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# C-Reactive Protein To Albumin Ratio As A Predictor Of Outcome In Patients With Sepsis

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***ABSTRACT:***
***Background:*** *Sepsis is a complex clinical state that accompanies severe infection and is marked by extensive organ dysfunction. Sepsis is a primary justification for admission to the intensive care unit (ICU) and is associated with significant morbidity and mortality rates. Both CRP and Albumin are commonly available and inexpensive assays in all hospitals, particularly critical care units, and are well established biomarkers in sepsis patients. By measuring the ratio of CRP to Albumin, it is possible to predict the mortality risk of sepsis patients and provide earlier intensive care for these patients.*
***Objectives:***
*1. To assess the CRP/Albumin ratio in patients with sepsis*
*2. To assess the outcome of sepsis using CRP/Albumin ratio*
***Methodology:*** *After getting written informed consent, a prospective observational study was conducted on consecutive patients above the age of 18 years satisfying the criteria for sepsis (According to the third international sepsis criteria: patients with SOFA score of >2) . Within 24 hours of admission to the hospital , the patients were subjected to basic lab investigations such as complete blood count, CRP , renal function test, liver function test, arterial blood gas analysis. Microbiological culture samples and serological tests were followed. Patients with SOFA score of >2 with demonstrable focus of infection , lab confirmed pathogen isolated from blood or proved by serological test were included in the final study sample after screening them for any exclusion criteria. CRP and albumin values were monitored on day of admission. For the purpose of standardization, the ratio was measured with CRP in mg/L and albumin in g/dLPatients were followed up for outcome until discharge of patient from the hospital or death of the patient (in-hospital mortality).*
***Results:*** *In our study, The Mean CRP : Albumin ratio of the study population was 30.1 (SD = 13.8). Median CRP : albumin ratio (CAR) level was 29.14 with an interquartile range of 20.42 – 38.47*
*Mean CRP : Albumin ratio (CAR) levels among non survivors were 42.1 +/- 11.2 while that among survivors were 23.6 +/- 10.3. Mean CAR levels were higher among non survivors than survivors and there is highly significant association between mean CAR levels and outcome (p value = <0.001). The AUC of the CRP/ALB ratio was 0.886. With Youden index of 0.6749 and the p value of <0.0001, an optimum cut off level of CAR was obtained >31.88. Sensitivity of 91.3% and specificity of 76.19% obtained for the ratio at the cut off level of 31.88. In relation to outcome in terms of mortality , CAR levels > 40 has the highest specificity (95.24%), and a high positive likelihood ratio of 9.13, PPV of 83.3%, NPV of 75.5% , however with a lower sensitivity (43.4%). CAR levels >26.6 has the highest sensitivity (91.3%) and negative predictive value (93.3%) , but has a lower specificity (66.6%) and likelihood ratios.*
***Conclusion:*** *CAR (CRP : Albumin Ratio) can be reliably used as a predictor of short term mortality in sepsis patients. CAR levels are higher among non survivors than survivors.*
*On the basis of this study this study, we propose, patients with cut off CAR levels > 40 should be treated with earlier goal directed therapy as they are associated with a high risk of mortality.*
***Keywords:*** *CRP : Albumin ratio, Sepsis, Mortality predictor*

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## I. Introduction

Sepsis is a complex clinical state that accompanies severe infection and is marked by extensive organ dysfunction[1]. Sepsis is a primary justification for admission to the intensive care unit (ICU) and is associated with significant morbidity and mortality rates[2].

In individuals with sepsis, an increase in CRP/Albumin is reported in conjunction with both rising CRP and lowered serum albumin levels, which is a negative acute-phase reactant.

C-reactive protein (CRP) is a readily available and routinely performed biomarker for monitoring inflammation in intensive care units. Early on in the progression of a disease, CRP levels are correlated with inflammatory levels[2]. Serum Albumin (Alb) is an indication of acute inflammation and is a negative acute phase reactant. Low Serum Albumin levels are common in hospitalised patients, with greater reductions in critically ill patients[3]. Therefore, when evaluating patients with varying underlying conditions, this marker alone can introduce bias, as albumin levels are affected by both chronic nutritional and inflammatory status[4]. Hypoalbuminaemia, regardless of its source, cannot be used as an indicator of nutritional status, but a low albumin level typically indicates a major protein deficiency[5]. In the context of the study, however, hypoalbuminemia is most likely the outcome of infection rather than a previous illness[5]. In infections and sepsis, metabolic demands are enhanced as a result of heightened temperature, which increases energy needs, and a hypercatabolic condition characterised by an increase in protein catabolism and urea nitrogen excretion. In addition to an anabolic demand occurring during infection, sepsis has been demonstrated to stimulate protein synthesis[6]. Because serum albumin is a negative acute-phase protein, the degree of hypoalbuminemia in critically ill patients correlates with the intensity of the infection-induced inflammatory response[6]. In ICU patients, a correlation between a low SA and infection has been identified, and low serum albumin levels have been observed in sepsis[6].

In previous research, it was determined that the CRP/albumin ratio may be utilised to estimate mortality in the ICU among diverse subgroups of critically sick patients[2,5].

This study seeks to assess the value of the CRP/Albumin ratio as a low-cost, readily accessible biomarker for predicting the outcome of sepsis.

## II. Materials and Methods

**Type of study:** This is a prospective observational study which was approved by the institutional review board and received the ethics committee approval from the institutional ethics committee.

**Study population:** All patients admitted to General medicine wards and medicine intensive care unit in Government Medical College, Kottayam who have fulfilled the inclusion criteria.

**Inclusion criteria:** Patients must satisfy all of the following :

- Clinically confirmed sepsis (satisfying the criteria for sepsis according to the third international sepsis criteria: patients with SOFA score of >2)
- Demonstrable focus of infection / Lab confirmed pathogen (PCR/Serology)
- Above the age of 18 years
- Patients with serum CRP and albumin concentrations obtained at admission to the medical wards and intensive care unit.

**Exclusion criteria:**

- Documented pre-existing organ dysfunction prior to admission (chronic kidney disease- Stage 4 and 5, chronic liver disease),
- Clinical evidence of connective tissue diseases , malignancies
- Pregnancy

**Procedure and Methodology:** After getting written informed consent, a prospective observational study was conducted on consecutive patients above the age of 18 years satisfying the criteria for sepsis (According to the third international sepsis criteria: patients with SOFA score of >2) , either with a demonstrable focus of infection clinically pertaining to origin of sepsis or lab confirmed pathogen isolated from blood or proved by serological test was included in the study population. A detailed history and clinical examination was conducted. Within 24 hours of admission to the hospital , the patients were subjected to basic lab investigations such as complete blood count, CRP , renal function test, liver function test, arterial blood gas analysis. GCS was calculated for the patient and urine output measured. SOFA score was then calculated with these parameters obtained. Microbiological culture samples and serological tests were followed through. Patients with SOFA score of >2 with demonstrable focus of infection , lab confirmed pathogen isolated from blood or proved by serological test were included in the final study sample after screening them for meeting any of the exclusion criteria. CRP was measured by latex enhanced immunoturbidimetry in the unit 'mg/L' terms for calculation of ratio. Serum albumin is determined using bromocrescol green method in 'g/dL'. For the purpose of standardization, the ratio was measured with CRP in mg/L and albumin in g/dL. CRP and albumin values were monitored on day of admission. Additional data such as, whether the patients had complications such as Aute lung injury, Hypotension and Renal failure was documented. Patients were followed up for outcome until discharge of patient from the hospital or death of the patient (in-hospital mortality).

**Sample size:**

According to the study done by Kim et al9, "The C-Reactive Protein/Albumin Ratio as an Independent Predictor of Mortality in Patients with Severe Sepsis or Septic Shock Treated with Early Goal-Directed Therapy" ,
CRP/Albumin ratio was calculated using CRP in 'mg/dl' units and Alb in terms of 'g/dl' units.
Normal ranges were 0.0–0.80 mg/dL for CRP and 3.5–5.3 g/dL (35-50 g/L) for albumin.
The mean CRP/Albumin ratio among sepsis patients is 5.298 +/- 4.258 ;
Standard deviation (SD) = 4.258
Relative precision (d) = 20% of mean = 20 x 5.298 / 100 = 1.05
$N = 4(SD)2 / d2$

$= 4 \times (4.258)2 / (1.05)2$

$= 65$

**Data collection procedure:** Data was entered in Microsoft excel and analyzed using IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.

**Statistical analysis:** Data was entered in Microsoft excel and analyzed using IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp. Quantitative variables were expressed as mean and standard deviation. Qualitative variable were expressed as frequency and percentage. Comparison of continuous variable between two group were analysed by student t test. Association between qualitative variables were analysed by Chi square test. ROC curve was ploted to CAR score to predict mortality, AUC with 95% CI was assessed for the accuracy measurement. Optimum cut of value to predict mortality was assessed with sensitivity, specificity, PPV and NPV were calculated. A p- value of <0.05 was considered statistically significant.

## III. Results:

Among the study population the minimum and maximum age was from 29 to 96 years.

Mean age of study population was 57.12 +/- 14.8 years. 35.4 % of the study population belonged to the age group 51-60 followed by 24.6 % belonging to the age group 41-50.

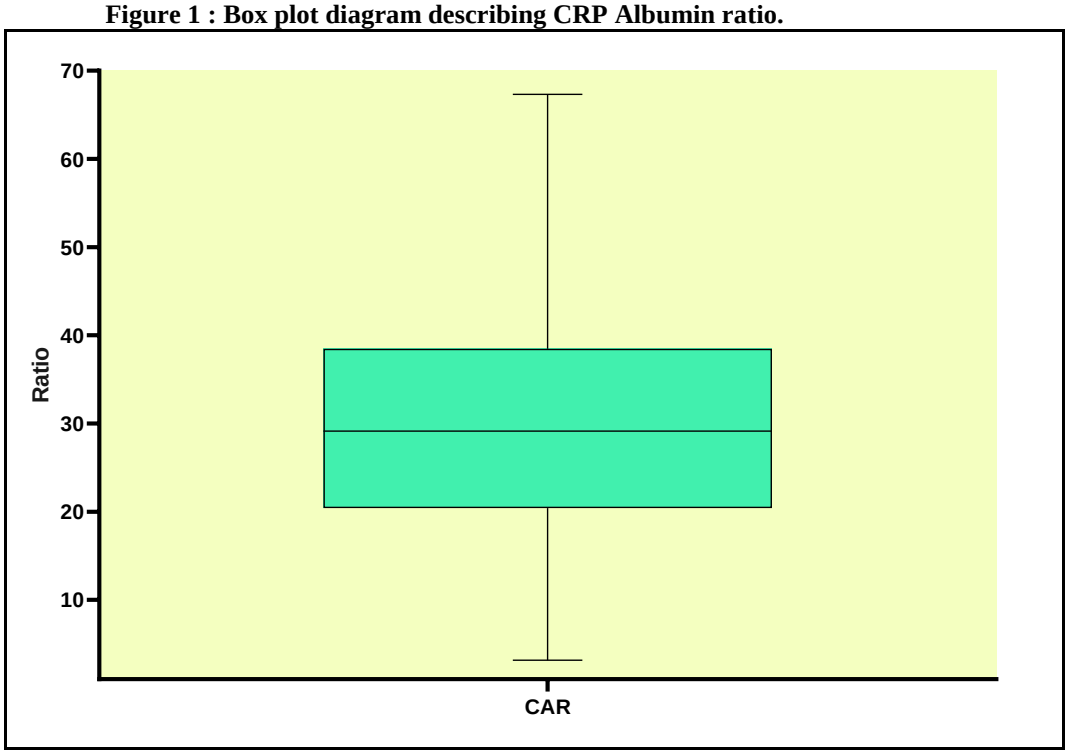
The patients in the study were grouped into survivors and non survivors on the basis of outcome. The survivors were the ones who were discharged from the hospital at the end of treatment course. Non survivors were the patients who died during hospital stay in ICU/ wards. Among the study population , 64.6% of the study group were survivors whereas 35.4% were non survivors.

In table no 1, among the study population of 65 patients, mean age was 57.12 (sd = 14.8) . The mean and median levels of CRP was 99.5 (SD = 40.9) and 100 respectively. Mean and median albumin levels were 3.4 (SD = 0.31) and 3.4 respectively. The Mean CRP : Albumin ratio of the study population was 30.1 (SD = 13.8). Median CRP : albumin ratio (CAR) level was 29.14 with an interquartile range of 20.42 – 38.47

**Table 1 : CRP : Albumin Ratio**

| | **N** | **Mean ± sd** | **Range** | **Median** | **IQR** |
|---|---|---|---|---|---|
| Age | 65 | 57.1 ± 14.8 | 4 - 90 | 56 | 48 - 65 |
| CRP Day1 | 65 | 99.5 ± 40.9 | 12 - 202 | 100 | 70 - 125 |
| ALB Day 1 | 65 | 3.4 ± 0.31 | 2.6 - 4 | 3.4 | 3.2 - 3.6 |
| CRP : Albumin Ratio | 65 | 30.1 ± 13.8 | 3.16 - 67.33 | 29.14 | 20.42 - 38.47 |

**Figure 1 : Box plot diagram describing CRP Albumin ratio.**




Lower and upper end of the whisker represents minimum and maximum value respectively. Lower border of the box represents 25$^{th}$ percentile and upper border of the box represents 75$^{th}$ percentile. Middle horizontal line represents median value.

Table no 2 shows Mean CRP : Albumin ratio (CAR) levels among non survivors were 42.1 +/- 11.2 while that among survivors were 23.6 +/- 10.3. Mean CAR levels were higher among non survivors than survivors and there is highly significant association between mean CAR levels and outcome (p value = <0.001).

**Table 2 : Mean CRP : Albumin Ratio among survivors and non survivors**

| **Outcome** | **N** | **CRP : Albumin Ratio** | | **t** | **p** |
|---|---|---|---|---|---|
| | | Mean | sd | | |
| Non survivors | 23 | 42.1 | 11.2 | 6.709 | <0.001 |
| Survivors | 42 | 23.6 | 10.3 | | |

**Figure 2 : ROC curve of CRP albumin ratio to predict mortality**

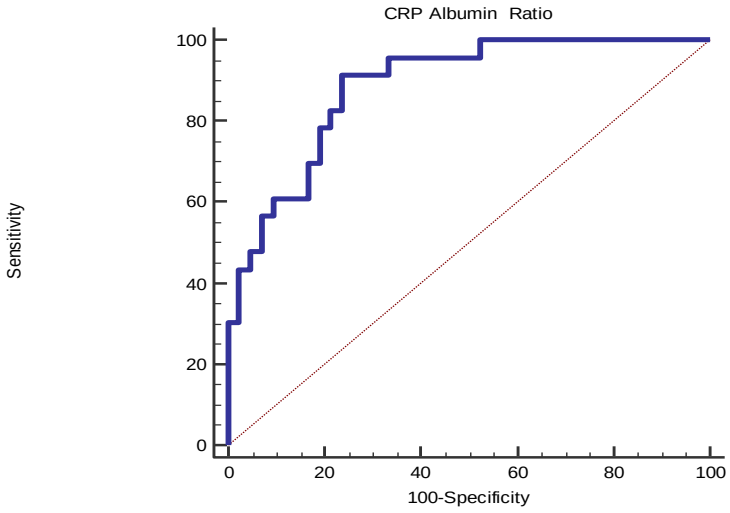


Table 3 shows the results of the area under curve (AUC) with 95% CI (0.783 to 0.952) in ROC analysis for 30-day mortality. The AUC of the CRP/ALB ratio was 0.886. With Youden index of 0.6749 and the p value of <0.0001, an optimum cut off level of CAR was obtained >31.88. Sensitivity of 91.3% and specificity of 76.19% obtained for the ratio at the cut off level of 31.88.

**Table 3 : ROC curve parameters**

| **ROC curve** | |
|---|---|
| **Variable :** | **CRP : Albumin Ratio** |
| Positive group : Survivors | 23 |
| Negative group : Non survivors | 42 |
| Area under the ROC curve (AUC) | 0.886 |
| Standard Error | 0.04 |
| 95% Confidence interval | 0.783 to 0.952 |
| z statistic | 9.664 |
| p | <0.0001 |
| Youden index | 0.6749 |
| Optimum cut off | >31.88 |
| ***Sensitivity*** | ***91.3*** |
| ***Specificity*** | ***76.19*** |

Table no 4 demonstrates that in relation to outcome in terms of mortality , CAR levels > 40 has the highest specificity (95.24%), and a high positive likelihood ratio of 9.13, PPV of 83.3%, NPV of 75.5% , however with a lower sensitivity (43.4%). CAR levels >26.6 has the highest sensitivity (91.3%) and negative predictive value (93.3%) , but has a lower specificity (66.6%) and likelihood ratios.

**Table 4 : Levels of CAR and its Sensitivity, Specificity, Likelihood ratio, Predictive values in relation to mortality**

| **CAR** | **Sensitivity** | **Specificity** | **+LR** | **-LR** | **+PV** | **-PV** |
|---|---|---|---|---|---|---|
| >26.67 | 91.3 | 66.67 | 2.74 | 0.13 | 60 | 93.3 |
| >31.88 | 91.3 | 76.19 | 3.83 | 0.11 | 67.7 | 94.1 |
| >34.05 | 78.26 | 80.95 | 4.11 | 0.27 | 69.2 | 87.2 |
| >34.38 | 69.57 | 80.95 | 3.65 | 0.38 | 66.7 | 82.9 |
| >38.24 | 56.52 | 92.86 | 7.91 | 0.47 | 81.3 | 79.6 |
| >38.75 | 47.83 | 92.86 | 6.7 | 0.56 | 78.6 | 76.5 |
| >40 | 43.48 | 95.24 | 9.13 | 0.59 | 83.3 | 75.5 |

## IV. Discussion:

Biomarkers are crucial in the early diagnosis, differential diagnosis, risk stratification, therapy monitoring, and prognosis of patients with sepsis. Over the past 20 years, sepsis patient mortality rates have stayed between 20% and 30% despite the use of antimicrobial medicines and enhanced life support. The present study included 65 patients admitted to the general medicine wards and medical intensive care unit in government Medical College Kottayam over a duration of one year.The mean age of the study population was 56.26 years with a standard deviation of 12.96. Most of the study population were middle aged . Only few were in the extremes of age due to the stringent exclusion criteria of this study. Analyzing Gender distribution in the present study, out of the 65 study population 58.5% were males and 41.5% were females. Outcome of the patients were measured in terms of mortality during hospital stay and patients were grouped into survivors and non survivors. Among the study population , 35.5 percent were non survivors. Mean age among the non survivors was 53 (sd : 13.3) and among survivors, mean age was 59.4. In our study , there was no significant statistical association between age and outcome among the patients with sepsis. However in a study by Ranzani et al, mean age among non survivors and survivors were 60(sd=19) and 48(sd=18) . In the study, mean age had a significant association with outcome among sepsis patients ( p value <0.001) [4] . This disparity could have been due to the lesser sample size as well as more patients being in the middle age group in our study. In another study by Kaplan et al, mean age (years) among nonsurvivors was 76 (62–93) and survivors was 68 (58–86). It did not have any statistically significant associations with the outcome of patients (p value = 0.768) [7]

There was no significant influence of gender on outcome in our study (p value = 0.814)

Among the study population, 44(67.7%) of the patients had developed renal failure during the course of ICU stay. When non –survivors and the survivors were compared with their incidence of renal failure , 18(78.3%) of the non survivors had renal failure whereas 26(61.9%) of the survivors had the same.

Acute Lung Injury was seen in 37(56.9%) of the patients during the course of ICU stay. When non – survivors and the survivors were compared for the incidence of Acute Lung Injury , 18(78.3%) of the non survivors had Acute Lung Injury whereas it was found in 19(45.2%) of the survivors .

Renal failure among survivors and non survivors did not show any statistical significance whereas acute lung injury was associated with higher mortality (p value of 0.01). In a study by Kim et al, The need for MV, RRT and use of vasoactive drugs were more frequent in patients who died during the 90 days after discharge[9.] Among the study population of 65 patients, The mean and median levels of CRP was 99.5 (SD = 40.9) and 100 respectively. Mean and median albumin levels were 3.4 (SD = 0.31) and 3.4 respectively. The Mean CRP : Albumin ratio of the study population was 30.1 (SD = 13.8). Median CRP : albumin ratio (CAR) level was 29.14 with an interquartile range of 20.42 – 38.47

In our study , Mean CRP : Albumin ratio (CAR) levels among non survivors were 42.1 +/- 11.2 while that among survivors were 23.6 +/- 10.3. Mean CAR levels were higher among non survivors than survivors and there is highly significant association between mean CAR levels and outcome (p value = <0.001).

| **Parameters** | **Outcome** | **Present study** | **Kaplan et al(2020)[7]** | **Ranzani et al(2013)[4]** |
|---|---|---|---|---|
| **CRP** | Non survivors | 128.7 (SD = 34.2) | 88.2(SD = 60.4) | 200 (118-325) |
| | Survivors | 83.5 (SD = 35.3) | 87.8(SD = 53.6) | 162 (75-263) |
| **Albumin** | Non survivors | 3.1 (SD = 0.2) | 2.62(SD = 0.58) | 2.3 (2.0-2.7) |
| | Survivors | 3.6 (SD = 0.2) | 2.81(SD = 0.68) | 2.5 (2.1-3.1) |
| **CAR** | Non survivors | 42.1 (SD = 11.2) | 37.05 (SD = 30.86) | 89 (51-146) |
| | Survivors | 23.6 (SD = 10.3) | 34.27(SD = 24.51) | 62 (30-112) |

| | **AUC for CAR** | **Standard error** | **P value** | **95% Confidence interval** | |
|---|---|---|---|---|---|
| | | | | **Lower limit** | **Upper limit** |
| Present study | 0.886 | 0.04 | <0.0001 | 0.783 | 0.952 |
| Kaplan et al(2020)[7] | 0.504 | 0.039 | 0.921 | 0.427 | 0.580 |
| Tak Kyu Oh et al(2018)[5] | 0.65 | Z SCORE = 6.76 | < 0.001 | 0.640 | 0.660 |

According to the study by Tak Kyu et al , a higher CRP/ALB ratio upon ICU admission was independently linked to a higher risk of 30 day mortality. The CRP/ALB ratio's prognostic ability, however, was discovered to be significantly inferior to that of the APACHE II or Charlson comorbidity index. The AUC of albumin was higher than the AUC of CRP or the CRP/ALB ratio, despite the fact that the AUC of CRP/ALB ratio was much higher than that of CRP alone. This study showed that utilising CRP/ALB ratio instead of albumin alone, APACHE II, or Charlson comorbidity index was not advised in predicting 30-day mortality after ICU admissions. The results pointed that CAR ratio's clinical utility in prediction of outcome in terms of mortality after 30-days was debatable[5.] Our study however only includes in hospital mortality/ short term outcomes and the utility of CAR is in line with other similar studies comparing the same[4,7]

The current study demonstrated the significant independent predictive value of the CAR in patients with sepsis.. The findings are strengthened by the stringent inclusion and exclusion criteria and level of statistical significance obtained in this study.

## V. Conclusion:

CAR (CRP : Albumin Ratio) can be reliably used as a predictor of short term mortality in sepsis patients. CAR levels are higher among non survivors than survivors.

On the basis of this study this study, we propose, patients with cut off CAR levels > 40 should be treated with earlier goal directed therapy as they are associated with a high risk of mortality.

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