

Original article

CRP-to-albumin ratio as a low-cost prognostic biomarker in Indian patients admitted with acute medical illnesses

Dr. Monika Gupta*

Assistant Professor, Dept of Biochemistry, Index Medical College, Indore (M.P.)

Corresponding author*

Abstract

Introduction: C-reactive protein to albumin ratio (CAR) is a biomarker which showed both inflammation and nutrition. The CAR represented as the potential marker to determine negative clinical outcome. The study aimed to analyse predictive ability of CAR with regard to 30-day mortality of ICU patients in India.

Method: The retrospective cohort study consisted of 180 adults ICU patients admitted from January 2009 through December 2010. The demographic variables, clinical factors, laboratory findings, APACHE II, Charlson's Comorbidity Index and CAR were measured and analysed. Univariate and Multivariate Cox proportional hazard analyses and ROC analysis were used to determine the independent predictors of 30-day mortality.

Result: The result findings showed 180 patients, 13 patients (7.2%) showed mortality within 30 days. Old age, APACHE II score, Charlson comorbidity index, carcinoma, and CAR showed independent associations with mortality, while high BMI and albumin were observed to be protective factors. CAR had an independent association with mortality (HR 1.13, $p < 0.001$), but CRP did not show any significance in multivariate analysis ($p = 0.072$).

Conclusion: The study concluded that the CRP-to-albumin ratio is the inexpensive, independent predictor for the short-term mortality among ICU patients and increases stratification of risk to establish the clinical severity scores.

Keywords: C-reactive protein, Albumin, CRP-to-albumin ratio, Intensive care unit, 30-day mortality

Introduction

C - reactive protein (CRP) is the acute phase reactant which is produced by the liver regarding the inflammation. The level of CRP rises in case of acute illness, which is reflected by the intensity of the inflammation [1]. The high level of CRP has been related to with the severity for various conditions of inflammation. The Albumin is produced by liver in order to maintain the oncotic pressure and transport substances. Low level of albumin is noted in the systemic inflammation, liver dysfunction, or malnutrition [2]. In acute pancreatitis, the most common condition is the hypoalbuminemia and is associated with reduced prognosis. The CRP/Albumin ratio gets combined with the CRP, indicated the inflammation, with albumin which demonstrated the nutritional and functional level. The CRP ratio is a significant tool for prognosis in case of the acute pancreatitis [3]. CRP ratio is applicable widely in clinical settings, which include the identification of the high risk patients those who required continuous ICU monitoring. Those patients require interventions for nutritional recommendation. The ratio helped the patients for the stratification in case of surgical intervention, and also selects patients for clinical trial studies [4]. CRP is used for the predicting the postoperative complications and provide guidance for safe discharge, which was followed by the colorectal surgery [5]. But some of the major challenges are associated with CRP which includes the slow kinetics leads to high values on the 2nd or 3rd day, which can be late for the intervention. The albumin level showed immediate response for the surgical stress and a significant predictor for

the deranged protein metabolism. The CRP to albumin ratio reflected the inflammatory and nutritional status and represented as a marker to identify the negative outcome. Recent studies showed the significant correlation between the negative outcomes among the colorectal cancer patients and high CRP to albumin ratio [6]. The CRP protein is an acute-phase reactant, which rises within 2 days during the onset and gets correlated with the necrosis, organ failure, and mortality [7]. The level of albumin in serum reflected the nutritional status, which indicated high severity. The CRP-to-albumin ratio (CAR) gets combined with the inflammatory and nutritional marker and increases the prognostic significance [8]. Some of the studies conducted in the Chinese and European populations demonstrated the accuracy of CAR regarding stratification of the severity index among population of acute pancreatitis [9, 10]. The aim of the study is

Method

Research design

The study was a retrospective observational cohort study to analyse the CRP to albumin ratio as a low cost marker for prognosis among Indian patients with the acute medical conditions. The study included 180 adult patients, who were admitted with the acute conditions. The study was conducted for a period of 1 year from July 2009 to June 2010. Demographic, clinical and laboratory parameters were analysed and measured from the patient records. The CRP and serum albumin values were taken during patient admission in ICU and estimated the CRP/albumin ratio. Informed consent was taken for the study. Patients were selected on the basis of certain predefined inclusion and exclusion criteria.

Inclusion criteria

- Patients of age above 18 years were included.
- Those who were admitted to the ICU department
- The availability of both of the serum CRP and albumin measurements within 1 day of admission in ICU was included.
- Complete medical information must be documented.

Exclusion criteria

- Patients admitted in ICU with missed CRP or the serum albumin values during admission.
- Patients with the missed clinical records were excluded from the study.
- Patients with repeated ICU admissions at the time of study period were excluded from the study.

Procedure

Patients were selected from the inclusion and exclusion criteria and informed consent were obtained from the study. Patient data were obtained by the hospital medical records to obtain the demographics, clinical history, comorbidities, laboratory results, and outcomes. Patient age, sex, body mass index (BMI), ICU admission category, ICU and total hospital length of stay, APACHE II score, Charlson Comorbidity Index, and comorbid conditions such as hypertension, diabetes mellitus, ischemic heart disease, chronic obstructive pulmonary disease (COPD), and cancer were acquired. Laboratory measures include the serum C-reactive protein (CRP) and serum albumin, obtained within the first 24 hours after ICU admission, were used in the study. The CRP/albumin ratio was determined as the quotient between the serum CRP and the albumin level. The main outcome measure used in the research was 30-day mortality after ICU admission. Independent predictors of death at 30 days post-ICU admission were determined by the use of univariable and multivariable Cox

regression analyses. The prognostic value of the CRP/albumin ratio was analysed against some well-known severity scores, including APACHE II and Charlson Comorbidity Index.

Statistical analysis

Data analysis was done by the SPSS Statistics 16. The mean $\pm$ SD is used to express the continuous variables and frequency (%) used for the categorical variables. Univariable and multivariable Cox regression analysis detected the identified predictor of the 30-day mortality. ROC analysis analysis showed the prognostic efficacy. The p-value <0.05 was considered for statistical significance.

Results

Table 1 demonstrated the baseline and clinical parameters of 180 ICU patients with a mean age of 65.4 ± 14.8 years in the study, and men were in majority (62.8%). The average body mass index (BMI) was 24.3 ± 4.1 kg/m², indicated healthy body weight. Majority (68.9%) of the participants had been admitted postoperatively, while 20.0% from the Internal Medicine department. Both the mean APACHE II score (22.1 ± 8.0) and the Charlson Comorbidity Index (1.7 ± 1.8) showed moderate severity of illnesses. The most common comorbidities were cancer (21.1%), hypertension (10.0%) and diabetes mellitus (5.6%). C-Reactive Protein (CRP) was significantly elevated at 71.8 ± 64.7 mg/L and albumin was low at 31.2 ± 5.1 g/L. The table showed 13 (7.2%) patients experienced 30-day mortality after ICU admission.

Table 1: The baseline demographics, clinical and laboratory parameters of the patients of the study

Characteristic	Total patients (n = 180) Mean $\pm$ SD / n (%)
Age, years	65.4 ± 14.8
Sex: Male	113 (62.8%)
Body Mass Index (kg/m ²)	24.3 ± 4.1
Postoperative admission	124 (68.9%)
Department of admission: Internal Medicine	36 (20.0%)
Length of ICU stay (days)	5.1 ± 8.9
Length of hospital stay (days)	34.7 ± 65.8
APACHE II score	22.1 ± 8.0
Charlson Comorbidity Index	1.7 ± 1.8
Comorbidity at ICU admission	
Hypertension	18 (10.0%)
Diabetes mellitus	10 (5.6%)

Ischemic heart disease	4 (2.2%)
COPD	2 (1.1%)
Cancer	38 (21.1%)
Albumin (g/L)	31.2 ± 5.1
C-Reactive Protein (mg/L)	71.8 ± 64.7
C-Reactive Protein/Albumin ratio	2.5 ± 2.4
30-day mortality after ICU admission	13 (7.2%)

Table 2 stated that the univariable Cox regression was conducted which revealed that older age patients significantly increased the mortality within the next 30 days (HR=1.02, $p<0.001$), while a high BMI reduced the risk of mortality (HR=0.94, $p<0.001$). Admission to ICU postoperatively had a protective effect (HR=0.61, $p<0.001$), while the admission to the Department of Internal Medicine increased the mortality risk over 3-fold (HR=3.21, $p<0.001$). The high severity of illness, which is defined as APACHE II (HR=1.08) and Charlson Comorbidity Index (HR=1.31), had a significant impact on mortality. High BP, diabetes, COPD, and cancer were significant risk factors for mortality, while ischemic heart disease was not ($p=0.248$).

Table 2: The analysis of the Univariable Cox Regression of the factors associated with the 30-Day Mortality

Variables	Hazard Ratio (95% CI)	P-value
Sex: Male (vs Female)	1.08 (0.91–1.29)	0.426
Age (per year)	1.02 (1.01–1.03)	<0.001
Body Mass Index (kg/m ²)	0.94 (0.92–0.96)	<0.001
Postoperative ICU admission	0.61 (0.50–0.74)	<0.001
Department of ICU admission: IM (Ref: Non-IM)	3.21 (2.70–3.82)	<0.001
APACHE II score	1.08 (1.07–1.10)	<0.001
Charlson Comorbidity Index	1.31 (1.27–1.36)	<0.001
Comorbidity at ICU admission		
Hypertension	1.42 (1.12–1.80)	0.003
Diabetes mellitus	1.45 (1.06–1.98)	0.019
Ischemic heart disease	1.34 (0.81–2.20)	0.248
COPD	2.17 (1.28–3.70)	0.004

Cancer	1.28 (1.06–1.54)	0.011
C-Reactive Protein (mg/L)	1.01 (1.00–1.02)	<0.001
Albumin (g/L)	0.88 (0.86–0.90)	<0.001
C-Reactive Protein/Albumin Ratio	1.12 (1.09–1.14)	<0.001

Table 3 showed the Multivariable Cox regression which had identified several independent predictors of 30-day mortality after adjustment for confounding variables. High age was a significant predictor (HR=1.01, **p=0.041**), whereas high BMI continued to demonstrate a protective association (HR=0.94, **p<0.001**). Patients admitted to the Internal Medicine department had high mortality risk than non-IM admissions (HR=1.74, **p<0.001**). Higher APACHE II scores (HR=1.08) and Charlson Comorbidity Index (HR=1.48) independently predicted poor outcomes. Cancer is an independent risk factor (HR=1.49, **p<0.001**). The CRP/albumin ratio showed strong prognostic significance (HR=1.13, **p<0.001**), whereas CRP alone was not independently associated with mortality (p=0.072). Contrastingly, high albumin levels remained protective, and the CRP–albumin interaction was statistically significant (**p=0.011**), indicating their combined influence on mortality risk.

Table 3: The demonstration of the Multivariable Cox Regression Analysis among patients with Independent Predictors of 30-Day Mortality

Variables	Hazard Ratio (95% CI)	P-value
Age (per year)	1.01 (1.00–1.02)	0.041
Body Mass Index (kg/m ²)	0.94 (0.92–0.97)	<0.001
Department of ICU admission: IM (Ref: Non-IM)	1.74 (1.42–2.12)	<0.001
APACHE II score	1.08 (1.06–1.09)	<0.001
Charlson Comorbidity Index	1.48 (1.41–1.56)	<0.001
Cancer	1.49 (1.22–1.81)	<0.001
C-Reactive Protein/Albumin Ratio (Model 1)	1.13 (1.10–1.15)	<0.001
C-Reactive Protein (mg/L) (Model 2)	1.00 (0.99–1.01)	0.072
Albumin (g/L) (Model 2)	0.88 (0.86–0.90)	<0.001
Interaction: C-Reactive Protein × Albumin (Model 2)	1.00 (1.00–1.01)	0.011

Table 4 showed that the distribution of clinical parameters, albumin demonstrated the highest predictive performance for 30-day mortality (estimate 0.76; 95% CI: 0.72–0.80), which was followed by the APACHE II score (0.75; 95% CI: 0.71–0.79). The Charlson Comorbidity Index also showed improved ability of discrimination with an estimate of 0.72 (95% CI: 0.68–0.76). The CRP/albumin ratio exhibited improved

predictive performance than CRP alone which suggested that combination of the inflammatory and nutritional markers improved the prognostic accuracy. Overall, albumin-based indicators outperformed CRP alone, while established severity indices such as APACHE II and Charlson Comorbidity Index remained reliable predictors of short-term mortality in ICU patients.

Table 4: The predictive ability of the clinical parameters for the 30-Day Mortality

Variable	Estimate (95% CI)
C-Reactive Protein (CRP)	0.63 (0.59–0.67)
Albumin	0.76 (0.72–0.80)
C-Reactive Protein/Albumin Ratio	0.68 (0.64–0.72)
APACHE II Score	0.75 (0.71–0.79)
Charlson Comorbidity Index	0.72 (0.68–0.76)

Discussion

The C-reactive protein-to-albumin ratio (CAR) is a reliable predictor to predict the severity of the acute pancreatitis. Several studies from the Asia and Europe showed high CAR which is associated with the organ failure, pancreatic necrosis, long term hospitalization and mortality. This outperformed the CRP and the severity scores. The cut off for the CAR indicated high sensitivity about 85%, 80% of specificity and 0.82 for the AUROC to predict the severity of the acute pancreatitis. CAR is an independent predictor for the multivariable adjustment, which highlighted the application is simple, not expensive and reliable prognostic biomarker to identify the risk among resource limited settings [11]. The application of the C-reactive protein-to-albumin ratio (CAR) is useful prognostic indicator among critically ill patients. Previously, it has been reported that a high CAR is indicative of both inflammation and poor nutrition, thus a better predictor of poor patient outcomes than CRP alone. In the current study, a high CAR was independently predictive of increased mortality over a period of 28 days; also, CAR was a significant predictor of mortality even after adjustment for the APACHE II score and other confounding factors. Furthermore, CAR had a stronger discriminative ability than CRP alone and was significantly predictive of poor survival [12].

CAR can be used as a reliable and inexpensive inflammatory prognostic biomarker for critically ill patients. Previous literature has suggested an association between high CAR levels and increased mortality in sepsis patients, patients with liver disorders, stroke, cancer, and intensive care unit admission. There are studies which shows the patients with AKI with high CAR, had significantly high mortality rate at 1-year follow-up. Moreover, CAR showed better prognosis than CRP and albumin as single marker and continued to remain an independent predictor of mortality even after adjustment for clinical factors [13]. C-reactive protein to albumin ratio (CAR) helps to estimate the inflammation and prognosis among critically ill sepsis patients. The prior

studies found that higher CAR at discharge from ICU predicted the high mortality rate within 90 days and provides improved prognostic utility rather than the CRP alone. In the current study, higher CAR was an independent predictor of mortality after discharge from ICU even after the possible confounders. This reflected the combination of the effect of inflammation as well as the nutrition which leads to effective patient outcome [14]. The study showed that the C-reactive protein to albumin ratio (CAR) is reliable as well as cost-effective biomarker for the early diagnosis of the severity of acute pancreatitis. It has been observed in the previous studies that the high CAR ratio has been associated with the severity, prolonged duration of stay in hospital, organ dysfunction and poor outcome. CAR had high diagnosing efficacy for the severe acute pancreatitis (AUC 0.862) with 100% sensitivity at the optimal cut-off value. Apart from these, the high CAR was significantly correlated with long hospital stay, while low CAR was an indicator for low risk of severity [15].

Conclusion

The study concluded that CRP/albumin ratio was a significant and independent predictor of 30-day mortality for the critically ill patients of the ICU. The elevated CRP level and reduced concentration of albumin which indicated systemic inflammatory processes and poor nutritional state, the combination of CRP and albumin in one ratio had effective prognostic significance than CRP. The high CRP/albumin ratio, APACHE II score, Charlson Comorbidity Index, cancer diagnosis, older age, and Internal Medicine ICU admission were independent predictors of high risk of death, while increased BMI and serum albumin level had adverse effect on mortality rate. The albumin and APACHE II had the best predictive value, whereas CRP/albumin ratio had effective ability to CRP. The study showed that CRP/albumin ratio is reliable, cheap and easily accessible biomarker which evaluates the patient's risks combined with conventional severity scoring systems.

REFERENCES

1. Cabrerizo S, Cuadras D, Gomez-Busto F, Artaza-Artabe I, Marín-Ciancas F, Malafarina V. Prognostic value of serum albumin combined with serum C-reactive protein levels in older hospitalized patients: continuing importance of serum albumin. *J Nutr Health Aging*. 2006;10(1):36–42.
2. Ridker, P. C-Reactive Protein and the Prediction of Cardiovascular Events Among Those at Intermediate Risk: Moving an Inflammatory Hypothesis Toward Consensus. *JACC*. 2007 May, 49 (21) 2129–2138. <https://doi.org/10.1016/j.jacc.2007.02.052>
3. Kannangai R, Kandathil AJ, Ebenezer DL, Mathai E, Prakash AJ, Abraham OC, Sudarsanam TD, Pulimood SA, Selvakumar R, Job V, Sridharan G. Usefulness of alternate prognostic serum and plasma markers for antiretroviral therapy for human immunodeficiency virus type 1 infection. *Clinical and Vaccine Immunology*. 2008 Jan;15(1):154-8.
4. Lyons O, Whelan B, Bennett K, O'Riordan D, Silke B. Serum albumin as an outcome predictor in hospital emergency medical admissions. *Eur J Intern Med*. 2010;21(1):17–20. (Data collected 2002–2008.)
5. Dhandapani SS, Aditya Gupta, Vivekanandhan S, Mahapatra AK, Mehta VS: Serum ionic magnesium in traumatic brain injury. *Indian J Neurotrauma* 2005, 2: 103-106
6. Vincent JL, Dubois MJ, Navickis RJ, Wilkes MM. Hypoalbuminemia in acute illness: is there a rationale for intervention? *Ann Surg*. 2003;237(3):319–334.

7. Adler RA, Funkhouser HL, Petkov VI, Elmore BL, Via PS, McMurtry CT, Adera T. Osteoporosis in pulmonary clinic patients: does point-of-care screening predict central dual-energy X-ray absorptiometry? *Chest*. 2003 Jun;123(6):2012-8. doi: 10.1378/chest.123.6.2012. PMID: 12796183.
8. Yap FH, Joynt GM, Buckley TA, Wong EL. Association of serum albumin concentration and mortality risk in critically ill patients. *Anaesth Intensive Care*. 2002 Apr;30(2):202-7.
9. Venugopal S.K., Devaraj S., Yuhanna I., Shaul P. and Jialal I.: Demonstration that C-reactive protein decreases eNOS expression and bioactivity in human aortic endothelial cells. *Circulation* 2002; 106: 1439.
10. Mackay A, Erskine J, Kerr O, Marshall L, Davidson A. C-Reactive protein and albumin as prognostic markers in intensive care. *Crit Care*. 2010;14(Suppl 1):P430. doi: 10.1186/cc8662. Epub 2010 Mar 1. PMCID: PMC2934304.
11. OP M, AgarwaF A, Krishnan R. Sudden death due to acute pancreatitis: autopsy observations. *Journal of Forensic Medicine & Toxicology*. 2008 Jul;25(2).
12. Hoogwerf B. Chronic inflammation adds to metabolic syndrome in the prediction of microalbuminuria. *Journal of the American College of Cardiology*. 2003 Jan 1.
13. Puneeth CS. *Correlation Between C-Reactive Protein and Lipid Abnormalities in Subjects with Acute Ischemic Stroke* (Doctoral dissertation, Rajiv Gandhi University of Health Sciences (India)).
14. Parikh NI, Vasan RS. Assessing the clinical utility of biomarkers in medicine. *Biomarkers in medicine*. 2007 Oct 1;1(3):419-36.
15. Kumar GR, Murali RB, Kumaran KM, Pugazhendhi T, Kumar SJ. Dysphagia in elderly male: A case report. *Indian J Gastroenterol*. 2010;29(1):A14-93.