)	
Side, n (%)				0.690*
Right	37 (33.0)	41 (36.6)	34 (30.4)	
Left	31 (30.7)	38 (37.6)	32 (31.7)	
Bilateral	1 (100.0)	-	-	
Smoker, n (%)				0.795*
No	56 (31.3)	67 (37.4)	56 (31.3)	
Yes	13 (37.1)	12 (34.3)	10 (28.6)	
Placement, n (%)				0.023*
Knee	64 (36.2)	63 (35.6)	50 (28.2)	
Hip	5 (13.5)	16 (43.2)	16 (43.2)	
Complication (other), n (%)				<0.001*
No	69 (35.6)	72 (37.1)	53 (27.3)	
Yes	-	7 (35.0)	13 (65.0)	
ESR, Avr±Sd	19.9±11.6•	19.8±15.5*	37.5±26.9**	<0.001**
CRP, Avr±Sd	5.1±3.8•	9.2±22.0*	23.9±36.7**	<0.001**
Plt vol, Avr±Sd	8.2±1.0	8.4±1.0	8.0±0.8	0.057**
Plt, Avr±Sd	296.5±96.1	284.9±91.9*	324.7±103.3*	0.016**
Leu, Avr±Sd	8.4±2.8	8.1±2.7	7.7±3.1	0.159**
Neu, Avr±Sd	5.7±2.4	5.3±2.4	5.3±3.0	0.152**
Lymph, Avr±Sd	3.8±15.9•	2.2±2.1*	1.6±0.6**	0.003**
Mono, Avr±Sd	0.5±0.2◊•	0.4±0.2◊	0.4±0.2•	0.010**
RDW, Avr±Sd	14.4±1.5	14.6±1.9*	15.5±1.7*	<0.001**
NLR, Avr±Sd	3.3±1.8	3.0±2.8	3.9±3.5	0.061**
MLR, Avr±Sd	0.3±0.2b◊	0.2±0.2◊*	0.3±0.2*	0.003**
PLR, Avr±Sd	174.2±86◊•	37.6±12.8◊*	222.4±111.6**	<0.001**
PMR, Avr±Sd	662.5±324•	711.2±258	811.8±291.7•	0.006**
LMR, Avr±Sd	7.7±30.6◊	5.3±3.1◊*	4.2±1.8*	0.003**
PltVol/Plt, Avr±Sd	0.031±0.011	0.032±0.010*	0.028±0.011*	0.005**

*: Chi Square Test, Avr±Sd: Average±Standard deviation, **: Kruskal Wallis Test, According to the Bonferroni correction, there was a signifficant difference in pairwise comparisons (between ◊: Group 1 and 2, •: Group 1 and 3, * Group 2 and 3) (p<0,016).

28.2% of those with knee arthroplasty were septic, 43.2% of those with hip arthroplasty were septic and there was a significant difference between the groups (p=0.023). There was a significant difference between the groups in terms of the presence of additional complications (p<0.001) (**Table 2**).

When the blood values of the patients were examined, there was a significant difference between the groups in terms of ESR, CRP, platelet, lymphocyte, monocytes, red blood cell distribution width (RDW), monocytes-to-lymphocyte rate (MLR), platelet-to-lymphocyte rate (PLR), platelet-to- monocytes (PMR), , lymphocyte-to-monocytes (LMR), and platelet volume/platelet (Pv/Plt) (**Table 2**).

The distribution of some blood parameters according to the groups is shown in **Figure 1**.

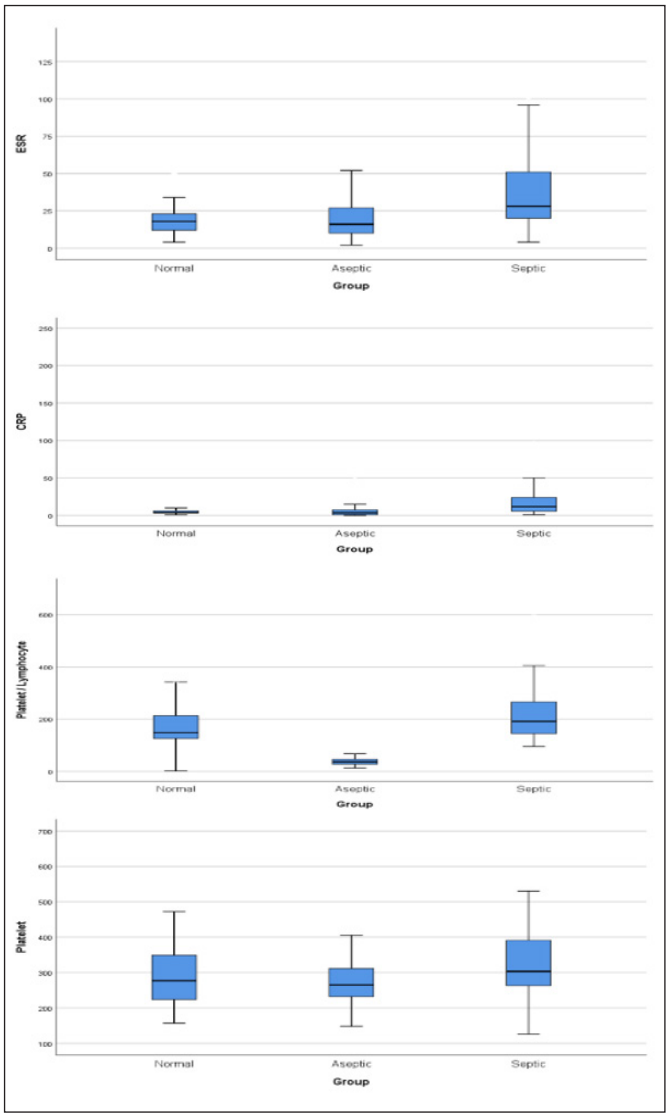

Figure 1. Distribution of some parameters according to the groups
ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein

In pairwise comparisons according to Bonferroni correction, group 1 and group 2 have some differences in terms of monocyte value (p=0.010), MLR (p=0.002), PLR (p=<0.001), LMR (p=0.002 group 1 and group 3 have some differences in terms of ESR (p<0.001), CRP (p<0.001), lymphocyte (p=0.013), monocytes (p=0.008), PLR (p=0.002), PMR (p=0.003); and group 2 and group 3 have some differences in terms of ESR (p<0.001), CRP (p<0.001), platelet (p=0.004), lymphocyte (p=0.001), RDW (p=0.001), MLR (p=0.007), PLR (p<0.001) and LMR (p=0.007) and Pv/Plt (p=0.001) (**Table 2**). As a result, preoperative ESR, CRP, lymphocyte, and PLR parameters were significantly different in the septic group compared to both the aseptic group and the control group. Therefore, the diagnostic performances of ESR, CRP, lymphocyte, and PLR in PJI relative to aseptic patients were evaluated by plotting receiving operating characteristic (ROC) curves (**Figure 2**).

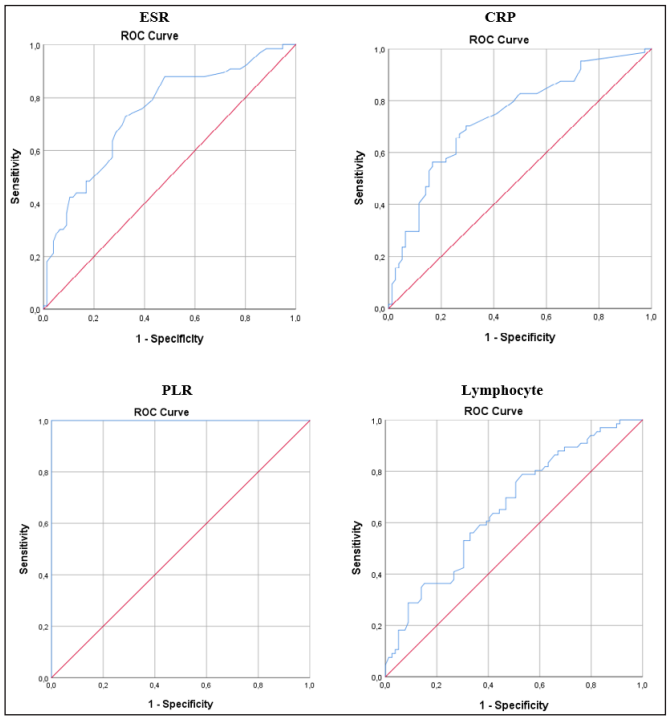

Figure 2: ROC analysis of some blood parameters

ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, PLR: Rplatelet-to-lymphocyte rate, ROC: Receiver operating curve

As a result of analysis, the cut-off values obtained for ESR, CRP, lymphocyte, and PLR parameters and specificity, sensitivity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV), and area under the ROC curve (AUC) values comprehensively presented in **Table 3**. It was observed that values of 21.5 for ESR, values of 6.74 for CRP, values of 1.725 for lymphocyte, and values of 85.5 for PLR were predictive of PJI ($p<0.001$, $p<0.001$, $p=0.001$, $p<0.001$, respectively). The combined effects of specificity, sensitivity, PPV, and NPV values for PLR were 100% (**Table 3**).

DISCUSSION

This study compared some preoperative blood parameters among patients who underwent primary arthroplasty, septic revision arthroplasty, and aseptic revision arthroplasty. Preoperative PLR, ESR, and CRP values were higher and lymphocyte values were lower in patients with septic revision arthroplasty compared to patients with aseptic revision arthroplasty and primary arthroplasty. Further analyzes were performed to evaluate the diagnostic performances of ESR, CRP, lymphocyte, and PLR in PJI relative to aseptic patients by ROC curves. The findings suggested that elevated ESR, CRP, and PLR values and decreased lymphocyte values are valuable parameters in diagnosing PJI.

Diagnosis of PJI is based on a detailed history and physical examination, along with a review of serological tests and radiographs (15). In addition, isolation of the causative organism from fluid or tissue cultures obtained from the affected joint is very important for treatment and prognosis, but usually it is difficult to obtain a positive culture in patients with clinically suspected PJI after arthroplasty. The literature agrees that almost half of PJI patients do not have growth in culture (16). Parvizi et al. (12) found culture negative in almost all patients with suspected diagnosis in their study published in 2018 . In our study, there was no growth in 27 (41%) of 66 PJI patients. We think that the reason for this is the antibiotics that were started in the outpatient clinic conditions in the preoperative period. This high rate reveals the importance of auxiliary findings of blood biomarkers in the diagnosis of PJI.

Many biomarkers have been defined in the diagnosis of PJI infection in recent years. Wyatt et al. (17) reported to have 100% sensitivity and 96% specificity, alpha defensin is an important biomarker for synovial fluid, but its high cost is suggestive. Although the major criteria are the same in different clinical studies, the minor criteria are different and there is no consensus yet (17-20). In 2018, Parvizi et al. (12) investigated the role of preoperative blood and synovial fluid values. They found significant elevation of CRP, ESR and D-dimer in the blood. Similarly, high CRP and ESR were found to be significant for PJI in this study.

The predictive role of blood biomarkers (monocytes, lymphocytes, neutrophils, platelets) in various diseases and cancers has been investigated, but studies investigating their predictive role in the diagnosis of PJI are very limited. Trimula et al. (18) reported that PLR, CRP, and ESR in PJI patients achieve significantly higher sensitivity and specificity rates of 97% or more for PJI (PLR: 99.03%; 98.80%). Paziuk et al. (19) showed that platelet count and mean platelet volume (MPV) were significantly higher in PJI patients compared to the aseptic revision group. Similarly, Xu et al. (20). showed that preoperative fibrinogen level and platelet count

Table 3. ROC curves evaluation of diagnostic performances of preoperative ESR, CRP, lymphocyte and PLR in septic revision arthroplasty

N=143	Cut off	Sensitivity (%)	Specificity (%)	PPV %	NPV %	AUC (%95 CI)	p
ESR	21.5	72.7	67.5	65.8	74.3	0.745 (0.663-0.826)	<0,001
CRP	6.74	70.3	70.5	66.2	74.3	0.738 (0.655-0.820)	<0,001
PLR	85.5	100.0	100.0	100.0	100.0	(1.000-1.000)	<0,001
Lymp	1.725	60.6	60.8	56.3	64.9	0.658 (0.569-0.746)	0,001

ROC: Receiving operating characteristic curves, Sens: Sensitivity, Spec: Specificity, PPV: Positive Predictive Value, NPV: Negative Predictive Value, AUC: Area under the ROC curve, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, Lymp: Lymphocyte, PLR: Platelet-to-lymphocyte rate

were predictive in the diagnosis of PJI. In this study, preoperative ESR, CRP, lymphocyte, monocytes, PLR and PMR values were found to be significantly different in the septic group compared to the control group. Also, preoperative ESR, CRP, lymphocyte, platelet, RDW, MLR, PLR, LMR and Pltvl/Plt values were found to be significantly different in the septic group compared to the aseptic group. In addition, ESR, CRP, lymphocyte, and PLR parameters were significantly different in the septic group compared to both the aseptic group and the control group. 21.5 cut-off value for ESR, 6.74 for CRP, 1.725 for lymphocyte, and 85.5 for PLR were found to be predictive for diagnosis of septic revision arthroplasty. Therefore the results suggested that it may be useful to evaluate these blood parameters when deciding on revision surgery.

There are some limitations of this study. For PJI, which is a combined diagnosis, it focused only on blood biomarkers and synovial fluid values were not mentioned. Another limitation is the retrospective nature of the study. In addition, some conditions that may affect blood parameters (drug use, another active infection, alcohol) were not recorded. The strength of this study is that it is the first to evaluate multiple blood biomarkers together in the diagnosis of PJI.

CONCLUSION

Lymphocyte, PLR, ESR, and CRP are easy biomarkers that are simply available from routine laboratory examination and may have diagnostic value in predicting PJI. Therefore, these parameters may be useful in deciding on revision arthroplasty for PJI.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara City Hospital No:1 Clinical Researches Ethics Committee (Date: 28.04.2021, Decision No: E1-21-1783).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: No conflict of interest was declared by the authors.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the manuscript, and they have approved the final version.

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