Serum albumin-to-globulin ratio and CRP-to-albumin ratio did not outperform serum CRP in diagnosing periprosthetic joint infections

From Medical University of Vienna, Vienna, Austria

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Correspondence should be sent to Irene Katharina Sigmund irene.sigmund@meduniwien.ac.at

M. Luger,[1] C. Böhler,[1] S. E. Puchner,[1] S. Apprich,[1] K. Staats,[1] R. Windhager,[1] I. K. Sigmund[1]

Department of Orthopaedics and Trauma Surgery, Medical University of Vienna, Vienna, Austria

Aims

Serum inflammatory parameters are widely used to aid in diagnosing a periprosthetic joint infection (PJI). Due to their limited performances in the literature, novel and more accurate biomarkers are needed. Serum albumin-to-globulin ratio (AGR) and serum CRP-to-albumin ratio (CAR) have previously been proposed as potential new parameters, but results were mixed. The aim of this study was to assess the diagnostic accuracy of AGR and CAR in diagnosing PJI and to compare them to the established and widely used marker CRP.

Methods

From 2015 to 2022, a consecutive series of 275 cases of revision total hip (n = 129) and knee arthroplasty (n = 146) were included in this retrospective cohort study. Based on the 2021 European Bone and Joint Infection Society (EBJIS) definition, 144 arthroplasties were classified as septic. Using receiver operating characteristic curve (ROC) analysis, the ideal thresholds and diagnostic performances were calculated. The areas under the curve (AUCs) were compared using the z-test.

Results

AGR, CAR, and CRP were associated with PJI ($p < 0.001$). Sensitivities were 62.5% (95% CI 54.3 to 70.0), 73.6% (95% CI 65.8 to 80.1), and 71.5% (95% CI 63.6 to 78.3), respectively. Specificities were calculated with 84.7% (95% CI 77.5 to 89.9), 86.3% (95% CI 79.2 to 91.2), and 87.8% (95% CI 80.9 to 92.4), respectively. The AUC of CRP (0.797 (95% CI 0.750 to 0.843)) was significantly higher than the AUC of AGR (0.736 (95% CI 0.686 to 0.786), $p < 0.001$), and similar to AUC of CAR (0.799 (95% CI 0.753 to 0.846), $p = 0.832$). Decreased sensitivities were observed in PJIs caused by low-virulence organisms (AGR: 60%, CAR: 78%) compared to high-virulence pathogens (AGR: 80%, $p = 0.042$; CAR: 88%, $p = 0.158$). Higher sensitivities were seen in acute haematogenous (AGR: 83%, CAR: 96%) compared to chronic PJIs (AGR: 54%, $p = 0.001$; CAR: 65%, $p < 0.001$).

Conclusion

Serum AGR and CAR showed limited diagnostic accuracy (especially in low-grade and chronic infections) and did not outperform the established marker CRP in our study. Hence, neither parameter can be recommended as an additional tool for diagnosing PJI.

Article focus

- This article evaluated the diagnostic accuracy of serum albumin-to-globulin ratio (AGR) and serum CRP-to-albumin ratio (CAR) in diagnosing periprosthetic joint infections (PJIs) when using the European Bone and Joint Infection Society definition.
- A comparison with the well-established inflammatory serum parameter CRP was performed.
- Additionally, a review of the existing literature on serum AGR and CAR was conducted.

Key messages

- In comparison to other studies, serum AGR and CAR showed limited diagnostic accuracy in our cohort, especially in low-grade and chronic infections.
- Neither serum marker outperformed the widely used and established marker CRP.

Strengths and limitations

- This is the largest cohort of revision arthroplasty cases to date evaluating the diagnostic performance of serum AGR and CAR in PJI
- This study is subject to the limitations of being retrospective.

Introduction

Periprosthetic joint infection (PJI) represents a severe complication associated with considerable morbidity, impaired quality of life, and healthcare expenditure. First and foremost, accurate diagnosis is necessary to minimize these negative impacts. Preoperative detection of low-grade infections caused by biofilm-forming microorganisms remains particularly challenging.[1] In absence of a test with 100% accuracy, a standardized diagnostic workup should be performed. Along with clinical features and synovial fluid (SF) analysis, serum inflammatory parameters are commonly used to diagnose PJI preoperatively.[2,3] Serum parameters are rapidly accessible, cheap, and widely available diagnostic tools, which may provide valuable information. However, their accuracy remains a limiting factor.[4] Currently, only serum CRP is part of the recently published European Bone and Joint Infection Society (EBJIS) definition of PJI.[2] Finding novel, specific serum parameters for diagnosing PJI continues to be a focus of research.

Changes in concentration of serum albumin and globulin can be observed during inflammatory response, infection, and active malignancy.[5] Several workgroups have proposed the serum albumin-to-globulin ratio (AGR) and serum CRP-to-albumin ratio (CAR) as potential new biomarkers for preoperative diagnosis of PJI.[6-8] However, there are conflicting results in the literature regarding diagnostic performance. Sensitivities and specificities showed considerable variation, and the diagnostic value of serum AGR and CAR have not yet been fully elucidated.

Therefore, the aim of this study was to assess the diagnostic accuracy of serum AGR and serum CAR in PJI based on the EBJIS criteria as reference standard. Additionally, a comparison with the well-established inflammatory serum parameter CRP was performed, and a review of the existing literature on serum AGR and CAR was carried out.

Methods

This retrospective cohort study of prospectively collected data was conducted at the Medical University of Vienna, a tertiary orthopaedic hospital specializing in treatment of PJI, and was done in accordance with the Declaration of Helsinki[9] and the STARD 2015 guideline for reporting diagnostic accuracy studies.[10] Ethical approval by the institutional ethical review board was obtained (EK 1585/2019). Patients undergoing revision surgery after total hip (THA) and total knee arthroplasty (TKA) from January 2015 to June 2022 were identified. Exclusion criteria were defined as follows: insufficient preoperative blood workup (missing albumin, globulin, or CRP), surgery within the last six weeks, antibiotic-loaded cement spacer in place, the second stage of a two-stage revision, and periprosthetic fractures. The 2021 EBJIS definition was used to define PJI.[2] CRP was excluded to avoid incorporation bias. All 'likely' infections (n = 16) according to the EBJIS criteria were assigned to the aseptic group, as this reflects clinical practice at our institution. If a 'likely' infection is diagnosed, the patient will be informed (about possible future consequences) and a close follow-up protocol is initiated, but patients do not receive further treatment (e.g. antibiotics or further surgery). As part of a standardized diagnostic workup at our institution, demographic data, comorbidities, clinical features, and results of serum inflammatory parameters, synovial fluid analysis, microbiology, histology, and radiographs were documented. Histological analysis was performed by a pathologist who specialized in PJI, and radiographs were interpreted by musculoskeletal radiologists at our hospital. A thorough literature search was carried out using PubMed, Embase, and the Cochrane Library to identify studies evaluating serum AGR and CAR for the diagnosis of PJI.

Demographic details

Of 555 patients, 280 had to be excluded due to an insufficient preoperative blood workup (n = 13), surgery within the last six weeks (n = 39), second stage of a two-stage revision (n = 169), and periprosthetic fracture (n = 59). Hence, 275 patients with a median age of 72.0 years (IQR 62.5 to 78.0) and a median BMI of 27.8 kg/m^2 (IQR 24.2 to 31.7) were included in our study. In total, 158 (57.5%) cases were female and 27 patients (9.8%) were treated with antibiotics preoperatively. Using the 2021 EBJIS criteria, 144 cases (52.4%) were identified as septic. No significant difference was observed between the septic and aseptic groups regarding age, sex, BMI, or localization (hip, knee). Conversely, the septic group had a significantly higher American Society of Anesthesiologists (ASA)[11] grade ($p < 0.001$, Mann-Whitney U test), and more septic cases received preoperative antibiotic treatment (17.4% of septic cases vs 1.5% of aseptic cases; $p < 0.001$, Fisher's exact test). Regarding median AGR, significantly lower levels were observed in the septic group ($p < 0.001$, Mann-Whitney U test). Median CAR and CRP were higher in septic patients ($p < 0.001$, Mann-Whitney U test; Table I).

Diagnostic tests

Blood samples were taken one to three days preoperatively from all included patients. Lithium-heparin plasma was used for automated particle-enhanced immunoturbidimetric analysis of serum CRP (cobas8000 c702 module; Roche Diagnostics International, Switzerland). Total serum protein and serum albumin were quantified via colorimetric assay from lithium-heparin plasma (cobas8000 c702 module). Subsequently, serum AGR was calculated from serum albumin and total serum protein. Furthermore, serum CAR was calculated for each patient and included in our analysis. Synovial fluid samples of the affected joint were sent for leucocyte count, granulocyte percentage, and microbiology. Intraoperatively, at least three tissue samples were collected for tissue culture and histopathological analysis, and

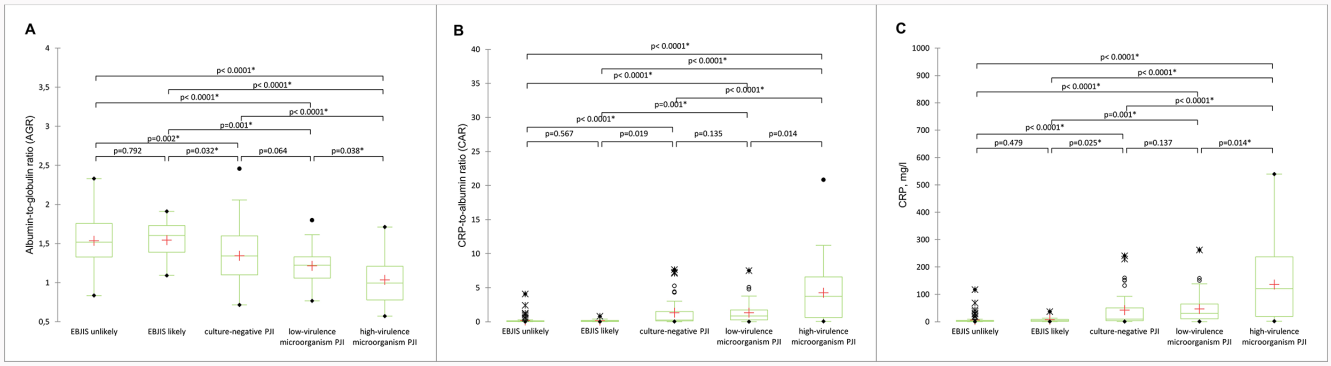

Fig. 1

Boxplots of a) serum albumin-to-globulin ratio (AGR), b) serum CRP-to-albumin ratio, and c) serum CRP levels in aseptic and septic subgroups. Asterisks (*) indicate a significant difference between groups (Dunn's test with Bonferroni correction). + indicates mean values, • minimum and maximum, and ○ outliers. EBJIS, European Bone and Joint Infection Society criteria for periprosthetic joint infection; PJI, periprosthetic joint infection.

Table I. Demographic data of all included patients.

Characteristic	Septic cases (n = 144)	Aseptic cases (n = 131)	p-value	Total (n = 275)
Median age, yrs (IQR)	72.0 (62.5 to 78.3)	71.0 (62.5 to 77.0)	0.746*	72.0 (62.5 to 78.0)
Female sex, n (%)	78 (54.2)	80 (61.1)	0.248†	158 (57.5)
Median BMI, kg/m^2 (IQR)	28.3 (24.1 to 31.7)	27.7 (24.3 to 31.6)	0.486*	27.8 (24.2 to 31.7)
ASA grade, n (%)			< 0.001‡	
I	3 (2.1)	10 (7.6)		13 (4.7)
II	52 (36.1)	64 (48.9)		116 (42.2)
III	79 (54.9)	55 (42.0)		134 (48.7)
IV	9 (6.3)	2 (1.5)		11 (4.0)
V	1 (0.7)	0 (0.0)		1 (0.4)
Localization, n (%)			0.894†	
Hip	67 (46.5)	62 (47.3)		129 (46.9)
Knee	77 (53.5)	69 (52.7)		146 (53.1)
Preoperative antibiotics, n (%)	16 (11.1)	1 (0.8)	< 0.001§	17 (6.2)
Rheumatoid arthritis, n (%)	9 (6.3)	9 (6.9)	0.835†	18 (6.5)
Serum parameters				
Median AGR (IQR)	1.17 (0.93 to 1.39)	1.53 (1.32 to 1.75)	< 0.001‡	1.35 (1.09 to 1.60)
Median CAR (IQR)	1.03 (0.19 to 4.09)	0.07 (0.04 to 0.14)	< 0.001‡	0.17 (0.06 to 1.19)
Median CRP, mg/l (IQR)	36.7 (8.0 to 138.9)	2.8 (1.4 to 5.5)	< 0.001‡	7.1 (2.3 to 42.5)
Median total serum protein, g/l (IQR)	68.8 (63.0 to 75.3)	69.7 (61.9 to 72.8)	0.196	69.4 (62.4 to 73.8)

*Independent-samples *t*-test.
†Chi-squared test.
‡Mann-Whitney U test.
§Fisher's exact test.
AGR, serum albumin-to-globulin ratio; ASA, American Society of Anesthesiologists; ASA, American Society of Anesthesiologists; CAR, serum CRP-to-albumin ratio.

explanted prostheses components were sent for sonication. All microbiological cultures were incubated for at least 14 days.[2] In addition, a qualitative alpha-defensin test was performed intraoperatively prior to capsulotomy.

For detailed analysis, all septic cases were stratified into a high-virulence (e.g. *Staphylococcus aureus*, streptococci, enterococci, and *Enterobacteriaceae*), a low-virulence (e.g. coagulase-negative staphylococci and *Cutibacterium* spp.), and a culture-negative subgroup, depending on synovial fluid, tissue, and sonication culture results. In polymicrobial infections, patients were assigned to the high-virulence group if a highly virulent pathogen was present.

Table II. Overview of detected microorganisms.

Microorganism, n (%)	Frequency in all infections (n = 144)
Coagulase-negative staphylococci	26 (18.1)
Staphylococcus aureus	24 (16.7)
Streptococci	7 (4.9)
Cutibacterium spp.	7 (4.9)
Enterococci	6 (4.2)
Enterobacteriaceae	5 (3.5)
Candida albicans	2 (1.4)
Others*	9 (6.3)
Polymicrobial	13 (9.0)
Culture-negative	45 (31.3)

*Others: *Finegoldia magna* (n = 2), *Pseudomonas aeruginosa*, *Mycobacterium* spp., *Corynebacterium aurimucosum*, *Actinomyces neuii*, *Bacteroides thetaiotaomicron*, *Parvimonas micra*, *Moraxella osloensis*.

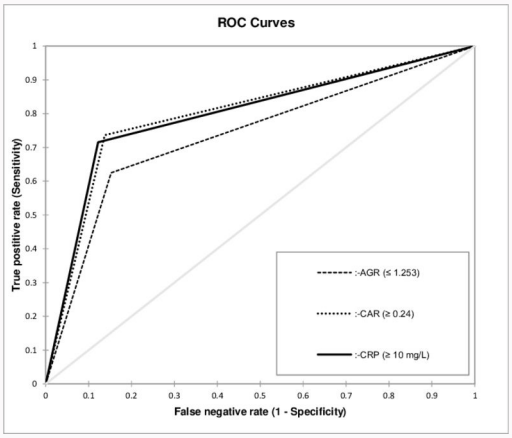

Fig. 2
Receiver operating characteristic (ROC) curves for accuracy of serum parameters in diagnosis of periprosthetic joint infection, depending on parameter and cut-off value. AGR, serum albumin-to-globulin ratio; CAR, serum CRP-to-albumin ratio.

Table III. Comparison of CRP, serum CRP-to-albumin ratio, and serum albumin-to-globulin ratio values of aseptic and septic subgroups.

	Aseptic cases (n = 131)		Septic cases (n = 144)			
Serum markers	EBJIS unlikely (n = 115)	EBJIS likely (n = 16)	Culture-negative PJI (n = 45)	Low-virulence microorganisms (n = 40)	High-virulence microorganisms (n = 59)	p-value*
Median AGR (IQR)	1.52 (1.33 to 1.76)	1.60 (1.39 to 1.73)	1.34 (1.10 to 1.60)	1.22 (1.06 to 1.33)	0.99 (0.78 to 1.21)	< 0.001
Median CAR (IQR)	0.07 (0.04 to 0.13)	0.12 (0.03 to 0.20)	0.25 (0.10 to 1.49)	0.83 (0.27 to 1.73)	3.73 (0.61 to 6.57)	< 0.001
Median CRP, mg/l (IQR)	2.7 (1.4 to 5.1)	4.8 (1.3 to 8.4)	9.5 (3.8 to 50.2)	30.2 (10.4 to 64.5)	121.1 (19.2 to 237.2)	< 0.001
Median total serum protein, g/l (IQR)	69.4 (60.5 to 72.8)	70.8 (68.0 to 72.8)	69.5 (61.8 to 75.2)	69.2 (64.0 to 73.4)	68.8 (63.2 to 75.9)	0.558*

*Kruskal-Wallis test.
AGR, serum albumin-to-globulin ratio; CAR, serum CRP-to-albumin ratio; EBJIS, European Bone and Joint Infection Society; PJI, periprosthetic joint infection.

Further subgroup analysis was performed to compare diagnostic accuracies of AGR, CAR, and CRP depending on virulence of the microorganism (high- vs low-virulence pathogens), timing of infection (acute vs chronic PJI), and localization (hip vs knee PJI). Acute haematogenous PJIs were defined as cases with a sudden onset of symptoms of < three weeks in a prior well-functioning prosthesis, and uneventful period > four weeks after implantation; all other infections were regarded as chronic PJI with mature biofilm.[1] In accordance with exclusion criteria, only acute haematogenous PJIs were analyzed (no early postoperative PJIs).

Statistical analysis

Categorical variables are given as absolute and relative frequencies (percentage), continuous variables are described as median and IQR. Chi-squared test, independent-samples *t*-test, Fisher's exact test, Mann-Whitney U test, and Kruskal-Wallis test were used wherever statistically suitable. Sensitivity, specificity, accuracy, positive (PPV) and negative predictive value (NPV), positive (LR+) and negative likelihood ratio (LR-), and areas under the receiver operating characteristic (ROC) curve (AUCs) with their respective 95% CIs were calculated for serum AGR, CRP, and CAR. Ideal cut-off values were determined using Youden's index, and AUCs were compared using the z-test (two-sided). For all tests, a significance level of $p < 0.05$ was applied. Statistical analysis was conducted in XLSTAT version 2023.1.2.1406 (Lumivero, USA).

Results

Microorganisms

Of 144 confirmed infections, 99 cases (68.8%) yielded positive microbial cultures. Coagulase-negative staphylococci were most frequently isolated (n = 26; 18.1% of all infections), followed by *Staphylococcus aureus* (n = 24; 16.7%), streptococci (n = 7; 4.9%), and *Cutibacterium* spp. (n = 7; 4.9%). All detected microorganisms are listed in Table II.

A detailed comparison of median serum AGR, CAR, and CRP values in aseptic and septic subgroups can be seen in Table III. Statistically significant lower AGR levels, and higher CAR and CRP levels, were seen in infections caused

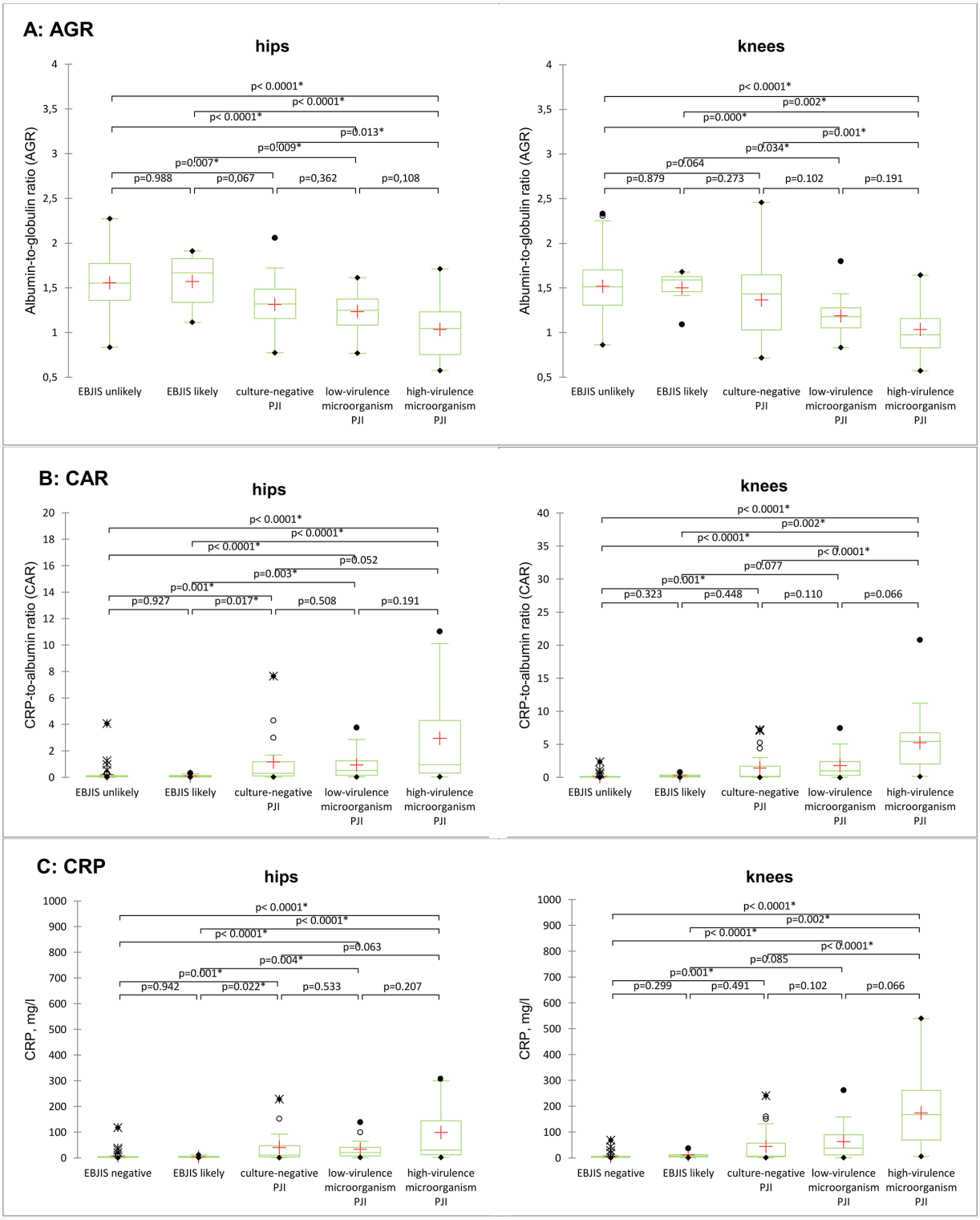

Fig. 3

Boxplots of a) serum albumin-to-globulin ratio (AGR) levels in hips and knees in aseptic and septic subgroups; b) serum CRP-to albumin ratio (CAR) levels in hips and knees in aseptic and septic subgroups; and c) serum CRP levels in hips and knees in aseptic and septic subgroups. Asterisks (*) indicate a significant difference between groups (Dunn's test with Bonferroni correction), + indicates mean values, • minimum and maximum, and ○ and represent outliers. EBJIS, European Bone and Joint Infection Society criteria for periprosthetic joint infection; PJI, periprosthetic joint infection.

by high-virulence microorganisms in comparison to infections caused by low-virulence microorganisms, culture-negative PJIs, and aseptic cases ($p < 0.05$, Table III). No difference was seen between low-grade infections and culture-negative PJIs (AGR: $p = 0.064$, CAR: $p = 0.153$, CRP: $p = 0.173$). Figure 1 illustrates median values in aseptic and septic subgroups with their p-values (Dunn's test with Bonferroni correction) between all groups.

Diagnostic accuracy of serum AGR and CAR

Table IV illustrates the diagnostic accuracies of serum AGR, CAR, and CRP with their respective cut-off values. The optimal

Table IV. Diagnostic accuracy of serum albumin-to-globulin ratio, serum CRP-to-albumin ratio, and serum CRP.

Diagnostic accuracy	AGR	CAR	CRP
Cut-off value	≤ 1.253	≥ 0.24	≥ 10 mg/l
Sensitivity, % (95% CI)	62.5 (54.3 to 70.0)	73.6 (65.8 to 80.1)	71.5 (63.6 to 78.3)
Specificity, % (95% CI)	84.7 (77.5 to 89.9)	86.3 (79.2 to 91.2)	87.8 (80.9 to 92.4)
Youden's index	0.472	0.599	0.593
PPV, % (95% CI)	81.8 (74.6 to 89.0)	85.5 (79.3 to 91.7)	86.6 (80.4 to 92.7)
NPV, % (95% CI)	67.3 (60.1 to 74.4)	74.8 (67.9 to 81.8)	73.7 (66.8 to 80.6)
LR+ (95% CI)	4.094 (2.682 to 6.248)	5.357 (3.450 to 8.319)	5.856 (3.658 to 9.375)
LR- (95% CI)	0.443 (0.354 to 0.553)	0.306 (0.231 to 0.405)	0.324 (0.248 to 0.423)
AUC (95% CI)	0.736 (0.686 to 0.786)	0.799 (0.753 to 0.846)	0.797 (0.750 to 0.843)

AGR, serum albumin-to-globulin ratio; AUC, area under the curve; CAR, serum CRP-to-albumin ratio; LR+, positive likelihood ratio; LR-, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

thresholds for AGR and CAR were 1.253 and 0.24; sensitivity was calculated at 62.5% (95% CI 54.3 to 70.0) and 73.6% (95% CI 65.8 to 80.1), and specificity at 84.7% (95% CI 77.5 to 89.9) and 86.3% (95% CI 79.2 to 91.2), respectively. When utilizing the 10 mg/l threshold for CRP as specified in the EBJIS definition of PJI,[2] a sensitivity of 71.5% (95% CI 63.6 to 78.3) and a specificity of 87.8% (95% CI 80.9 to 92.4) were observed.

The AUC of serum AGR was significantly lower than the AUCs of the other parameters ($p < 0.001$, z-test for independent samples); no statistically significant difference was observed between CRP and CAR ($p = 0.832$, z-test for independent samples). Figure 2 displays the ROC curves of all analyzed parameters.

Table V shows diagnostic accuracies of AGR, CAR, and CRP in subgroup analyses. A better diagnostic performance was observed in PJI with high-virulence microorganisms compared to PJI with low-virulence microorganisms for all three parameters (AGR: $p < 0.001$; CAR: $p = 0.005$; CRP: $p = 0.003$, z-test for independent samples). Similarly, higher accuracies were calculated in acute haematogenous infections than in chronic infections ($p < 0.001$, z-test for independent samples). Higher sensitivities and specificities were found in the knee subgroup; however, results were only significant for AGR ($p = 0.043$). CAR yielded a p-value of 0.225, and CRP a p-value of 0.134.

In each of the subanalyses, AGR showed inferior performance compared to CAR and CRP (hip: AGR vs CAR $p = 0.002$; AGR vs CRP $p = 0.005$; knee: AGR vs CAR $p = 0.012$; AGR vs CRP $p = 0.012$; acute haematogenous: AGR vs CAR $p < 0.001$; chronic: AGR vs CAR $p = 0.001$, AGR vs CRP $p = 0.004$; high-virulence: AGR vs CAR $p = 0.004$, AGR vs CRP $p = 0.005$; low-virulence: AGR vs CAR $p < 0.001$; AGR vs CRP $p < 0.001$, all z-test). Figure 3 shows boxplots of serum AGR, CAR, and CRP in hips and knees.

Of the 144 confirmed cases, 41 had a serum CRP concentration of < 10 mg/l. Of these, 9/41 (22%) had an AGR of ≤ 1.253 and 4/41 (10%) a CAR of ≥ 0.24.

Discussion

At AUCs of 0.736 and 0.799, serum AGR and CAR showed limited accuracy in diagnosing PJI preoperatively in our study. With sensitivities of only 63% and 74%, the number of false-negative cases was high, which is likely due to low-virulence microorganisms capable of forming biofilm in chronic infections, resulting in a reduced release of systemic inflammatory biomarkers.[12] Indeed, our subanalysis showed decreased sensitivities in PJIs caused by low-virulence organisms (AGR: 60%, CAR: 78%) compared to high-virulence pathogens (AGR: 80%, CAR: 88%). Similarly, higher sensitivities were observed in acute haematogenous (AGR: 83%, CAR: 96%) compared to chronic PJIs (AGR: 54%, CAR: 65%). Additionally, specificities of AGR (85%) and CAR (86%) were only moderate in our cohort, indicating a certain number of false-positive cases. This may be due to patient factors associated with a rise in systemic inflammatory parameters,[6] and/or reduced overall protein synthesis in patients with liver disfunction and malnutrition.[13,14] However, regarding specificity, almost no changes were seen between acute haematogenous (AGR: 86%, CAR: 86%) and chronic infections (AGR: 85%, CAR: 86%) and PJIs with high-virulence pathogens (AGR: 85%, CAR: 86%) and PJIs with low-virulence microorganisms (AGR: 85%, CAR: 86%). Although none of the evaluated parameters (AGR, CAR) demonstrated an adequate performance, they showed a good correlation with systemic severity of infection as levels increased from aseptic cases towards culture-negative cases, and low-virulence PJIs towards high-virulence microorganism PJIs (Table III).

It needs to be highlighted that serum albumin and globulin may be influenced by undernutrition and malnutrition, which are commonly seen in the elderly and hospitalized population. Furthermore, AGR reaches its bottom values after approximately five to seven days after an inflammatory stimulus, whereas CRP shows its highest concentrations after 36 to 48 hours,[5,15] suggesting higher diagnostic values (AUC) of CRP in acute infections, which we were also able to demonstrate. These drawbacks may also apply to CAR, but possibly

Table V. Subgroup analysis (high- vs low-virulence microorganisms; acute haematogenous vs chronic infections; hip vs knee) of diagnostic accuracy of serum parameters.

Diagnostic accuracy	Virulence of detected microorganism(s)		Type of infection		Localization	
	High (n = 59)	Low (n = 40)	Acute (n = 47)	Chronic (n = 63)	Hip (n = 129)	Knee (n = 146)
AGR						
Cut-off value	≤ 1.253	≤ 1.253	≤ 1.253	≤ 1.253	≤ 1.253	≤ 1.253
Sensitivity, % (95% CI)	79.7 (67.5 to 88.0)	60.0 (44.6 to 73.6)	83.0 (69.5 to 91.3)	54.0 (41.8 to 65.7)	56.7 (44.8 to 67.9)	67.5 (56.4 to 76.9)
Specificity, % (95% CI)	84.7 (77.5 to 89.9)	84.7 (77.5 to 89.9)	86.3 (79.0 to 91.3)	84.6 (77.3 to 89.9)	85.5 (74.3 to 92.3)	84.1 (73.4 to 91.0)
Youden's index	0.644	0.447	0.693	0.386	0.422	0.516
PPV, % (95% CI)	70.1 (59.2 to 81.1)	54.5 (39.8 to 69.3)	69.6 (57.6 to 81.7)	63.0 (50.1 to 75.8)	80.9 (69.6 to 92.1)	82.5 (73.2 to 91.9)
NPV, % (95% CI)	90.2 (85.0 to 95.5)	87.4 (81.6 to 93.2)	93.0 (88.4 to 97.7)	79.1 (72.4 to 85.9)	64.6 (54.3 to 75.0)	69.9 (60.0 to 79.7)
LR+ (95% CI)	5.218 (3.416 to 7.969)	3.930 (2.441 to 6.327)	6.053 (3.820 to 9.589)	3.508 (2.207 to 5.575)	3.907 (2.062 to 7.404)	4.236 (2.411 to 7.442)
LR- (95% CI)	0.240 (0.144 to 0.400)	0.472 (0.321 to 0.695)	0.197 (0.105 to 0.372)	0.544 (0.412 to 0.718)	0.506 (0.378 to 0.678)	0.386 (0.275 to 0.542)
AUC (95% CI)	0.822 (0.762 to 0.882)	0.724 (0.641 to 0.807)	0.846 (0.784 to 0.909)	0.734 (0.666 to 0.802)	0.711 (0.637 to 0.785)	0.758 (0.690 to 0.826)
CAR						
Cut-off value	≥ 0.24	≥ 0.24	≥ 0.24	≥ 0.24	≥ 0.24	≥ 0.24
Sensitivity, % (95% CI)	88.1 (77.1 to 94.4)	77.5 (62.2 to 87.8)	95.7 (84.8 to 99.5)	65.1 (52.7 to 75.7)	73.1 (61.4 to 82.3)	74.0 (63.2 to 82.5)
Specificity, % (95% CI)	86.3 (79.2 to 91.2)	86.3 (79.2 to 91.2)	86.3 (79.0 to 91.3)	86.2 (79.0 to 91.1)	84.1 (72.9 to 91.3)	88.6 (78.7 to 94.3)
Youden's index	0.744	0.638	0.820	0.512	0.570	0.624
PPV, % (95% CI)	74.3 (64.0 to 84.5)	63.3 (49.8 to 76.8)	72.6 (61.5 to 83.7)	69.5 (57.7 to 81.2)	83.1 (73.5 to 92.6)	87.7 (79.7 to 95.7)
NPV, % (95% CI)	94.2 (90.0 to 98.4)	92.6 (88.0 to 97.3)	98.2 (95.6 to 100.0)	83.6 (77.3 to 89.9)	74.6 (64.5 to 84.8)	75.6 (66.3 to 84.9)
LR+ (95% CI)	6.414 (4.135 to 9.951)	5.640 (3.559 to 8.938)	6.984 (4.472 to 10.905)	4.700 (2.951 to 7.486)	4.607 (2.562 to 8.285)	6.477 (3.330 to 12.601)
LR- (95% CI)	0.138 (0.068 to 0.277)	0.261 (0.146 to 0.465)	0.049 (0.013 to 0.192)	0.405 (0.287 to 0.572)	0.319 (0.212 to 0.481)	0.293 (0.199 to 0.432)
AUC (95% CI)	0.872 (0.821 to 0.923)	0.819 (0.747 to 0.891)	0.910 (0.868 to 0.952)	0.756 (0.690 to 0.823)	0.785 (0.714 to 0.856)	0.812 (0.750 to 0.874)
CRP						
Cut-off value	≥ 10 mg/l	≥ 10 mg/l	≥ 10 mg/l	≥ 10 mg/l	≥ 10 mg/l	≥ 10 mg/l
Sensitivity, % (95% CI)	86.4 (75.1 to 93.2)	75.0 (59.6 to 85.9)	95.7 (84.8 to 99.5)	61.9 (49.5 to 72.9)	68.7 (56.7 to 78.5)	74.0 (63.2 to 82.5)
Specificity, % (95% CI)	87.8 (80.9 to 92.4)	87.8 (80.9 to 92.4)	87.9 (80.8 to 92.6)	87.7 (80.8 to 92.3)	87.3 (76.5 to 93.6)	88.6 (78.7 to 94.3)
Youden's index	0.742	0.628	0.836	0.496	0.558	0.624
PPV, % (95% CI)	76.1 (65.9 to 86.3)	65.2 (51.5 to 79.0)	75.0 (64.0 to 86.0)	70.9 (58.9 to 82.9)	85.2 (75.7 to 94.7)	87.7 (79.7 to 95.7)
NPV, % (95% CI)	93.5 (89.1 to 97.9)	92.0 (87.2 to 96.8)	98.2 (95.7 to 100.0)	82.6 (76.3 to 88.9)	72.4 (62.3 to 82.4)	75.6 (66.3 to 84.9)
LR+ (95% CI)	7.077 (4.423 to 11.325)	6.141 (3.752 to 10.051)	7.915 (4.906 to 12.769)	5.030 (3.057 to 8.277)	5.407 (2.774 to 10.538)	6.477 (3.330 to 12.601)

(*Continued*)

(*Continued*)

Diagnostic accuracy	Virulence of detected microorganism(s)		Type of infection		Localization	
	High (n = 59)	Low (n = 40)	Acute (n = 47)	Chronic (n = 63)	Hip (n = 129)	Knee (n = 146)
LR- (95% CI)	0.154 (0.081 to 0.295)	0.285 (0.166 to 0.489)	0.048 (0.012 to 0.188)	0.434 (0.315 to 0.599)	0.359 (0.249 to 0.518)	0.293 (0.199 to 0.432)
AUC (95% CI)	0.871 (0.819 to 0.923)	0.814 (0.740 to 0.887)	0.918 (0.877 to 0.959)	0.748 (0.681 to 0.815)	0.779 (0.709 to 0.849)	0.812 (0.750 to 0.874)

AGR, serum albumin-to-globulin ratio; AUC, area under the curve; CAR, serum CRP-to-albumin ratio; LR+, positive likelihood ratio; LR-, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

Table VI. Comparison of the literature for serum albumin-to-globulin ratio.

Literature	Infection definition*	Patients, n	Localization	AGR threshold	AUC	Sensitivity	Specificity
Ye et al[6]	MSIS 2018	38 PJI, 89 aseptic, 127 total	100 hips, 27 knees	1.2	0.779	65.79	78.95
Wang et al[7]	MSIS 2013	82 PJI, 139 aseptic, 221 total	141 hips, 80 knees	1.2	0.845	66.25	93.48
Shang et al[19]	MSIS 2018	79 PJI, 127 aseptic, 206 total	110 hips, 116 knees	1.165	0.826	67.1	86.7
Jiao et al[20]	MSIS 2014	53 PJI, 62 aseptic, 115 total	hip, knee numbers unspecified	1.32	0.779	81.13	72.58
Zhang et al[21]	MSIS 2013	89 PJI, 152 aseptic, 241 total	187 hips, 54 knees	1.2	0.851	65.17	86.84
Wu et al[22]	MSIS 2014	47 PJI, 117 aseptic, 164 total	115 hips, 49 knees	1.19	0.767	68.09	76.07
Choe et al[8]	ICM 2018	51 PJI, 45 aseptic, 334 hip osteoarthritis control, 430 total	Hip	1.2	0.960	98	86
Wang et al[23]	MSIS 2014	56 PJI, 106 aseptic, 162 total	108 hips, 54 knees	1.31	0.899	91.07	73.58
Dong et al[24]	MSIS 2014	64 PJI, 118 aseptic, 182 total	121 hips, 61 knees	1.295	0.855	84.6	75.8
Present study	EBJIS 2021	144 PJI, 131 aseptic, 275 total	129 hips, 146 knees	1.253	0.737	62.5	84.7

*As specified by the authors of the respective study.
AGR, albumin-to-globulin ratio; AUC, area under the curve; EBJIS, European Bone and Joint Infection Society; ICM, International Consensus Meeting; MSIS, Musculoskeletal Infection Society; PJI, periprosthetic joint infection.

to a lesser extent as both CRP and albumin are assessed at the same time. Additionally, albumin and globulin may not only be altered by infections with a specific pathogen, but also by a general inflammatory state in the body. All these possible limitations need to be considered when interpreting the results of AGR and CAR.

Nevertheless, it seems that these serum parameters perform better in acute haematogenous PJIs and high-virulence organisms compared to chronic infections and low-virulence pathogens. This was also observed in other serum inflammatory parameters such as serum CRP and fibrinogen.[4,16–18] In acute planktonic infections, these markers are highly elevated due to the increased immune response. This is attributable to certain characteristics of these bacteria leading to higher invasiveness and increased systemic involvement of infection.[12]

Nevertheless, in only 22% (9/41, AGR) and 10% (4/41, CAR) of serum CRP negative infections, AGR and CAR indicated an infection. Additionally, serum AGR and CAR did not outperform the widely used and established marker CRP in our study. Specifically, serum CRP (AUC: 0.797) performed statistically significant better than AGR (0.736) and similar to

Table VII. Comparison of the literature for serum CRP-to-albumin ratio.

Literature-CAR	Infection definition*	No. of patients	Localization	CAR threshold	AUC	Sensitivity	Specificity
Choe et al[8]	ICM 2018	51 PJI, 45 aseptic 334 hip osteoarthritis control 430 total	Hip	1.1	0.970	92	95
Shi et al[27]	MSIS 2018	87 PJI, 157 aseptic 244 total	166 hips, 78 knees	0.28	0.931	80.2	95.2
Wu et al[28]	MSIS 2014	187 PJI, 268 aseptic 455 total	344 hips, 111 knees	0.13	0.880	85.0	78.4
Sang et al[29]	MSIS 2014	79 PJI, 79 aseptic 158 total	90 hips, 68 knees	0.23	0.831	72.15	82.28
Present study	EBJIS 2021	144 PJI, 131 aseptic 275 total	129 hips, 146 knees	0.24	0.799	73.6	86.3

*As specified by the authors of the respective study.
AUC, area under the curve; CAR, CRP-to-albumin ratio; EBJIS, European Bone and Joint Infection Society; ICM, International Consensus Meeting; MSIS, Musculosceletal Infection Society; PJI, periprosthetic joint infection.

CAR (0.799) in all of our analyses, indicating no additional advantage of the two new proposed serum parameters AGR and CAR (Table IV). However, serum CRP also showed an overall insufficient performance in diagnosing PJI. Hence, it can only be used as a suggestive rather than confirmatory criterion in diagnosing PJI, as previously recommended by EBJIS.[2]

When comparing our serum AGR results with those in the literature, the calculated cut-off values in all published studies are relatively similar to ours (Table VI).[6–8,19–24] However, although some study groups reported similar diagnostic performances (AUCs),[6,20,22] others observed higher accuracies in their studies.[7,8,19,21,23,24] These heterogenous findings may be attributed to differences in detected microorganisms (high- and low-virulence pathogens), incubation period of microbiological cultures, exclusion criteria (inflammatory diseases, liver and renal dysfunction, malnourishment, history of malignancy, etc.), infection definitions (Musculoskeletal Infection Society (MSIS)/International Consensus Meeting (ICM) 2013/14 or ICM 2018),[25,26] and preoperative timing of measurement of the serum parameters. All previous studies excluded patients with comorbidities, confounding AGR (selection bias). Therefore, results may not be generalizable in clinical practice. Additionally, in our study, a higher number of infected cases was included, leading to a more accurate analysis.

Regarding CAR, better performances were observed in previous published studies in comparison to our results (Table VII).[8,27–29] Choe et al[8] recently found excellent diagnostic accuracies of serum CAR and proposed it as a valuable additional biomarker for diagnosing PJI. Their analyses yielded an excellent diagnostic accuracy with an AUC of 0.97 at a threshold of 1.1. In 2023, three other workgroups published their findings on CAR in diagnosing PJI.[27–29] Thresholds of 0.13 to 1.1 were proposed, with varying sensitivities and specificities. Interestingly, the studies using ICM 2018 criteria showed higher AUCs in comparison to our study. It is known that an underdiagnosis of low-grade infections may be possible with these criteria, as the authors pointed out.[26] This indicates a higher number of acute infections in their cohorts. In our study, we demonstrated a better performance in acute infections compared to chronic infections with a similar AUC (acute: 0.910) compared to the studies using ICM 2018 criteria (Choe et al[8] (AUC: 0.970), Shi et al[27] (0.931)). However, the MSIS 2013 criteria showed an even lower identification rate of chronic infections in the literature,[26,30] but in the studies using these criteria, such a high performance could not be observed. Therefore, this cannot be the only explanation for these different results. Similar to the literature on AGR, some possible confounding factors have to be considered when comparing results (differences in isolated pathogens, incubation period of microbiological cultures, infection definitions, and preoperative timing of measurement of CAR). Additionally, all previous studies excluded patients based on comorbidities.

To our knowledge, this is the largest cohort of revision arthroplasty cases to date evaluating the diagnostic performance of serum AGR and CAR in PJI, and the first one investigating a European population. No patients were excluded for comorbidities, limiting selection bias.

However, this study has several limitations. We used the EBJIS definition for diagnosis of PJI. There is some concern among the scientific community that it could potentially misdiagnose some aseptic failures as PJI. However, it has been demonstrated that the EBJIS definition does not over-diagnose PJI compared to the ICM 2018 and Infectious Diseases Society of America 2013[31] definitions.[30,32] Additionally, this study is limited by its retrospective design. Not all parameters included in the EBJIS definition were available to all patients (sinus tract: n = 275/275, pus: n = 275/275, serum CRP/AGR/CAR: n = 275/275, clinical features: n = 275/275, synovial fluid white blood cell count: n = 153/275, synovial fluid percentage of polymorphomuclear neutrophils: n = 92/275, α defensin lateral flow test: n = 147/275, SF-culture: n = 220/275, tissue culture: n = 237/275, sonication: n = 257/275, histology: n = 268/275), which is a common problem in clinical practice. Finally, subgroup analysis is limited by the small sample sizes.

Overall, serum AGR and CAR showed limited diagnostic accuracy in our study. Low sensitivities, especially in low-grade and chronic infections, limit their performance enormously in preoperative diagnosis. Additionally, they did not outperform the widely used and established marker CRP. Hence, it seems that only little – if any – supplementary preoperative insight is gained by evaluating serum AGR and CAR in diagnosing PJI.

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Author information

M. Luger, MD, Registrar
C. Böhler, Prof. MD, Orthopaedic Consultant
S. E. Puchner, PD, MD, Orthopaedic Consultant
S. Apprich, PD, MD, Orthopaedic Consultant
K. Staats, PD, MD, Orthopaedic Surgeon
R. Windhager, Univ Prof, MD, Head of Department
I. K. Sigmund, PD, MD, Orthopaedic Consultant

Department of Orthopaedics and Trauma Surgery, Medical University of Vienna, Vienna, Austria.

Author contributions

M. Luger: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing.

C. Böhler: Conceptualization, Data curation, Investigation, Writing – review & editing.
S. E. Puchner: Conceptualization, Data curation, Investigation, Writing – review & editing.
S. Apprich: Conceptualization, Data curation, Investigation, Writing – review & editing.
K. Staats: Conceptualization, Data curation, Investigation, Writing – review & editing.
R. Windhager: Conceptualization, Data curation, Investigation, Writing – review & editing.
I. K. Sigmund: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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