

Assessment of the Diagnostic Efficacy of C-Reactive Protein (CRP)/Albumin to Globulin Ratio (AGR) Test as a Good Diagnostic Tool for Periprosthetic Joint Infection

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Abstract

Aim: To assess C-reactive protein (CRP)/albumin to globulin ratio (AGR) test as a good diagnostic tool for periprosthetic joint infection.

Materials and Methods: This study was done in the department of Orthopaedics, SKMCH, Muzaffarpur, Bihar, India for six months. The study design involved a retrospective analysis of clinical data obtained from patients who were diagnosed with peri prosthetic joint infections. The collected data consists of various parameters such as age, gender and pre-operative serum markers including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), globulin (GLB), Albumin to globulin ratio (A/G), CRP/AGR ratio.

Results: Among 30 patients 21 had positive culture results, 9 patients had negative culture results. Based on the culture reports the most common organism involved is *Staphylococcus aureus* 85.71% followed by *Staph. Epidermidis* 14.28%. Average values for culture sensitive CRP/AGR values 69 (Ranging from 29 to 96). Average CRP value is 66.85 mg/L (ranging from 46 mg/L to 94 mg/L). ESR average value of 55mm/hr (ranging from 27 mm/hr to 98 mm/hr). Average values for culture negative CRP/AGR 15.22 (ranging from 8 to 44). CRP average value 15.77 mg/L ranging from (11 mg/L to 23 mg/L). ESR 32.77 mm/hr ranging from (27 mm/hr to 39 mm/hr). For culture sensitive patients the diagnosing accuracy for in culture patients CRP is 91.75%, ESR is 69.46%, CRP/AGR 93.75%, (whereas in culture negative the threshold for diagnosing accuracy for CRP is 60%, CRP/AGR is 61%, ESR is 51%).

Conclusion: In conclusion, our findings indicate that the patients diagnosed with PJI (Periprosthetic joint infection) exhibited significantly elevated levels of ESR, CRP, CRP/AGR. These biomarkers show promising results for the diagnosis of PJI. However, when used alone, CRP/AGR demonstrated excellent diagnostic performance, followed by CRP and ESR with good diagnostic performance.

Keywords: C-reactive protein, Albumin, Globulin, Periprosthetic joint infection

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Introduction

Periprosthetic joint infection (PJI) remains a challenging complication following total knee arthroplasty (TKA) and total hip arthroplasty (THA), significantly affecting patient outcomes and healthcare costs. Prompt and accurate diagnosis of PJI is crucial for timely intervention and improved patient management. Traditionally, diagnosis has relied on a combination of clinical signs, biomarkers, and imaging studies. Among these biomarkers, C-reactive protein (CRP) and the CRP/albumin to globulin ratio (AGR) have emerged as promising tools due to their sensitivity and specificity in detecting inflammation and infection.

[1] Diagnosing PJI is complex due to nonspecific clinical presentations and the overlapping symptoms with aseptic loosening and other complications. Biomarkers play a pivotal role in distinguishing between infectious and non-infectious aetiologies, guiding clinicians in making informed decisions regarding treatment strategies. CRP, an acute-phase reactant synthesized by the liver in response to inflammation, has long been utilized as a marker of systemic inflammation and infection. Elevated levels of CRP are indicative of an inflammatory response but lack specificity for diagnosing PJI alone. [2] The addition of albumin and globulin to

CRP measurements as part of the CRP/AGR ratio aims to enhance diagnostic accuracy by integrating markers of systemic inflammation and nutritional status. Albumin, a major protein in plasma, reflects the nutritional and inflammatory status of the patient. Globulins, including immunoglobulins and acute-phase proteins, contribute to the immune response against infection. The CRP/AGR ratio thus provides a more comprehensive assessment, considering both the inflammatory response (CRP) and the immune-nutritional status (albumin and globulin), which can aid in differentiating PJI from other causes of joint pain and dysfunction. [3] Over the years, diagnostic criteria for PJI have evolved to incorporate both clinical parameters and biomarkers. The Musculoskeletal Infection Society (MSIS) criteria and the International Consensus Meeting (ICM) criteria provide standardized guidelines for diagnosing PJI, emphasizing the role of biomarkers alongside clinical findings and microbiological cultures. While traditional biomarkers like CRP and erythrocyte sedimentation rate (ESR) have been cornerstone tests, their limitations in specificity and sensitivity have prompted exploration into novel biomarkers and diagnostic algorithms.⁴ Recent advancements have focused on enhancing the accuracy of biomarkers through combinations and ratios. The CRP/AGR ratio represents one such innovation, harnessing the synergistic information provided by CRP, albumin, and globulin. Studies have demonstrated that this ratio can offer superior diagnostic performance compared to individual biomarkers alone, particularly in distinguishing between septic and aseptic joint failures. This improvement is crucial given the clinical implications of misdiagnosis, including unnecessary revision surgeries or delays in appropriate treatment. [4]

Moreover, the incorporation of CRP/AGR into diagnostic algorithms has been advocated by recent guidelines and expert consensus statements. The Infectious Diseases Society of America (IDSA) and the European Bone and Joint Infection Society (EBJIS) recommend integrating biomarker panels like CRP/AGR into clinical decision-making algorithms to improve diagnostic accuracy and optimize patient outcomes. These guidelines underscore the importance of adopting evidence-based approaches that leverage biomarkers effectively in the management of PJI. [5] Despite its promise, the CRP/AGR ratio is not without limitations. Variability in albumin and globulin levels due to nutritional status, liver function, and systemic conditions may impact the ratio's interpretation. Furthermore, the optimal cutoff values for CRP/AGR require further validation across different patient populations and clinical settings. Future research should focus on standardizing protocols for biomarker measurement, conducting prospective studies to validate

diagnostic algorithms, and exploring additional biomarkers or imaging modalities to enhance diagnostic precision. [6] The CRP/AGR ratio represents a valuable advancement in the diagnostic armamentarium for periprosthetic joint infection. By integrating CRP with albumin and globulin, this ratio provides a comprehensive assessment of systemic inflammation and nutritional status, aiding clinicians in distinguishing infectious from non-infectious aetiologies. Ongoing research and clinical validation efforts are essential to refine diagnostic algorithms and establish the CRP/AGR ratio as a standard biomarker panel in the management of PJI. Adopting evidence-based approaches that incorporate biomarkers effectively can ultimately improve patient outcomes and optimize healthcare resource utilization in the management of this challenging complication of joint arthroplasty. [7] This study aims to evaluate the diagnostic accuracy of CRP, ALB, GLB, AGR and fibrinogen as biomarker for PJI.

Materials and Methods

This study was done in the department of Orthopaedics, SKMCH, Muzaffarpur, Bihar, India for six months. The study design involved a retrospective analysis of clinical data obtained from patients who were diagnosed with peri prosthetic joint infections. The collected data consists of various parameters such as age, gender and pre-operative serum markers including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), globulin (GLB), Albumin to globulin ratio (A/G), CRP/AGR ratio.

The study included individuals who met specific criteria for patient inclusion, which were as follows: patients diagnosed with Periprosthetic Joint Infection (PJI) after undergoing total knee arthroplasty or total hip arthroplasty within 90 days, considered Acute, and more than 90 days, considered Chronic prosthetic joint infection. Additionally, patients who had been diagnosed with loosening and received appropriate treatments in our department, such as revision arthroplasty or spacer insertion surgery, during the mentioned study period were also included. Patient should have the following lab values in pre-operative measurements of CRP, ESR, GLB, A/G and CRP/AGR. Patients excluded in the study, who has been previously diagnosed with systemic inflammatory disease such as Inflammatory bowel disease, gout, sarcoidosis, multiple myeloma, lymphocytic leukemia, rheumatoid arthritis. Presence of any tumors, History of trauma or dislocation within the past two weeks, missing key data required for analysis, Patients not willing for re-surgery and post-operative period follow up. A total of 46 patients were admitted in our hospital and diagnosed either with periprosthetic joint infection (PJI) or aseptic loosening during the specified study period. Among

them, 30 patients met the inclusion as well the exclusion criteria. PJI was diagnosed under MSIS (Musculo skeletal infection Society Criteria. Blood samples were collected from all the patients in morning after they get admitted in our hospital. These samples were utilized to measure the values of C-reactive protein (CRP), globulin (GLB), erythrocyte sedimentation rate (ESR), albumin-to-globulin ratio (A/G), CRP and Albumin globulin ratio (CRP/AGR). Quantitative data are analysed using IBM SPSS version 22, given in mean +/- standard deviation and compared through non-parametric tests as appropriate, with P value <0.05.

Results

We conducted a retrospective analysis of patients with Periprosthetic joint infection following TKA or THA group consisted of 30 patients. CRP, ESR and CRP/AGR ratio were taken into comparison in the study. The average age was 58.4 years ranging from

47 to 72 years. Among 30 patients 21 had positive culture results, 9 patients had negative culture results . Based on the culture reports the most common organism involved is Staphylococcus aureus 85.71% followed by Staph. Epidermidis 14.28%. Average values for culture sensitive CRP/AGR values 69 (Ranging from 29 to 96) . Average CRP value is 66.85 mg/L (ranging from 46 mg/L to 94 mg/L) . ESR average value of 55mm/hr(ranging from 27 mm/hr to 98 mm/hr) . Average values for culture negative CRP/AGR 15.22 (ranging from 8 to 44) . CRP average value 15.77 mg/L ranging from (11 mg/L to 23 mg/L) . ESR 32.77 mm/hr ranging from (27 mm/hr to 39 mm/hr) . For culture sensitive patients the diagnosing accuracy for in culture patients CRP is 91.75%, ESR is 69.46%, CRP/AGR 93.75%, (whereas in culture negative the threshold for diagnosing accuracy for CRP is 60%, CRP/AGR is 61%, ESR is 51%.

Table 1: Demographic and Culture Results

Parameter	Value
Number of Patients	30
Average Age (years)	58.4 (Range: 47-72)
Positive Culture Results	21 patients (70%)
Negative Culture Results	9 patients (30%)
Most Common Organism	Staphylococcus aureus (85.71%)
	Staphylococcus epidermidis (14.28%)

Table 2: Biomarker Values (Average and Range)

Biomarker	Culture Positive	Culture Negative
CRP (mg/L)	66.85 (Range: 46-94)	15.77 (Range: 11-23)
ESR (mm/hr)	55 (Range: 27-98)	32.77 (Range: 27-39)
CRP/AGR	69 (Range: 29-96)	15.22 (Range: 8-44)

Table 3: Diagnostic Accuracy

Biomarker	Culture Positive (%)	Culture Negative (%)
CRP	91.75%	60%
ESR	69.46%	51%
CRP/AGR	93.75%	61%

Discussion

Periprosthetic joint infection (PJI) is a serious complication that can occur following total knee arthroplasty (TKA) or total hip arthroplasty (THA) and often leads to the need for joint revision surgery. The incidence of PJI in THA or TKA is estimated to be around 2.0%-2.4%. Accurate diagnosis of PJI is crucial for preserving the implanted prosthesis, resting joint function and reducing the morbidity rates. However, diagnosing PJI remains challenging due to the absence of a definitive gold standard test with absolute accuracy. In our study we aim to evaluate the diagnostic accuracy of CRP, Albumin, Globulin Albumin to globulin ratio, ESR as biomarker for PJI. Angkananard et al. [7]

highlighted the usefulness of NLR as a predictor for infected patient outcomes. Meyer et al. on the other hand discovered a correlation between A/G ratio values and infection status. Additionally, Schmilovitz-Weiss et al. [8] reported that the A/G ratio can predict cancer patient outcomes. These findings have prompted numerous researchers to investigate the associations between GLB, NLR, A/G ratio and PJI. Yu et al., in their study demonstrated that NLR values were more accurate than CRO levels in the early diagnosis of PJI. In a separate study Yu et al found both GLB and A/G ratio to hold promising biomarker in diagnosing PJI.

Gaertner et al. [9] provided evidence of antiinfection functions of platelets, specifically in the collection

and bundling of bacterial functions. Similarly, Parvizi et al. [10] demonstrated that PVR (platelet volume ratio) increased in patients with PJI, with diagnostic sensitivity, specificity. However, the diagnostic value of platelet count and PVR was found to be mixed compared to Globulin, AGR and fibrinogen. In a multicenter cohort study conducted by Benito et al. [11], they analyzed 2288 cases of PJI with microbiological diagnosis. Their research revealed that staph aureus, Staph. Epidermidis, Pseudomonas aeruginosa, Enterococcus, faecalis and Propionibacterium, acinus, in decreasing order accounted for more than 80% of PJI's. In our study, Staph epidermidis was most prevalent pathogen, followed by staphylococcus aureus. There were no significant changes in level of GLB, AGR, fibrinogen and CRP between culture positive and culture negative PJI patients. However, the diagnostic accuracies of these biomarkers were lower in culture negative PJI compared to culture positive PJI. According to our literature review, our study demonstrates that CRP/AGR offers superior diagnostic performance for PJI when compared to traditional biomarkers such as CRP and ESR. The culture result of the pathogen is the most valuable indicator when diagnosing PJI and can assist in selecting appropriate antibiotics. However, in certain cases, the microbiological culture may yield negative results due to various factors such as microbiological, host and antibiotic interactions. Previous studies have reported that the occurrence of culture negative PJI range from 5% to 42%. We observed a significant difference in CRP, ESR, AGR between culture positive PJI subgroup and culture negative PJI group, suggesting that these biomarkers hold potential for predicting negative culture outcomes. Nonetheless, all tested biomarkers demonstrated lower diagnostic accuracies for culture negative PJI compared to culture positive PJI. Therefore, it's crucial to prioritise the diagnosis of culture negative PJI. [12,13]

Limitations in our study, being a retrospective study its subject to inherent limitations associated with this study design. The exclusion of patient with autoimmune diseases introduces some bias, there is no universally accepted gold standard for diagnosing PJI. MSIS (Musculoskeletal infection society) criteria however, is considered the best diagnostic method, although they have low sensitivity for patients with low-virulence bacterial infections.

Conclusion

In conclusion, our findings indicate that the patients diagnosed with PJI (Periprosthetic joint infection) exhibited significantly elevated levels of ESR, CRP, CRP/AGR. These biomarkers show promising results for the diagnosis of PJI. However, when used alone, CRP/AGR demonstrated excellent diagnostic

performance, followed by CRP and ESR with good diagnostic performance.

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