Journal of Orthopaedic Surgery and Research

RESEARCH

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The diagnostic accuracy of blood C-reactive protein and erythrocyte sedimentation rate in periprosthetic joint infections – A 10-year analysis of 1510 revision hip and knee arthroplasties from a single orthopaedic center

Dariusz Grzelecki[1*], Maciej Kocon[1], Rafał Mazur[1], Aleksandra Grajek[2] and Jacek Kowalczewski[1]

Abstract

Background Despite the availability of many highly accurate biomarkers and novel criteria, serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are still the basis for diagnosing periprosthetic joint infection (PJI). This study aims to analyze the influence of different demographical and clinical factors on the cut-off values and accuracy of CRP and ESR in diagnosing chronic PJI.

Methods A total number of 4757 patients (with ICD-10 codes T84.0 and T84.5) operated on between January 2014 to December 2023 in a single orthopaedic center were screened in terms of the inclusion and exclusion criteria. Finally, 1510 patients (1032 aseptic revisions and 478 periprosthetic joint infections [PJI]) were included in the analysis. The best cut-off values, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for both CRP and ESR for all cohort and for subgroups divided depending on the demographical (gender, joint and BMI) and clinical factors (prosthesis fixation, specific diagnostic criteria, and virulence of the bacteria) were calculated.

Results For all cohort, the best cut-off value for CRP was 9.6 mg/L with an area under the curve (AUC) of 0.93 and for ESR was 29 mm/h with the AUC of 0.891. For CRP the sensitivity was higher (84.9%) than for ESR (75.1%), with the same values of specificity (90.5% and 90.8%, respectively). According to the specific subgroups, for CRP higher sensitivity was observed for males (89.6%) than for females (82.6%) if lower thresholds were used. Similarly, when the higher cut-off value for CRP was applied, better specificity for high-virulent (94.8%) than for low-virulent pathogens (88.9%) was observed. For ESR, superior sensitivity values were observed if a fistula was observed, for lower BMI thresholds and for infections caused by high-virulent pathogens. Higher optimal threshold and better specificity were

*Correspondence:
Dariusz Grzelecki
dariuszgrzelecki@gmail.com

Full list of author information is available at the end of the article

observed for knees than for hips, without the appearance of fistula, when minor criteria were used and infection was caused by high-virulent pathogens.

Conclusions Our study indicates better sensitivity for CRP than ESR and similar specificity values for diagnosing chronic PJI. If results oscillate close to 10 mg/L for CRP and between 25 and 30 mm/h for ESR we propose to use different cut-off values depending on the demographic and/or clinical factors to increase diagnostic accuracy.

Keywords Revision knee arthroplasty, Revision hip arthroplasty, Periprosthetic joint infection, C-reactive protein, Erythrocyte sedimentation rate

Background

Periprosthetic joint infections (PJI) are major complications of total joint arthroplasty (TJA). With the increasing number of primary and revision TJAs performed worldwide, the number of patients with PJI will proportionally increase [1]. Due to the significant costs of treating septic complications after TJI and the associated higher mortality, further research into improving diagnostic, treatment and prophylaxis is justified [2, 3]. Appropriate differentiation between PJI and aseptic failure is crucial to implement effective treatment protocol. However, there is still no standard definition that may indicate patient with PJI with 100% accuracy [4, 5]. Although, many novel blood and synovial fluid biomarkers of PJI were assessed and validated in recent years [6–9], the role of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) is still undisputable [10–12]. Nevertheless, many factors may influence this marker values such as inflammatory diseases (e.g. rheumatoid arthritis, ankylosing spondylitis) phase and treatment, coexisting systemic and local infections or inflammations, malignancies, preoperative antibiotic administration and type of culprit pathogen (e.g. *Cutibacterium spp.* and other pathogens causing low-grade infections) [13–15].

Major criteria of PJI were not changed over the years, but the minor ones basing on a combination of different blood and synovial biomarkers, histological and microbiological findings raise some doubts and still have no sufficient evidence for support to use them in routine clinical practice [4, 16]. Validation of Musculoskeletal Infection Society (MSIS) and both International Consensus Meeting (ICM) definitions on the same group of patients was performed and revealed similar 99.5% specificity but different sensitivities [4]. The sensitivity of ICM 2018 criteria is 97.7%, and was higher comparing with ICM 2013 (86.9%) and MSIS (79.3%) definitions [4, 16, 17]. This increased sensitivity is strongly related to the application of synovial fluid tests. However, in many cases, joint aspiration is not possible preoperatively. For this reason, blood markers are still frequently used as screening tools for diagnosing PJI. The newest definitions, the ICM 2018 and European Bone and Joint Infection Society (EBJIS) recognizing blood CRP as the first-line biomarker with standard cut-offs for chronic PJI 10 mg/L, but only ICM 2018 includes ESR with a 30 mm/h cut-off value [4, 5]. Depending on the study design, applied thresholds for positive results, inclusion and exclusion criteria pooled sensitivity and specificity may vary in a wide range [18, 19]. Thus, the reasonable question that was tried to answer by several authors recently, is whether the hips and knees TJA, males and females, and obesity grade (according to the body mass index [BMI] values related with thresholds: (1) Overweight [> 25 kg/m2]; (2) class I obesity [> 30 kg/m2]; (3) class II obesity [> 35 kg/m2]) may cause that cut-off values, sensitivity and specificity for CRP and ESR differ significantly [20–22]. Moreover, does the applied criteria confirming PJI (fistula draining to the joint space, two positive cultures of the same pathogen or minor ICM 2018 criteria, except CRP and ESR), radiological signs of loosened implant, and virulence of culprit pathogen may change these thresholds, and diagnostic accuracy for the assessed biomarkers [23].

The aim of this study is to analyze the influence of different factors on the cut-off values, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of CRP and ESR in diagnosing chronic PJI of the hip and knee.

Methods

A retrospective analysis of all patients admitted to single orthopaedic center – authors institution, from January 2014 to December 2023 with International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes T84.0 (mechanical complication of internal joint prosthesis) and T84.5 (infection and inflammatory reaction due to internal joint prosthesis) was performed. To the PJI group were included patients with chronic PJI (> 4 weeks from surgical procedure or the occurrence of the first signs of the hematogenous infection). The exclusion criteria were stated as all diseases and conditions that may increase concentration of inflammatory markers and that may cause false results. The exclusion criteria consisted early PJI (< 4 weeks the occurrence of the first signs of infection), inconclusive cases according to the applied definition of PJI, patients with chronic autoimmune diseases (e.g. rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis), malignancies, periprosthetic fractures and early dislocations, those who had

the exchange of joint spacer to revision prosthesis and patients without available complete CRP and ESR results. From a total number of 4757 patients (with codes T84.0 and T84.5) who were admitted to the hospital in the mentioned time period, after initial screening and removing diagnostic stays and readmissions before the surgery, 4002 patients were identified. Finally, 1510 patients met the inclusion and exclusion criteria (483 males and 1027 females). Among this group, 1032 patients were operated due to the aseptic issues (arTJA group) and 478 due to PJI. 552 patients underwent rTKA and 958 rTHA. CRP and ESR markers were determined in all patients during the admission to the hospital, before the surgery. Flow diagrams of the inclusion and exclusion criteria are presented in Figs. 1 and 2. Demographic and clinical data are presented in Table 1.

Ethical approval

This study has received Bioethics Committee approval no. 43/2023 and was conducted according to the Declaration of Helsinki from 1964.

Data analyses

Statistical analysis was performed using Microsoft Excel 2019 (Microsoft) and Statistica 13.3 (Tibco). The Shapiro-Wilk test was done to determine the normality of the data distribution. For the assessment of the differences between the groups, due to a lack of normal distribution, the non-parametric Mann-Whitney U test and Fisher exact test were used. Demographic and clinical data results were presented as medians (with Interquartile Range; IQR). P-value < 0.05 was considered statistically significant. The best cut-off values for each CRP and ESR test were calculated according to the determination of Youden's index and the Receiver Operating Characteristic

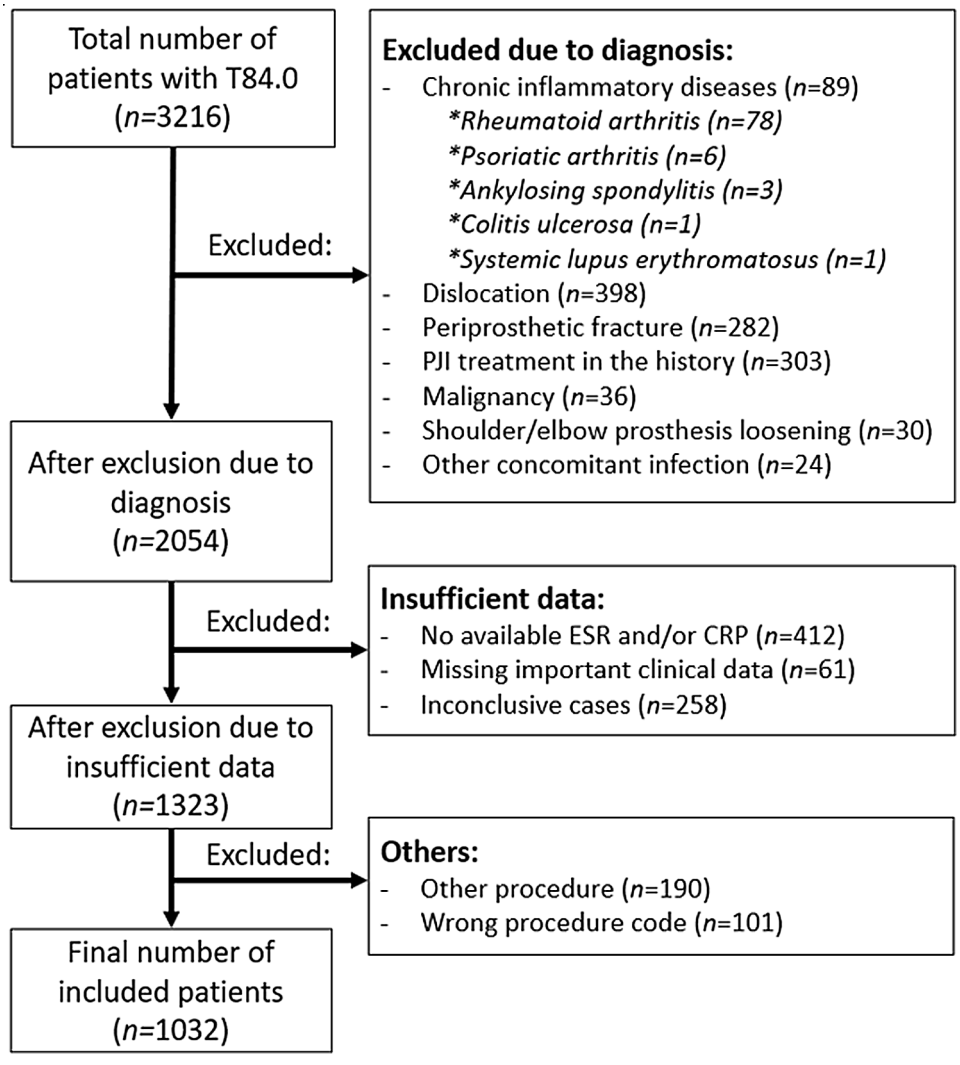

Fig. 1 Flow diagram of the inclusion and exclusion criteria in the arTJA group (T84.0)

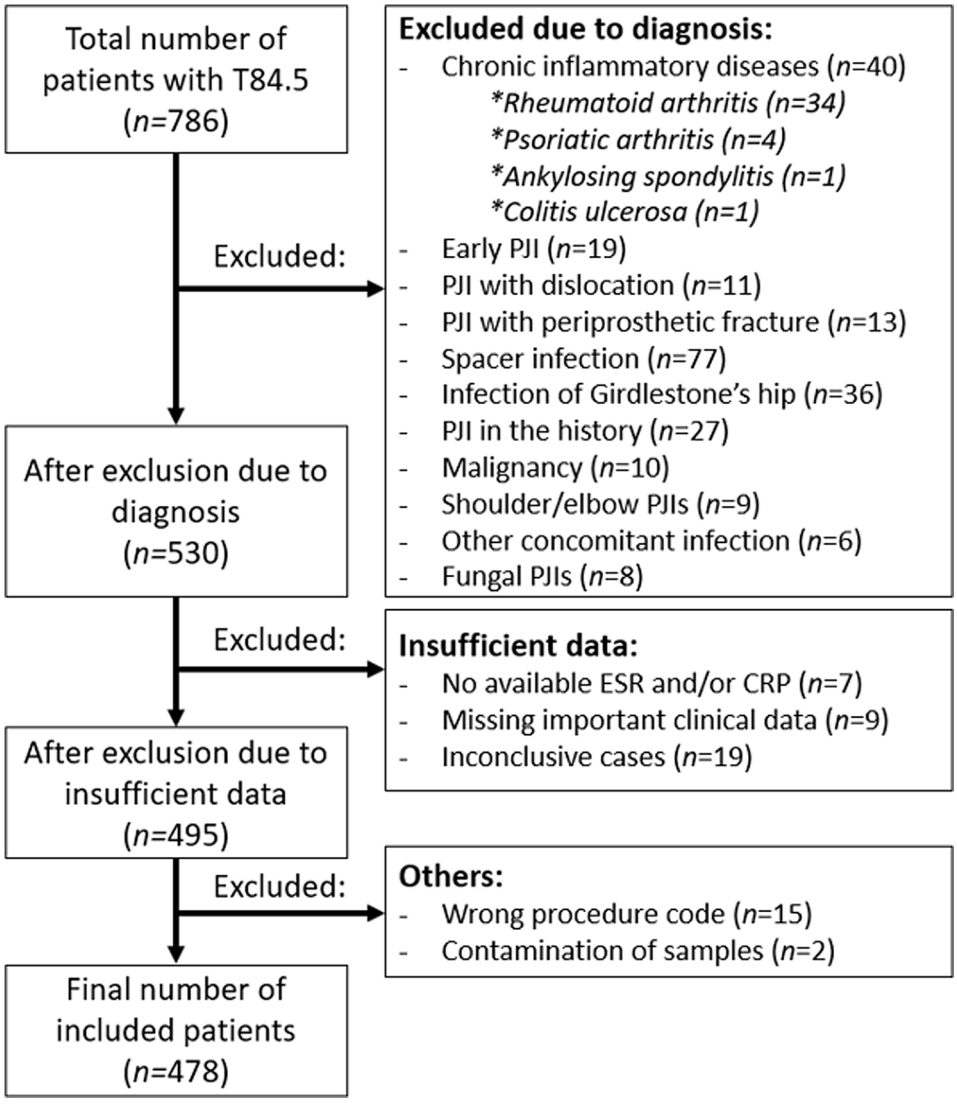

Fig. 2 Flow diagram of the inclusion and exclusion criteria in the PJI group (T84.5)

(ROC) curve. Sensitivity, specificity, PPV, and NPV were calculated regarding the received cut-off values.

Results

Patients who underwent revision THA or TKA due to aseptic reasons were included in the arTJA group. Particular diagnoses are presented in Table 2. Among all patients with PJIs, 148 (31%) had fistula and/or prosthesis visualization through the skin was appeared, in 232 (48.5%) minimum of two positive cultures of the pathogen with the same phenotype was confirmed, and in 98 (20.5%) the diagnosis was made following minor criteria (except CRP, ESR, and alpha-defensin tests). In all rTJA performed due to PJI tissue samples were collected for culturing. In 280 revisions synovial fluid was not collected and in 39 revisions sonication was not performed. In rTHA performed due to PJI, the best accuracy in the identification of pathogen has sonication (87.8%) which was very similar to tissue culturing (87.4%), but higher than for synovial fluid (67%). For PJI after rTKA sonication has also the best accuracy (82.5%), higher than tissue (76.2%) and synovial fluid (66.4%) culturing. The most frequent, culprit pathogen in hip and knee PJIs was Methicillin-sensitive *Staphylococcus aureus* (MSSA). In 55 (11.5%) tissue samples, 8 (4%) synovial fluid samples, and 56 (12.8%) sonication fluid samples two pathogens were identified. Culture-negative results In 83 (17.4%) tissue samples, 66 (33.3%) synovial fluid samples, and 73 (16.6%) sonication fluid samples the results of culturing were negative. The results of the microbiological culturing for septic rTHA and rTKA are presented in Tables 3 and 4.

Table 1 Demographic and clinical data. Continuous results are presented as medians with interquartile range (IQR)

	arTJA (*n* = 1032)	PJI (*n* = 478)	*p*-value
Males/Females	281 / 751	202 / 276	**< 0.01***
Hip/Knee	681 / 351	277 / 201	**< 0.01***
Age (years)	69 (61–76)	69 (62–76)	0.52**
Weight (kg)	80 (69–90)	83 (72–95)	**< 0.01****
BMI (kg/m^2)	29 (26-32.2)	29.7 (26.6–33)	**< 0.01****
Blood CRP (mg/L)	2.95 (1.3–5.4)	34.1 (14.5–65.4)	**< 0.01****
ESR (mm/h)	12 (7–18)	45 (29–75)	**< 0.01****
Time of the surgery (min)	105 (80.5–135)	120 (90–140)	**< 0.01****
Time from surgery to discharge (days)	8 (6–11)	15 (11–18)	**< 0.01****
Time from primary TJA to revision (months)	70 (24–144)	36 (13–72)	**< 0.01****

***Fisher exact test; **Mann-Whitney U test

Table 2 The diagnosis in the arTJA group

Diagnosis	Hip (*n* = 681)	Knee (*n* = 351)	Total (*n* = 1032)	Percentage value (total) [%]
Aseptic loosening	479	173	652	63.2
Instability	35	54	89	8.6
Implant malposition	9	76	85	8.2
Undiagnosed joint pain	84	33	121	11.6
Implant damage	74	4	78	7.6
Limiter range of motion and/or arthrofibrosis	0	11	11	0.1

Table 3 Microbiological culture results rTHA PJI group. Results are presented as n (%)

Microorganism	Tissues (*n* = 277)	Synovial Fluid (*n* = 94)	Sonication (*n* = 245)
Staphylococcus spp.	**155 (56%)**	**45 (48%)**	**141 (57.5%)**
MSSA	76 (49%)	27 (60%)	73 (52%)
MRSA	3 (2%)	1 (2.2%)	2 (1.3%)
MSCNS	25 (16%)	4 (9%)	28 (19.8%)
MRCNS	51 (33%)	13 (28.8%)	38 (26.9%)
Streptococcus spp.	**11 (4%)**	**5 (5.3%)**	**8 (3.3%)**
S. pyogenes (gr. A)	1 (9%)	0	1 (12.5%)
S. agalactiae (gr. B)	7 (64%)	3 (60%)	5 (62.5%)
S. gr. C	1 (9%)	1 (20%)	0
S. gr. „viridans"	1 (9%)	1 (20%)	1 (12.5%)
S. gr. G	1 (9%)	0	1 (12.5%)
Enterococcus spp.	**12 (4.3%)**	**3 (3.1%)**	**11 (4.5%)**
E. faecalis	11 (92%)	3 (100%)	11 (100%)
E. faecium	1 (8%)	0	0
Enterobacteraes	**12 (4.3%)**	**5 (5.3%)**	**10 (4.1%)**
E. coli	4 (33.3%)	2 (40%)	3 (30%)
K. pneumoniae	3 (25%)	0	3 (30%)
E. cloacae	4 (33.3%)	1 (20%)	3 (30%)
Salmonella spp.	1 (8.4%)	2 (40%)	0
P. mirabilis	0	0	1 (10%)
Non-fermenting	**2 (0.7%)**	**1 (1.1%)**	**3 (1.2%)**
A. baumanii	1 (50%)	0	1 (33.3%)
P. aeruginosa	1 (50%)	1 (100%)	2 (66.7%)
Anaerobes	**10 (3.7%)**	**1 (1.1%)**	**6 (2.4%)**
C. acnes	4 (40%)	0	2 (33.3%)
Peptostreptococcus gr.	4 (40%)	0	3 (50%)
Clostridium spp.	1 (10%)	1 (100%)	1 (16.7%)
P. melanogenica	1 (10%)	0	0
Corynebacterium spp.	**2 (0.7%)**	**0**	**1 (0.4%)**
2 pathogens	**38 (13.7%)**	**3 (3.1%)**	**35 (14.4.%)**
Negative culture	**35 (12.6%)**	**31 (33%)**	**30 (12.2%)**

Abbreviations: MRSA - methicillin-resistant *Staphylococcus aureus;* MSSA - Methicillin-sensitive *Staphylococcus aureus;* MRCNS - methicillin-resistant coagulase-negative *Staphylococcus;* MSCNS - methicillin-resistant coagulase-negative *Staphylococcus*

Total (all patients)

Median value of CRP in the arTJA group was 2.95 mg/L (1.3–5.4) and in the PJI group was 34.1 mg/L (IQR 14.5–65.4). The best cut-off value to differentiate arTJA from PJI was 9.6 mg/L. For this value sensitivity and specificity were 84.9% and 90.5%, respectively. Median value of ESR in the arTJA group was 12 mm/h (7–18) and in the PJI group was 45 mm/h (29–75) (Fig. 3). For the ESR the best cut-off value was calculated at 29 mm/h. Sensitivity was 75.1% and specificity was 90.8% (Fig. 4).

Male/Female

281 males after arTJA and 202 with PJI were analyzed according to CRP and ESR values. Cut-off value for positive result in the male group was 8.5 mg/L. Sensitivity was 89.6% and specificity was 90%. For the ESR threshold was calculated at 25 mm/h, and values of sensitivity and specificity were 78.7% and 89%, respectively. 751 females after arTJA and 276 with PJI undergone similar analysis. For CRP threshold for positive results was 10.8 mg/L. Sensitivity was 82.6% and specificity was 91.9%. For the ESR cut-off value was 29 mm/h, and sensitivity and specificity were 76. 8% and 90.1%, respectively.

Hip/Knee

201 patients with PJI after TKA and 351 arTKA were analyzed to indicate the best cut-off value, and diagnostic accuracy of CRP and ESR. The best threshold in relation to operated knee joint was 9.6 mg/L. Sensitivity was 86.1% and specificity was 92.3%. For ESR the best threshold was calculated at 29 mm/h. Sensitivity was 80.6% and specificity was 92%. 277 patients with PJI after THA and 681 patients who undergone arTHA were analyzed. The best cut-off value for CRP was 10.7 mg/L. Sensitivity and specificity were 82.7% and 91.6%, respectively. For the ESR the ideal cut-off value was 25 mm/h. Sensitivity and specificity were 78% and 84.3%, respectively.

Table 4 Microbiological culture results rTKA PJI group. Results are presented as n (%)

Microorganism	Tissues (*n* = 201)	Synovial Fluid (*n* = 104)	Sonication (*n* = 203)
Staphylococcus spp.	**93 (46.3%)**	**45 (43.2%)**	100 (49.3%)
MSSA	38 (40.9%)	20 (44.5%)	41 (41%)
MRSA	3 (3.2%)	1 (2.2%)	4 (4%)
MSCNS	17 (18.3%)	10 (22.2%)	17 (17%)
MRCNS	35 (37.6%)	14 (31.1%)	38 (38%)
Streptococcus spp.	**15 (7.5%)**	**11 (10.6%)**	20 (9.9%)
S. agalactiae (gr. B)	4 (26.6%)	4 (36.4%)	6 (30%)
S. gr. C	1 (6.7%)	1 (9.6%)	2 (10%)
S. gr. „viridans"	9 (60%)	6 (54.5%)	11 (55%)
S. gr. G	1 (6.7%)	0	1 (5%)
Enterococcus spp.	**10 (5%)**	**3 (2.9%)**	**7 (3.4%)**
E. faecalis	9 (90%)	3 (100%)	7 (100%)
E. faecium	1 (10%)	0	0
Enterobacteraes	**13 (6.5%)**	**2 (1.9%)**	**10 (4.9%)**
E. coli	3 (23%)	0	3 (30%)
K. pneumoniae	1 (7.7%)	1 (50%)	0
E. cloacae	4 (30.9%)	1 (50%)	2 (20%)
Serratia spp.	3 (23%)	0	3 (30%)
P. mirabilis	2 (15.4%)	0	2 (20%)
Non-fermenting	**2 (1%)**	**1 (0.9%)**	**0**
A. baumanii	1 (50%)	0	0
P. aeruginosa	1 (50%)	1 (100%)	0
Anaerobes	**3 (1.5%)**	**2 (1.9%)**	**2 (1%)**
C. acnes	3 (100%)	2 (100%)	2 (100%)
2 pathogens	**17 (8.4%)**	**5 (4.8%)**	**21 (10.3%)**
Negative culture	**48 (23.8%)**	**35 (33.6%)**	**43 (21.2%)**

Abbreviations: MRSA - methicillin-resistant *Staphylococcus aureus;* MSSA - Methicillin-sensitive *Staphylococcus aureus;* MRCNS - methicillin-resistant coagulase-negative *Staphylococcus;* MSCNS - methicillin-sensitive coagulase-negative *Staphylococcus*

Loosened/well fixed prosthesis

652 aseptic loosening and 322 septic loosening prostheses were included to analysis of CRP and ESR values. The best threshold for CRP to differentiate aseptic and septic complications was 9.6 mg/L. Sensitivity was 86.6% and specificity was 89.4%. For the ESR the best threshold was 28 mm/h. Sensitivity was 76.7% and specificity was 89.4%. 380 arTJAs and 156 PJIs without radiological signs of implant loosening were found. The ideal cut-off value for blood CRP was 8 mg/L and for ESR was 29 mm/h. Sensitivity and specificity values for CRP were 85.3% and 89.7%, and for ESR were 75% and 89.7%, respectively.

ICM 2018 criteria

Despite the occurrence of fistula draining to the joint is the evident major criteria recognizing during the physical examination, the first analysis was performed depending on the appearance (148 patients) or not (330 patients) fistula in the PJI group. When the fistula was occurred cut-off value for CRP was calculated at 9.3 mg/L, sensitivity was 86.5% and specificity was 89.2%. For the ESR the best cut-off value was calculated at 21 mm/h and sensitivity was 87.2% and specificity was 82.2%. In the group of patients with PJI and no fistula occurrence, for CRP cut off value was 10.1 mg/L and for ESR was 29 mm/h. Sensitivity and specificity for CRP were 83.9% and 91.5%, and for ESR were 73.9% and 90.8%, respectively.

Second analysis was performed according to the major and minor criteria of ICM 2018. 380 patients with PJI were diagnosed according to the major criteria and 98 to the minor. For major criteria subgroup best cut-off value for CRP was 9.6 mg/L and for ESR was 24 mm/h. For CRP sensitivity was 83.4% and specificity was 90.5%, and for ESR sensitivity was 78.9% and specificity was 84.6%. For the patients diagnosed according to minor criteria cut-off value for CRP was 13.7 mg/L and for ESR was 30 mm/h. For CRP sensitivity was 89.8% and specificity was 94.7%, and for ESR sensitivity was 84.7% and specificity was 90.9%.

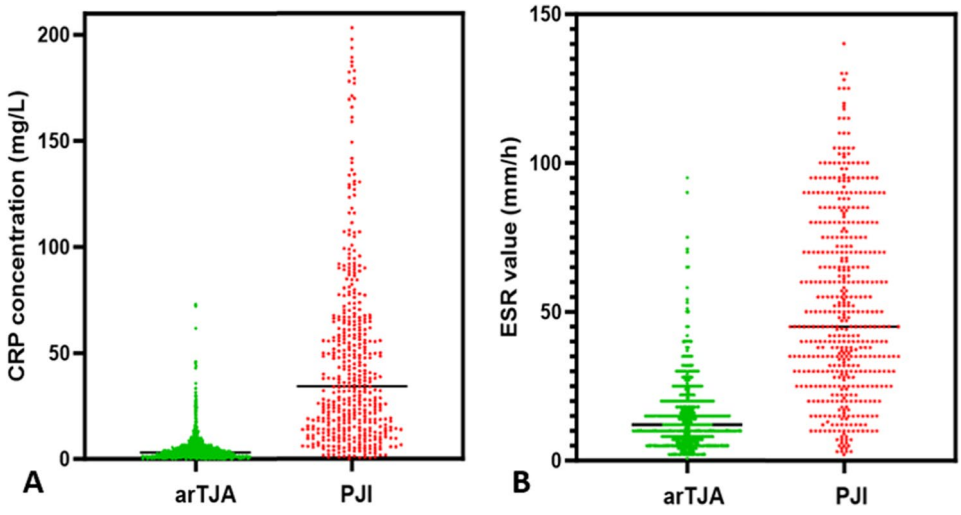

Fig. 3 Scatter plot for (**A**) CRP and (**B**) ESR in arTJA and PJI groups. Bars on plot represent median value

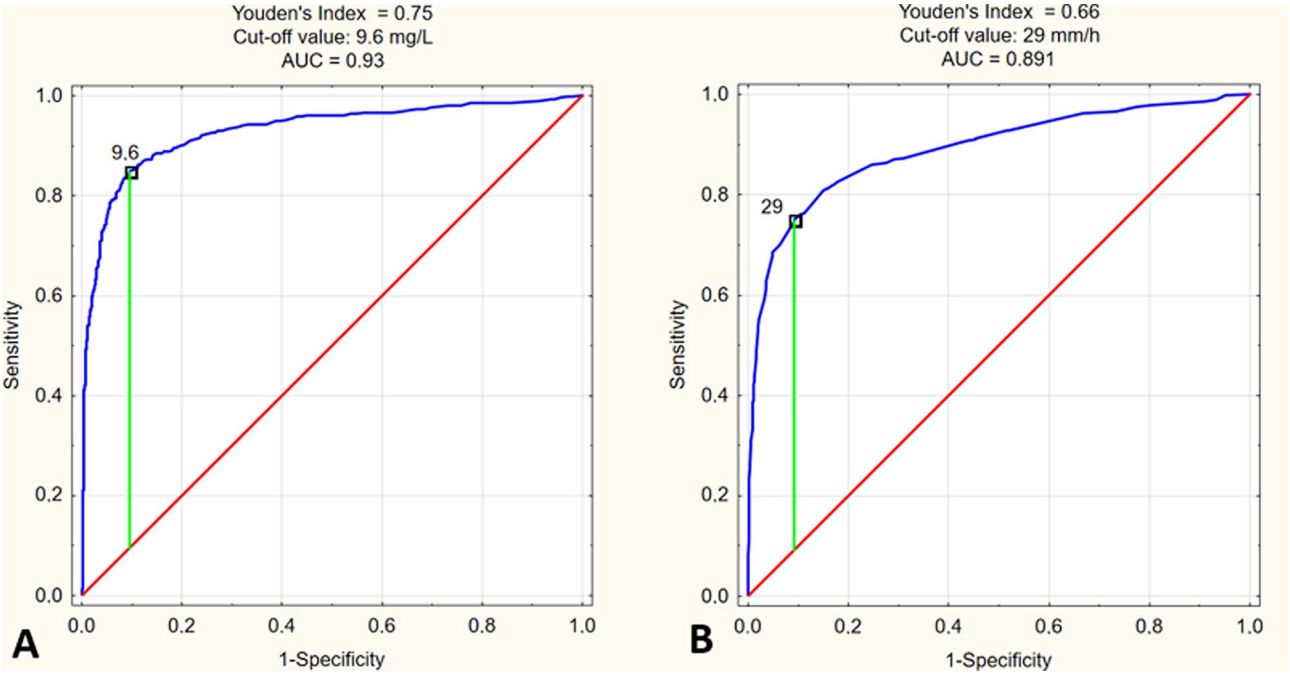

Fig. 4 Receiver operating characteristic (ROC) curves for (A) CRP and (B) ESR calculated for all patients included in this study. AUC = area under curve

BMI

For patients with BMI < 25 kg/m^2 cut-off value for CRP was 5.9 mg/L and ESR was 25 mm/h. For CRP sensitivity was 88.8% and specificity was 85.3%, and for ESR sensitivity was 85% and for 88.6%. For patients with BMI ≥ 25 kg/m^2, positive concentration of CRP was 9.6 mg/L and for ESR was 29 mm/h. Sensitivity calculated for CRP was 85% and specificity was 90.9%. For ESR sensitivity was 73% and for specificity was 90.6%.

For patients with BMI < 30 kg/m^2 the optimal threshold was 9.1 mg/L and for ESR was 24 mm/h. Sensitivity for CRP was 83.8% and specificity was 90%. For the ESR sensitivity was 81.7% and specificity was 86.3%. For patients with BMI ≥ 30 kg/m^2, cut-off value for CRP was 9.6 mg/L and for ESR was 30 mm/h. Sensitivity for CRP was 86.5% and specificity was 90.2%. Sensitivity for ESR was 74.4% and specificity was 89.7%.

For patients with BMI < 35 kg/m^2 the best cut-off value was 9 mg/L and for ESR was 25 mm/h. Sensitivity for CRP was 84.7% and specificity was 87.7%. For the ESR sensitivity was 79.9% and specificity was 85.5%. For patients with BMI ≥ 35 kg/m^2, cut-off value for CRP was 9.8 mg/L and for ESR was 30 mm/h. Sensitivity for CRP was 88.4% and specificity was 89.4%. Sensitivity for ESR was 76.8% and specificity was 91.2%.

Virulence of the bacteria

According to virulence profile of bacteria proposed by Boyle et al. additional analysis of the optimal CRP and ESR cut off value and calculation of markers accuracy was performed [24]. For low-virulent bacteria cut-off value for CRP was 9 mg/L and for high-virulent was 13.8 mg/L. Sensitivity values were 83% and 85.2%, and specificity were 88.9% and 94.8%, respectively. For low-virulent bacteria cut-off value for ESR was 24 mm/h and for high-virulent was 29 mm/h. Sensitivity were 76.1 mm/h and 83.3%, and specificity were 84.6% and 90.8%, respectively.

The results were summarized in the Tables 5 and 6. ROC curves for specific subgroups are presented in Supplement Figs. 1–9.

Discussion

Despite in recent studies several biomarkers determined in blood and synovial fluid with excellent accuracy were investigated, CRP and ESR are still the basic markers used for diagnosing PJI. However, there is still no consensus concerning the optimal value of the threshold for positive results. Current recommendations [4, 5] propose using the same values for different cohorts even though, in different infections or inflammatory diseases, the cut of values may be different depending on patient's sex, type of infection, or localization [25–29]. It also influences diagnostic accuracy. Thus, there is a need to answer, is there a need to use different thresholds for CRP and ESR depending on demographical and clinical factors in orthopaedic infections associated with joint implants. The optimal cut-off value for CRP in the whole of our cohort was 9.6 mg/L, which is lower than proposed by MSIS, ICM, and EBJIS criteria [4, 5, 17]. For ESR the optimal threshold in our research was comparable to those included in standard definitions of PJI. Moreover, according to the ICM 2018 threshold for CRP

Table 5 Diagnostic values of CRP in patients with confirmed PJI compared with those undergoing arTJA. AUC = area under curve; PPV = positive predictive value; NPV = negative predictive value

	Cut-off value (mg/L)	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Total	9.6	0.93	84.9	90.5	80.6	92.9
Gender						
Males	8.5	0.947	89.6	90	86.6	92.3
Females	10.8	0.919	82.6	91.9	78.9	93.5
Joint						
Knee	9.6	0.934	86.1	92.3	86.5	92
Hip	10.7	0.972	82.7	91.6	80	92.9
Prosthesis fixation						
Loosened	9.6	0.93	86.6	89.4	80.2	93.1
Well-fixed	8	0.931	85.3	89.7	77.3	93.7
ICM 2018 criteria						
Fistula	9.3	0.94	86.5	89.2	53.6	97.9
Lack of fistula	10.1	0.926	83.9	91.5	75.1	94.7
Major criteria	9.6	0.922	83.4	90.5	76.4	93.7
Minor criteria	13.7	0.962	89.8	94.7	61.5	99
BMI						
<25 kg/m^2	5.9	0.92	88.8	85.3	72.4	94.6
≥25 kg/m^2	9.6	0.931	85	90.9	81.7	92.7
<30 kg/m^2	9.1	0.926	83.8	90	77.9	92.9
≥30 kg/m^2	9.6	0.932	86.5	90.2	82.5	92.6
<35 kg/m^2	9	0.972	84.7	87.7	78.6	92.9
≥35 kg/m^2	9.8	0.935	88.4	89.4	83.6	92.7
Virulence of the bacteria						
Low-virulence	9	0.918	83	88.9	53.5	96.6
High-virulence	13.8	0.945	85.2	94.8	76.8	96.9

(10 mg/L) sensitivity was 83.7% and specificity 91.2%, and for ESR (30 mm/h) sensitivity was 74.7% and specificity 90.9%.

It is proven that for different blood biomarkers and diseases, reference ranges differ depending on the patient's sex [30–32]. This trend was observed also for CRP in our research, where the cut-off value for men was lower and for women higher than 10 mg/L. Contrary to our findings, Shi et al. who performed the gender-specific analysis found that the best cut-off value for men is higher (10.64 mg/L) than for women (8.86 mg/L) [22]. Similar results were observed in terms of sensitivity and specificity that were better for women. On the other hand, Padua et al. received lower accuracy for CRP for females and higher for males. However, they applied a standard cut-off value (10 mg/L) in the analysis [33]. For ESR, the optimal thresholds were below 30 mm/h, and for men was lower than for women. Received results of sensitivity and specificity for men and women were very similar, which stay in line with those observed by Shi et al. [22], but differ significantly when the same, standard threshold (30 mm/h) was applied [33].

Concerning the operated joint, several studies revealed significant differences in optimal cut-off values for different biomarkers determined in blood [34–36]. In our study lower cut-off value for CRP for the hip than for the knee was revealed, which stays in line with the literature findings. Alijanipour et al. observed higher optimal cut-off values than those proposed for ICM, with better sensitivity for the knee (96.6%) than for the hip (88.1%) [20]. However, they used MSIS 2011 diagnostic standard with low sensitivity (79.3%) [4]. In the case of ESR, calculated thresholds were higher than proposed by standard criteria, but values of sensitivity and specificity were lower than in our study. Similarly, Unter Ecker et al., for CRP received higher cut-off value, sensitivity and specificity for rTKA than for rTKA [23]. Moreover, they found that for high-virulent pathogens the results are significantly higher than for low-virulent ($p < 0.0001$). The same results were obtained in our study, concerning pathogen virulence. Higher results of sensitivity (85.2%) and specificity (94.8%) were obtained for high-virulent pathogens, with a higher threshold for positive results (13.8 mg/L) than for low-virulent (83%, 88.9% and 9 mg/L, respectively). We agree with other authors, that for low-grade pathogens, CRP with the cut-off value proposed by ICM may lead to misdiagnosing even up to 50% of patients with PJI and cannot be used as a single indicator [14, 37–39].

Because the fact the prevalence of obesity increased significantly last decades and it is a well-known and important risk factor for early and chronic PJI, the analysis of the accuracy biomarkers of PJI in relation to BMI

Table 6 ESR in patients with confirmed PJI compared with those undergoing arTJA. AUC = area under curve; PPV = positive predictive value; NPV = negative predictive value

	Cut-off value (mm/h)	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Total	29	0.891	75.1	90.8	79.1	88.7
Gender						
Males	25	0.891	78.7	89	83.7	85.3
Females	29	0.901	76.8	90.1	74.1	91.4
Joint						
Knee	29	0.915	80.6	92	85.3	89.2
Hip	25	0.874	78	84.3	66.9	90.3
Prosthesis fixation						
Loosened	28	0.885	76.7	89.4	78.2	88.6
Well-fixed	29	0.904	75	89.7	92.9	89.7
ICM 2018 criteria						
Fistula	21	0.922	87.2	82.2	41.2	97.8
Lack of fistula	29	0.878	73.9	90.8	72	91.6
Major criteria	24	0.883	78.9	84.6	65.4	91.6
Minor criteria	30	0.926	84.7	90.9	46.9	98.4
BMI						
<25 kg/m^2	25	0.915	85	88.6	76.4	93.1
≥25 kg/m^2	29	0.879	73	90.6	78.6	87.6
<30 kg/m^2	24	0.895	81.7	86.3	71.5	91.8
≥30 kg/m^2	30	0.874	74.4	89.7	79.4	86.8
<35 kg/m^2	25	0.89	79.9	85.5	71.2	90.5
≥35 kg/m^2	30	0.854	76.8	91.2	84.1	86.6
Virulence of the bacteria						
Low-virulence	24	0.863	76.1	84.6	47.4	95.1
High-virulence	29	0.916	83.3	90.8	64.8	96.4

value is justified [40–42]. Interesting research was conducted by Liu et al. who investigated differences in obese (BMI ≥ 30 kg/m^2) and non-obese (< 30 kg/m^2) patients [43]. For the group of patients with higher BMI, the optimal thresholds for CRP and ESR are higher than in patients with < 30 kg/m^2. Moreover, they found that these cut-off values were higher than proposed by ICM. Comparing the results of sensitivity, for obese patients was lower than for non-obese (80.9% vs. 95.8%) and specificity was higher (96.2% vs. 78.6%). Contrary to these findings, in obese patients, ESR sensitivity was higher than for non-obese (92.3% vs. 91.7%), but specificity was lower (76.9 vs. 85.7%). Unfortunately, these results do not completely stay in line with ours, where the optimal threshold was lower than proposed by ICM, and sensitivity value was higher both for CRP and ESR in patients with BMI ≥ 30 kg/m2.

Our study has some limitations, that should be considered before analyzing results. First, this is a retrospective research, which decreased its clinical value. However, we have collected data from a large number of patients operated on in a single orthopaedic center in the last 10 years. Although we have used very restricted inclusion and exclusion criteria, and analyzed the influence on several demographic and clinical factors. The second limitation is related to different reagents applied in the hospital. Despite we evaluated data collected over this long time all reagents were validated and had the same cut-off value proposed by the manufacturers to diagnose inflammation or infection. Moreover, in our study, we used ICM 2018 criteria retrospectively, based on the available data. Between 2014 and 2017, ICM 2013 criteria were routinely used in the hospital. We are aware that the proposed ICM criteria do have not 100% accuracy, but currently, this is the best available diagnostic standard [4]. To avoid the influence of false positive and false negative results on the final accuracy of the investigated markers, inconclusive patients were excluded from the analysis. Lastly, the influence of several important factors which may influence on the blood biomarkers, such as smoking status and the administration of antibiotics before the surgery. This factors were not analyzed due to unclear information in the history of many patients, especially those who were operated on before 2018. However, none of the patients included in this study received antibiotics a minimum of 2 weeks before the determination of CRP and ESR.

Conclusions

Results of our study indicate better sensitivity for CRP than ESR and similar specificity values in diagnosing PJI. To achieve the most reliable results of sensitivity and

specificity of investigated biomarkers, we propose to use different cut-off values for positive results depending on the patient's demographics (sex, operated joint and obesity) if results oscillating close to 10 mg/L for CRP and between 25 and 30 mm/h for ESR. Moreover, there is a need to aware that several clinical factors such as the virulence of bacteria, the presence or not the fistula, and meeting the major or minor ICM 2018 criteria are strongly influence the markers' cut-off values.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13018-025-05531-7.

Supplementary Material 1

Acknowledgements
Not applicable.

Author contributions
D.G. – Conceptualization, methodology, investigation, data analysis, writing—original draft preparation, writing—review and editing, visualizationM.K. – Conceptualization, data collection, investigation, data analysisR.M. – data collection, data analysisA.G. - data collection, data analysisJ.K. Conceptualization, formal analysis, writing—review and editingAll authors have read and agreed to the published version of the manuscript.

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study has received Bioethics Committee approval no. 43/2023 and was conducted according to the Declaration of Helsinki from 1964.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Orthopedics and Rheumoorthopedics, Centre of Postgraduate Medical Education, Professor Adam Gruca Orthopedic and Trauma Teaching Hospital, Konarskiego 13, Otwock 05- 400, Poland
[2]Central Laboratory of Professor Adam Gruca Orthopedic and Trauma Teaching Hospital, Konarskiego 13, Otwock 05-400, Poland

Received: 13 October 2024 / Accepted: 22 January 2025
Published online: 14 March 2025

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