

Diagnostic Value of C-Reactive Protein and C-Reactive Protein-to-Albumin Ratio in Differentiating Bacterial from Viral Meningitis

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ABSTRACT

Objective: To evaluate the diagnostic efficiency of C-reactive protein (CRP) and CRP-to-albumin ratio (CAR) in differentiating bacterial meningitis from viral meningitis

Study Type: Cross-sectional study

Place and Duration of Study: Department of Neurology and Medicine, Pakistan Emirates Military Hospital, Rawalpindi, Pakistan, from Dec 23 to May 24

Methodology: Patients of both genders ≥ 18 years old with suspected or confirmed diagnosis of meningitis, either viral or bacterial, were included. Patients with sepsis, systemic infections other than CNS, and protein-losing nephropathies were excluded. After a detailed relevant history and examination, samples for serum CRP, albumin, and cerebrospinal fluid were collected. The patient was labelled as a case of bacterial or viral meningitis based on clinical history, examination, and cerebrospinal fluid (CSF) studies.

Results: A total of ninety-four ($n=94$) individuals with a mean age of 50.86 ± 11.80 years were included. The mean serum albumin was 32.57 ± 3.23 g/L, while the median CRP level was 27.50 (16.75-53.00) mg/L. The median CAR was 0.78 (0.53-1.75). In patients, fever (92; 97.87%) was the most common symptom, followed by vomiting (57; 60.64%) and headache (54; 57.45%). The serum albumin levels and patients' age had no relation to meningitis variants, as p -value was 0.344 and 0.111, respectively. The serum CRP levels and CAR were strongly related to the type of meningitis, with $p < 0.001$.

Conclusion: The serum CRP to Albumin ratio, along with serum CRP levels, can be used as a tool to differentiate bacterial from viral meningitis, at least when cultures and CSF studies are awaited, and prompt prophylactic treatment is required.

Keywords: Bacterial Infections, Cerebrospinal Fluid, Diagnostic Tests, Meningitis

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INTRODUCTION

Central nervous system infections like encephalitis and meningitis, either viral or bacterial, have variable mortality and morbidity ranging from as low as 1% to as high as 10% in some studies.¹ Among these infections, meningitis is most common, and viral meningitis has been even more commonly reported, but definitive incidence has yet to be reported.² Meningitis has been reported in all age groups, including newborn infants to adults in their extreme ages.³ Due to the sensitive and critical nature of the disease, a prompt diagnosis is often required to decide on antiviral or antibacterial therapy, but laboratories take their time, and antimicrobial therapy has no role if it is inadequate.⁴ Adequate antimicrobial treatment decreases mortality below 15%.⁵

Meningitis presents with a variable clinical

picture that may comprise fever, headache, myalgias, neck stiffness, altered sense of consciousness, lumbago, photophobia, convulsions, vomiting, and irritability.^{6,7} The serum CRP has long been used for evaluation and diagnosis of meningitis and has been found more raised in bacterial form than in the viral variant.⁸ Similarly, serum albumin has also been studied for various infections, including meningitis, and was found to be low in the discussed disease.⁹ The new markers have been always in debate including serum CRP to Albumin ratio (CAR). It has been studied in many diseases, including sepsis, malignancies, and meningitis.¹⁰

Very limited research has been done on this marker in CNS infections, and we were unable to find any in our population. So, this research was planned to test the serum CRP-to-albumin ratio (SCAR) as a diagnostic marker for meningitis. This study will help clinicians to make better treatment choices well before the CSF studies, viral polymerase chain reaction (PCR), and bacterial culture reports are available.

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METHODOLOGY

After approval of the study protocol from the institutional ethics committee vide certificate number # A/28/ERC/84/24, this cross-sectional study was conducted at the Department of Neurology and the Department of Medicine, Pak Emirates Military Hospital, Rawalpindi, Pakistan, from Dec 23 to May 24. A total of 38 cases were required, keeping α -error of 0.05, type-II error of 0.20, and area under the curve for serum CAR of 0.756 for meningitis, using an online sample size calculator.¹¹ Informed consent was obtained from all individuals before inclusion in the study. The consecutive convenience sampling technique was used to enrol patients.

Inclusion Criteria: Patients of both genders ≥ 18 years old with suspected or confirmed diagnosis of meningitis, either viral or bacterial, were included in the study.

Exclusion Criteria: Patients with sepsis, systemic infections other than CNS, chronic liver disease, burns, malnutrition, chronic kidney disease, including protein-losing nephropathies, were excluded. Moreover, patients with any conditions that could alter serum albumin and CRP levels were also excluded. Patients who were unwilling to participate were also excluded.

All participants meeting the inclusion and exclusion criteria underwent a detailed relevant history and examination. The basic demographic details, like age and gender, were recorded. The clinical symptoms, such as fever, headache, photophobia, convulsions, drowsiness, and vomiting, etc were also recorded. Other causes and sources of infection and fever were also excluded through history and physical examinations. Samples for serum CRP and serum Albumin were collected. The samples were labelled and sent to the hospital laboratory as per laid protocols. The patient was labelled as a case of bacterial or viral meningitis based on the clinical history, examination, and cerebrospinal fluid (CSF) studies, as shown in Figure. Those cases suspected of meningitis but not meeting the criteria of either bacterial or viral infection were excluded from the study.

The statistical analysis was done using Statistical Package for Social Sciences (SPSS) Version 25.0. The normality of data was checked using the Shapiro-Wilk test. Percentages and frequencies were used for gender, clinical features, and outcomes. Age and serum albumin were normally distributed and

represented using mean $\pm$ SD, while serum CRP and serum CAR were not normally distributed, so represented using median and interquartile range. The Mann-Whitney U test was used for skewed variables (serum CRP and CAR), while independent samples t-test was used for normally distributed variables (serum albumin). The p -value ≤ 0.05 was taken as significant.

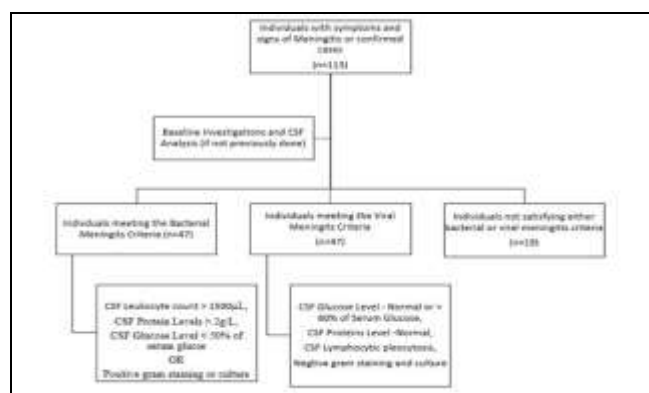


Figure: Sample Population Enrolment Flowchart (n=113)

RESULTS

A total of ninety-four (n=94) individuals with a mean age of 50.86 ± 11.80 years were included in the study. There were 54 (57.45%) males and 40 (42.55%) females. The mean serum albumin was 32.57 ± 3.23 g/L, while the median CRP level was 27.50 (16.75-53.00) mg/L. The median CAR was 0.78 (0.53-1.75). In patients, fever 92 (97.87%) was the most common symptom, followed by vomiting 57 [60.64%) and headache 54 [57.45%). Further details are given in Table-I.

The serum CRP levels were strongly related to the type of meningitis with $p < 0.001$. Serum CRP to Albumin ratio (CAR) was also statistically related to meningitis ($p < 0.001$), suggesting a marked difference in CAR levels between the two disease groups. The details of the statistical analysis are given in Table-II.

DISCUSSION

The current research signifies that meningitis is among those diseases that have very high morbidity and mortality if left untreated. This study was done to see the role of serum CRP and serum CRP-to-albumin ratio in differentiating bacterial from viral meningitis. In this research, there were 94 individuals with a median age of 50.86 ± 11.80 years. Mean serum albumin was 32.57 ± 3.23 g/L, while median CRP levels were 27.50 (16.75-53.00) mg/L. The raised serum CRP levels were also found by Lee et al., similar to the findings of

our study.¹² The fever 92(97.87%) and vomiting 57 (60.64%) were the most common symptoms. In coherence, Alnomasy *et al.*, also found fever, vomiting, and headache as the most common clinical features, along with convulsions and diarrhea.¹³ Similarly, fever, headache, and vomiting were the most common symptoms reported by patients in a study conducted by Liu *et al.*, in China. There were 54 (57.45%) males and 40 (42.55%) females. They also reported an increased number of males suffering from meningitis.¹⁴

Table-I: Clinical Features and Basic Details of Patients (n=94)

Clinical Features and Demographics	Descriptive Statistics
Mean Age (years)	50.86±11.80
Gender n(%)	
Male	54 (57.45%)
Female	40 (42.55%)
Clinical Features n(%)	
Fever	92(97.87%)
Headache	54 (57.45%)
Vomiting	57 (60.64%)
Convulsions	37 (39.36%)
Kernig's Sign	25 (26.60%)
Lethargy	46 (48.94%)
Neck Stiffness	28 (29.79%)
Photophobia	20 (21.28%)
ASOC	34 (36.17%)
Median Serum CRP Levels (mg/L)	27.50 (16.75-53.00)
Mean Serum Albumin Level (g/L)	32.57±3.23
Median Serum CAR	0.78 (0.53-1.75)
Outcome n(%)	
Non-Survivors	6 (6.38%)
Survivors	88 (93.62%)

CRP: C-reactive protein; ASOC: Altered sense of consciousness; CAR: C-Reactive protein to albumin ratio

Table-II: Relationship of Serum Crp, Serum Albumin, And Serum Car In Differentiating Meningitis Types (n=94)

Variable	Meningitis Groups		p-value
	Bacterial (n=47)	Viral (n=47)	
Mean Serum Albumin (g/L)	32.04±3.51	33.11±2.87	0.111
Median Serum CRP (mg/L)	52.00 (34.00-72.00)	18.00 (13.00-24.00)	<0.001
Median Serum CAR	1.73 (1.10-2.15)	0.56 (0.43-0.72)	<0.001

CRP: C-reactive protein; CAR: C-Reactive protein to albumin ratio

The role of serum CRP in meningitis has been reported to varying degrees. Estimation of C-reactive protein in serum is the cheapest, sensitive, and specific test to differentiate bacterial from viral infections. It is a simple qualitative as well as quantitative test and can be done as a bedside investigation. With serum C-reactive protein, a definite etiological diagnosis can be

made rapidly at the time of admission itself, as reported by Rajesh *et al.*¹⁵

In our study, the serum CRP levels were significantly associated with meningitis. This difference in findings might be due to time intervals at which CRP was taken, population demographics, and comorbidities. Meningitis is a clinical syndrome characterized by inflammation of the meninges. The classic triad of meningitis consists of fever, headache, and neck stiffness.¹ Bacterial meningitis occurs in about 3 people per 100,000 annually in Western countries. Population-wide studies have shown that viral meningitis is more common at 10.9 per 100,000 population.⁸ Though it has been widely used in the past to differentiate bacterial from viral variants of meningitis, as reported by Haider *et al.*,¹⁶ Hypoalbuminemia has been reported by Yildirim *et al.*, to have an association with severe systemic disease like sepsis, septic shock, and multi-organ system involvement.¹⁷ Though the serum albumin levels were not statistically significant, they were comparatively low in bacterial meningitis in our study. In research done by Feketea *et al.*, low serum albumin levels in meningitis have been frequently reported. This decrease in albumin levels can be explained by the inflammatory cascade started by infection, especially in bacterial infections.¹⁸

The CRP to Albumin ratio has been studied for various diseases as a novel marker of disease severity and prognosis. Its prognostic and diagnostic role is well known for sepsis. It has also been used for carotid artery stenosis as an independent marker and for predicting severity of acute pancreatitis.¹⁹ Apart from sepsis, it has also been used for other infections like COVID-19 and tumours like colorectal cancer.²⁰ The serum CRP-to-albumin ratio has been evaluated on a very limited scale for meningitis, and we failed to find any relevant study in our population.

In this study, serum CRP was evaluated for differentiating bacterial from viral meningitis. We found a statistically significant relation between serum CRP and both variants of meningitis in the study. This shows that serum CRP, as in other conditions, whether infectious or malignant, can be used for differentiating bacterial and viral meningitis. Combining the two markers (CRP and Albumin) into a ratio magnifies the inflammatory signal, helping clinicians identify severe bacterial central nervous system infections earlier than relying on CRP alone. However, established universal cutoff values for the CRP-to-albumin ratio specifically

in meningitis remain less standardized than standalone serum or cerebrospinal fluid (CSF) CRP measurements.

LIMITATION OF STUDY

This single-point cross-sectional study lacked follow-up and serial measurements and had a small sample. Larger prospective, multicentre studies comparing CAR with other markers are needed to identify a more reliable predictor for differentiating viral from bacterial meningitis when CSF studies are unavailable.

CONCLUSION

The serum C-reactive protein-to-albumin ratio (CAR), together with serum C-reactive protein levels, may serve as a useful and readily available tool for differentiating bacterial meningitis from viral meningitis, particularly while definitive cerebrospinal fluid findings and culture results are awaited. However, larger prospective, multicentre studies with more diverse patient populations are required to validate these findings, establish reliable diagnostic cut-off values, and clarify the clinical utility of these biomarkers.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

MF & AK: Data acquisition, data analysis, critical review, approval of the final version to be published.

MI & FA: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

MHL & QUAA: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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