JMedSci

Journal of the Medical Sciences
(Berkala Ilmu Kedokteran)

Volume 55, Number 4, 2023; 342-351
https://doi.org/10.19106/JMedSci005504202306

High-sensitivity C-reactive protein/albumin (hs-CRP/albumin) ratio as a predictor of deterioration of clinical outcome in central nervous system infections

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Submitted: 2023-02-20
Accepted : 2023-10-04

ABSTRACT

Central nervous system (CNS) infections such as encephalitis, meningitis, or myelitis have high morbidity and mortality in Indonesia. High sensitivity C-reactive protein (hs-CRP) is a sensitive marker of acute inflammation, while albumin is the most abundant protein component in plasma and cerebrospinal fluid (CSF). Infection triggers an inflammatory response so that an increase in the hs-CRP/albumin ratio (CAR) can be a predictor of worsening clinical outcome in patients with CNS infections. However, studies examining the predictor value of serum and CSF CAR on worsening clinical outcomes of patients are limited, particularly in CNS infections. The purpose of this study was to prove the CAR as a predictor of worsening clinical outcome in patients with CNS infections. It was an observational study using a prospective cohort design. Fifty subjects recruited until October 2021 at Dr. Sardjito General Hospital were involved. The multivariate regression analysis showed that serum CAR (OR=3.604; 95%CI=1.487-8.736; p =0.005) could be a single predictor. However, by combining three variables, namely serum CAR, CSF CAR, and decreased consciousness at admission, could be a stronger predictor of worsening clinical outcome in patients with CNS infection (AUC = 97.1%; 95%CI = 0.929-1.00; p <0.001). The optimal cut-off value for serum CAR was 1.35 (Youden index = 0.88, sensitivity = 96%, specificity = 92%) while for CSF CAR was 0.14 (Youden index = 0.60, sensitivity = 76%, specificity = 84%). In conclusion, a combination predictive model of three variables, namely serum CAR, CSF CAR, and awareness at admission can be a stronger predictor of clinical outcome in patients with CNS infection than serum CAR alone.

ABSTRAK

Infeksi sistem saraf pusat (SSP) seperti ensefalitis, meningitis, atau mielitis memiliki morbiditas dan mortalitas yang tinggi di Indonesia. *High sensitivity C-reactive protein* (hs-CRP) adalah marker inflamasi akut yang sensitif sedangkan albumin adalah komponen protein terbanyak dalam plasma dan cairan serebrospinal (CSS). Infeksi memicu terjadinya respons inflamasi sehingga peningkatan rasio hs-CRP/albumin (RCA) dapat menjadi prediktor perburukan luaran klinis pada pasien infeksi SSP. Namun penelitian tentang nilai prediktor RCA pada serum dan CSS terhadap perburukan luaran klinis pasien khususnya pada infeksi SSP masih terbatas. Penelitian ini bertujuan untuk membuktikan RCA sebagai prediktor perburukan luaran klinis pasien infeksi SSP. Ini adalah penelitian observasional menggunakan rancangan kohort prospektif. Sebanyak 50 subjek yang direkrut hingga Oktober 2021 di RSUP Dr Sardjito Yogyakarta dilibatkan dalam penelitian. Analisis regresi multivariat menunjukkan RCA serum (OR=3.604; 95%CI =1.487-8.736; p =0,005) dapat

Keywords:
central nervous system infection;
Barthel index;
CSF hs-CRP/albumin ratio;
serum hs-CRP/albumin ratio;
cut-off value

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menjadi prediktor tunggal. Namun, dengan mengkombinasi tiga variabel yaitu RCA serum, RCA CSS, dan penurunan kesadaran saat admisi dapat menjadikan prediktor yang lebih kuat terhadap perburukan luaran klinis pasien infeksi SPP (AUC =97.1%; 95%CI =0.929-1,00; p <0.001). Nilai ambang batas optimal untuk RCA serum adalah 1.35 (indeks Youden =0.88, sensitivitas =96%, spesifisitas =92%) sedangkan untuk RCA CSS adalah 0.14 (indeks Youden =0,60, sensitivitas =76%, spesifisitas =84%). Simpulan, model prediktif kombinasi tiga variabel yaitu RCA serum, RCA CSS, dan kesadaran saat admisi dapat menjadi prediktor yang lebih kuat untuk perburukan luaran klinis pasien infeksi SPP dibandingkan RCA serum saja.

INTRODUCTION

Central nervous system (CNS) infections such as encephalitis, meningitis, or myelitis have high morbidity and mortality in Indonesia. Meningitis is more common with an incidence of 5 million cases per year which bacterial infection causes more severe sequelae (case fatality rate >14.3%).[1,2] Inflammation is a core aspect of body's immune response to infections including CNS infections. Colonization of the pathogen in the blood causes a response in hepatocytes to increase the production of C-reactive protein (CRP) and decrease albumin. Pathogens invade the CNS, multiply, then activate body's immunity causing vasculitis, obstruction of cerebrospinal fluid (CSF) flow, neurotoxic environment, and damage to the blood-brain barrier. This condition causes components of the blood to more enter CSF, including CRP and albumin.[3]

High-sensitivity C-reactive protein (hs-CRP) is a sensitive marker of acute inflammation which can detect CRP levels as low as 0.1 mg/L.[4] The CRP levels, either in serum or CSF, will increase significantly in an acute phase of bacterial infection compared to viral infections.[5,6] Previous studies showed that high CRP levels on admission were associated with poor clinical outcome and mortality.[7,8] Albumin is the most abundant protein component in plasma and CSF. Hypoalbumin during the acute phase of inflammation is caused by the binding of albumin to oxidative stress and hypercatabolic conditions leading to increased diffusion of fluid from intravascular to brain tissue. This condition causes brain edema and increased intracranial pressure (ICP) which worsens the patient's clinical outcome.[7,9] Among various inflammatory biomarkers, CRP and albumin have the most significant influence on the clinical outcome because they undergo significant changes during the acute phase of inflammation.[10]

The hs-CRP/albumin ratio (CAR) is a novel inflammatory biomarker combination which is better than CRP alone, albumin, glucose, neutrophil/lymphocyte ratio, or leukocyte count as a predictor of mortality in critically ill patients, systemic infection/sepsis, subarachnoid hemorrhage, cancer, and brain trauma.[8,10] Increased serum CAR was associated with higher mortality at both 90 and 180 days in septic patients, with cut-off values >2 and >5.09.[8,11] The assessment of clinical outcome deterioration utilized the Barthel index (BI) to evaluate daily functional abilities.[12] The hs-CRP and albumin are often used as clinical predictors of patients. Combining these two strong predictors of inflammation will increase their sensitivity as a prognostic factor. However, studies concerning the value

of CAR either in serum or CSF associated with the deterioration of clinical outcomes in CNS infections are limited.

The purpose of this study was to investigate the CAR as a predictor of deterioration of clinical outcome in patients with CNS infections and to determine the cut-off value.

MATERIAL AND METHODS

Study design and oversight

It was an observational analytic study using a prospective cohort method to determine CAR in serum and CSF as a predictor of deterioration of clinical outcome in patients with CNS infections. Based on the unpaired numerical analytical formula, the required number of samples in this study was 50 patients. The inclusion criteria for this study were 1) patients with a clinical diagnosis of CNS infection (meningitis, encephalitis, or myelitis) who underwent lumbar puncture; 2) adults (18 years and older); 3) willing to participate in the study. The exclusion criteria used were patients with conditions that caused hypoalbumin other than infection, namely: protein malnutrition, liver disorders (hepatic cirrhosis), kidney disorders (nephrotic syndrome, kidney failure), wounds extensive burns, heart problems (pericarditis and congestive heart failure), mucosal disease (inflammatory bowel disease), and hemodilution (ascites). The consciousness of patients was assessed using the Glasgow coma scale (GCS). 'Compos mentis' was indicated by a full GCS score of 15. The decreased consciousness was considered if the GCS score was lower than 15.

The dependent variable in this study was the deterioration of a patient's clinical outcome, which was measured by the difference in Barthel index values when the patients were discharged compared to when they were admitted. The Barthel index is a standardized tool used to assess functional independence and activities of daily living. It is an ordinal scale that measures a person's ability to complete activities of daily living (ADL). The independent variables were serum CAR and CSF CAR, which were obtained through lumbar puncture. The samples were then examined using the Electrochemiluminescence immunoassay (ECLIA) method in the Clinical Pathology Laboratory at Dr. Sardjito General Hospital, Yogyakarta.

The confounder variables were 1) characteristics patients (age, consciousness at admission, focal neurological deficit, clinical diagnosis); 2) patient's comorbid disease (seizures, HIV, diabetes mellitus, cancer, pulmonary disorders, sepsis); 3) empirical therapy. The category of worsening clinical outcome defined as a minimum decrease of 1 score (from a total score of 20) in BI at the time of discharge compared to the time of admission or the patient was declared dead. The category without worsening clinical outcome defined as a minimum increase of 1 score (from a total score of 20) or no change in BI at the time of discharge compared to the time of admission.

This study was a joint study between the Department of Neurology and the Department of Clinical Pathology, Dr. Sardjito General Hospital, Yogyakarta. The study was approved by the Medical and Health Research Ethics Committee, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada with the number KE/FK/0590/EC/2021 and obtained a permission letter from Dr. Sardjito General Hospital, Yogyakarta with the number LB.02.01/Xl.2.2/35433/2021. All research subjects and their families involved in the study sample were given an explanation and signed an informed consent.

Statistical analysis

This study was an observational analytic study using a prospective cohort method. Variables with p value <0.25

in bivariate analysis were included in further analysis using multivariate logistic regression with etiologic concept framework. Chi-square or Fisher tests were used to determine the difference between the two proportions of nominal variables, while the Mann-Whitney test was used for numerical variables. Analysis of receiver operating characteristics (ROC) and area under the curve (AUC) curves were used to evaluate the best predictor model for deterioration of clinical outcome. The ROC curve analysis was performed and Youden's index calculation, sensitivity, specificity, and 95%CI were performed to determine the cut-off value of CAR. Youden index can be measured by the formula = max (sensitivity + specificity-1). The Statistical Package for Social Science (SPSS) 21 program was used with statistical test results were considered significant if $p < 0.05$.

RESULTS

The number of subjects who met the inclusion and exclusion criteria and recruited until October 2021 was 50 subjects. The basic clinical characteristics of the subjects are presented in TABLE 1.

TABLE 1. Characteristics of patients (n = 50)

Parameter	[n (%)]
Age	
• ≥65 y.o.	1 (2)
• <65 y.o.	49 (98)
Sex	
• Male	22 (44)
• Female	28 (54)
Comorbidities	
• Consciousness at admission	
✓ Decreased of consciousness	12 (24)
✓ Compos mentis	38 (76)
• Focal neurologic deficit	49 (98)
• Clinical diagnosis	
✓ Meningitis/encephalitis	36 (72)
✓ Myelitis	14 (28)
• Seizure	9 (18)
• HIV	11 (22)
• Diabetes mellitus	2 (4)
• Malignancy	2 (4)
• Pulmonary disorders	21 (42)
• Sepsis	2 (4)
• Empirical therapy	45 (90)

The age of subjects was mostly <65 years (n=49 subjects, 98%), male (n=22 subjects, 44%) and female (n=28 subjects, 54%). Consciousness status at admission was measured by GCS, namely decreased consciousness with GCS <15 (n=12 subjects, 24%) while subjects without decreased consciousness numbered 38 subjects (76%). The clinical diagnosis was divided into two, namely, the brain infection (meningitis/encephalitis) in 36 subjects (72%) and the spinal cord infection (myelitis) in 14 subjects (28%). Comorbid disease factors that could affect clinical outcomes included seizures in 11 subjects (18%), HIV in 9 subjects (18%), diabetes mellitus in 2 subjects (4%), malignancy in 2 subjects (4%), lung disorders in 21 subjects (42 %), and sepsis in 2 subjects (4%). Most of the subjects had received empirical therapy in the form of antibiotics or antivirals according to clinical diagnosis as many as 45 patients (90%) while the rest only received steroid therapy.

One significant confounder variable (p <0.25), namely decreased consciousness at admission (OR =2.47; 95% CI=0.634-9.625; p =0.185) was observed (TABLE 2). Therefore, it was included in the multivariate analysis along with the main variables. The two main variables had a significant relationship to deterioration of clinical outcomes (p < 0.001). The multivariate regression analysis showed that the serum CAR (OR=3.604; 95%CI=1.487-8.736; p=0.005) could be a single predictor of deterioration of clinical outcome in patients with CNS infection (TABLE 3).

TABLE 2. Results of bivariate analysis

Variable	OR	95%CI	p
Age ≥65 y.o.	0.500	0.368-0.652	0.490
Male	1.926	0.621-5.977	0.254
Comorbidities			
• Decreased consciousness	2.471	0.634-9.625	0.185
• Focal neurologic deficit	2.042	1.534-2.717	0.500
• Clinical diagnosis	0.671	0.193-2.329	0.429
• Seizure	0.762	0.179-3.249	0.500
• HIV	2.042	0.513-8.119	0.306
• Diabetes mellitus	0.490	0.368-0.652	0.500
• Malignancy	1.00	0.059-16.928	0.755
• Pulmonary disorders	1.397	0.449-4.350	0.564
• Sepsis	1.00	0.059-16.928	0.755
• Empirical therapy	1.568	0.239-10.300	0.500
CAR serum	-	1.42 (0.00-146.9)	<0.001
CAR CSF	-	0.00 (0.00-509)	<0.001

TABLE 3. Multivariate analysis of main and confounder variables

Variable	OR	95%CI	p
Serum hs-CRP/albumin ratio	3.604	1.487-8.736	0.005
CSF hs-CRP/albumin ratio	1.119	0.778-1.609	0.545
Consciousness at admission	2.853	0.291-27.924	0.368

There were 6 variations of the predictor models which were tested further to get the most powerful predictor model. Predictor model 1 or gold standard was a combination of serum CAR, CSF CAR, and consciousness at admission. Other predictor models were created for comparison with the gold standard predictor model. Specifically, predictor model 2 included serum CAR and CAR CSF, predictor model 3 was serum CAR and consciousness at admission, predictor model 4 was CAR CSF and consciousness at admission, predictor model 5 was the serum CAR only and the predictor model 6 is the CSF CAR only. The analysis showed that predictor model 1 (combination of serum CAR, CSF CAR, and decreased consciousness at admission) was the best model compared to other predictor models. Other predictor models had a change in OR >10% from the gold standard and lower precision of serum CAR and CSF CAR. The results of this study showed that the serum CAR (OR=3.604; 95%CI=1.487-8.736; p=0.005) could be a single predictor of deterioration of clinical outcome in CNS infection. However, combination of three variables, namely serum CAR, CSF CAR, and decreased consciousness at admission, was a stronger predictor (AUC = 97.1%; 95%CI = 0.929-1.00; p <0.001). The AUC value is 97.1% with a very strong interpretation (FIGURE 1).

Determination of the cut-off value can make it easier for clinicians to determine the management and predict prognosis of the patient. The optimal cut-off value for serum CAR was 1.35 (Youden index =0.88, sensitivity =96%, specificity =92%). This means that patients with serum CAR values greater than 1.35 had greater risk of worsening clinical outcomes. Meanwhile, the optimal cut-off value for the CAR CSF ratio was 0.14 (Youden index =0.60, sensitivity =76%, specificity =84%).

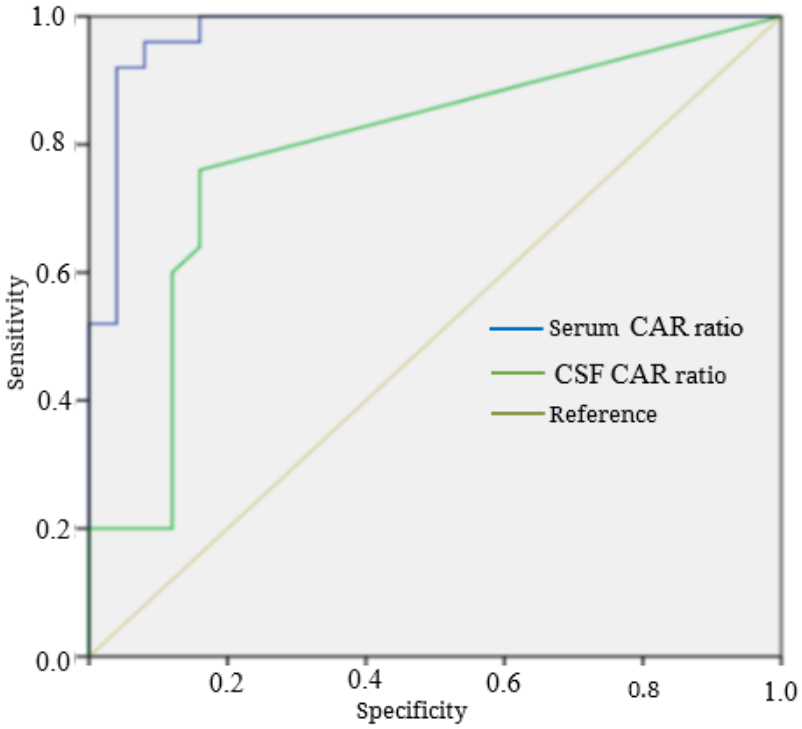

FIGURE 1. ROC curve of serum CAR and CSF CAR

TABLE 4. Optimal cut-off values of serum CAR and CSF CAR

Variable	Cut-off value	Youden index	Sensitivity (%)	Specificity (%)
Serum hs-CRP/albumin ratio	1.35	0.88	96	92
CSF hs-CRP/albumin ratio	0.14	0.60	76	84

DISCUSSION

The results of this study indicate that serum CAR could be a single predictor of deterioration of clinical outcome in CNS infection. However, the combination of three variables, namely serum CAR, CSF CAR, and decreased consciousness at admission, was a stronger predictor. This result is similar to previous studies that showed a significant relationship between hs-CRP as a predictor of the deterioration of clinical outcome in meningitis. Serum hs-CRP was used to distinguish bacterial from non-bacterial meningitis. The level of hs-CRP in either serum or CSF were both significantly elevated in bacterial infections with worse prognosis. Several comorbidities that could worsen the clinical outcome had been analyzed. They were older age, sex, decreased consciousness at admission, focal neurological deficits, clinical diagnosis, seizures, HIV, diabetes mellitus, cancer, pulmonary disorders, sepsis, and no empiric therapy. This study showed that decreased consciousness was the only factor that significantly affected the clinical outcome. However, when infection and multiple organ dysfunction syndrome occur in the body for other reasons, the level of hs-CRP was significantly increased, so that the CNS bacterial infection could not be determined or the viral infection could not be completely eliminated by a single detection of hs-CRP.[13,14] Serum and CSF levels of hs-CRP were significantly higher in the group of patients with deterioration of clinical outcome so that these two biomarkers could be used as a monitor for the clinical deterioration of patients.[15]

Other than intracranial infections, CRP levels have also been reported to increase in spinal cord infections, namely myelitis. This study showed that the group with worsening clinical outcome diagnosed with myelitis was 23%. The previous studies showed that poor clinical outcome in myelitis was 11%. An increase in serum CRP (>10 mg/L) only occurred in 6% of myelitis subjects.[16] Another study proved that an increase in CRP occurred in 66% of patients diagnosed with myelitis.[17] Similar results also occurred in myelitis patients with COVID-19 that there was a mild increase in CRP levels.[18]

CRP levels have been shown to increase in several conditions that increase the body's inflammatory process such as sepsis, critically ill patients in the intensive care unit, heart failure, and disease conditions involving the brain including stroke and CNS infections. This condition is associated with a worse clinical outcome.[7] Hypoalbumin conditions are also associated with poor clinical outcomes. A meta-analysis showed that hypoalbumin could be a predictor of poor clinical outcomes in critically ill patients admitted to the intensive care unit. This hypoalbumin condition could be caused by previous disease conditions or general conditions of

the patient such as liver, kidney, and malnutrition.[7,19] The combination of two strong inflammatory biomarkers namely CRP and albumin can be a better predictor of clinical outcome than either CRP or albumin alone.[7,10] Previous studies proved that serum CAR could be used as a single predictor of mortality in patients with sepsis and septic shock in 28 days and 90 days. Studies with shorter follow-up showed that serum CAR could be used as a single predictor of in-hospital mortality in traumatic brain injury.[8,9,11]

This study showed that CAR in CSF could not be used as a single predictor because of several conditions. The level of hs-CRP in CSF is strongly influenced by its level in serum because CRP is not produced in the brain or spinal cord. An increased level of hs-CRP in serum will normally be followed by an increase in CSF except in certain conditions. In the case of bacterial meningitis/encephalitis infection, if there is no pleocytosis in the CSF, the CRP level will only slightly increase. Low levels of CRP in CSF can be caused by CNS infection without CSF pleocytosis or serum leukocytosis. Second, CNS infection without inflammation of the meninges results in slower diffusion of CRP from serum across the blood-brain barrier. Third, it is possible that CRP has bound to damaged surrounding tissue before crossing the blood-brain barrier.[13,20] Fourth, the unchanged albumin value in conditions of CNS infection may be due to the absence of an increase in CSF leukocytes or mild-moderate infection conditions.[21,22]

The optimal cut-off value in this study for serum CAR was 1.35. While the optimal cut-off value for the CSF CAR ratio was 0.14. Previous studies showed that the serum CAR cut-off values are >2 and >5.09 for mortality in 90 and 180 days in septic patients, respectively.[8.11] Other studies showed serum CAR values >1.22 at admission were associated with in-hospital mortality in hemorrhagic stroke patients.[22] A recent study in COVID-19 patients showed a serum CAR with a cut-off value >0.9 could indicate poor patient clinical, long hospitalization time, and higher mortality.[23] There was no previous study to determine the cut-off value of CSF CAR.

The limitation of this study was the limited duration of the study. The follow-up time for clinical outcomes was quite short. It was performed only until the patient was discharged from the hospital. In the future, it is hoped that further research can be carried out with a longer clinical outcome follow-up time.

CONCLUSION

Elevated serum CAR can be a single predictor of deterioration of clinical outcome in patients with CNS infections. A stronger predictive model in the combination of three variables, namely serum CAR, CSF CAR, and decreased consciousness at admission, is a better predictor. The cut-off value of the serum CAR is 1.35 while the CSF CAR is 0.14. Patients with serum CAR values greater than 1.35 have significantly higher risk of worsening clinical outcome.

ACKNOWLEDGEMENT

The authors would like to thank all of the residents and staffs of the Department of Neurology, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, for their valuable assistance during the study. This study was funded by the regular research funding from the Dr. Sardjito Hospital, Yogyakarta, Indonesia.

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