Original Research

CRP/Albumin ratio (car) as a diagnostic marker, severity marker and prognostic markers of sepsis

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ABSTRACT:
Sepsis is a systemic, deleterious host response to infection. It is associated with high morbidity and mortality. Sepsis is a major cause of Emergency Medicine Department admission. Acute phase reactants (APR) are involved in the pathophysiological process that occurs during an inflammation and tissue injury. C-reactive protein (CRP) is a positive acute phase protein whereas serum albumin (ALB) is a negative acute phase protein. CRP/Albumin ratio can be a useful method to identify the severity and prognosis in sepsis. Hence, we did this study to identify the role of CRP/Albumin ratio (CAR) as a diagnostic and prognostic marker in sepsis presenting to the emergency department (ED). **Methodology:** 2-year prospective survey of 66 septic patients who was admitted to the ED of a tertiary care center in South India. Patients more than 18 years with suspected infection along with two or more criteria of sepsis were included in the study. CRP and Albumin were analysed from the venous blood sample on admission to the ED itself. Chi square test was done to find the association between categorical variables. ROC curve and AUC was used. Severity of sepsis based on severe sepsis and septic shock and prognosis was evaluated: **Result** 66 patients who fulfilled the inclusion criteria were included in the study. In our study population, the mean age was 57.15 ± 16.54 years and 68.2% were males. 50% developed septic shock. In a 45-day follow up, non-Survivor and survivor were 59.1% and 40.9% respectively. The mortality rate of patients admitted with severe sepsis and septic shock are 30.3% and 87.9%, respectively. CRP/Albumin ratio (p value = 0.049) was found to be statistically significant when compared to CRP alone (p value = 0.139) for predicting the severity of sepsis. CRP/Albumin ratio (p value = 0.008) was found to be statistically more significant when compared to CRP alone (p value = 0.050) for predicting the prognosis. We were also able to find a statistical correlation (p < 0.001) between severity of the disease and the prognosis. **Conclusion**: CRP/Albumin ratio (CAR) is a useful diagnostic and prognostic marker in sepsis.
Keywords: Sepsis, Septic shock, CRP/Albumin ratio (CAR), Emergency Department (ED).

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INTRODUCTION

Sepsis is defined as the presence of infection together with systemic manifestations of infection. Sepsis is a systemic, deleterious host response to infection leading to severe sepsis (acute organ dysfunction secondary to documented or suspected infection) and septic shock (severe sepsis plus hypotension not reversed with fluid resuscitation). It is associated with high morbidity and mortality.[1,2]

Sepsis is a major cause of ED admission. For emergency medicine (EM) physicians, the focus will most likely be on differential diagnosis and investigating the strong clues of sepsis. Prompt and effective decision making is critical, early diagnosis for sepsis not only decreases the mortality rate, but it is also necessary for EM physicians to perform further therapy steps (i.e., fluid therapy, appropriate antibiotic use) simultaneously.[3]

Any inflammatory process will result in increase in concentration of the Acute phase reactants (APR). APR is the involved in the pathophysiological process that occurs during an Inflammation and tissue injury. Acute-phase proteins are a heterogeneous group of plasma proteins, whose plasma concentrations increase (positive acute-phase proteins) or decrease (negative acute-phase proteins) in response to inflammation. This response is called the acute-phase reaction (also called acute-phase response). These have a proportionate rise with the strength/ severity of the insult. CRP is a positive acute phase protein whereas albumin is a negative acute phase protein.[4] Both these correlates well with the intensity of the inflammatory response, triggered by infection. Hence, CRP value increases and albumin value decreases for all types of inflammatory conditions including sepsis depending on the strength/severity of the insult and normal within days or weeks once the inflammatory response is self-limited or treated. In healthy adult CRP value will be <10 mg/l.[5] CRP gets elevated in most of the invasive infections.[6, 7] Normal value of Albumin is 3.5 to 5 g/dL and hypoalbuminemia is when the albumin level below 3.5g/dL. A low serum albumin concentration in critical illness is associated with a poor outcome.[8, 9] Studies have also suggested hypoalbuminemia as an independent predictor of mortality. [10]

CRP/albumin ratio, a combination of markers for systemic inflammation and nutritional status, has been evaluated as an independent prognostic marker in sepsis.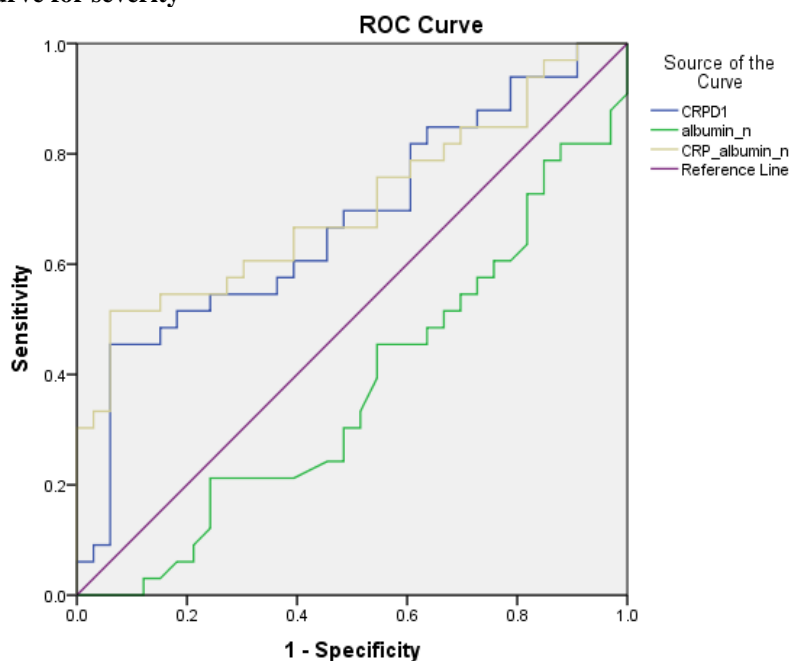[11] CRP/albumin ratio (CAR value) at admission can be used to stratify patients according to the severity of disease.[12] According to Yu Y et al, CRP/Albumin ratio at admission can independently predict sepsis in condition like severe burns.[13] In a critically ill patient requiring intensive care therapy, CRP/Albumin ratio can be a useful method to identify the severity and prognosis of sepsis. Albumin level also correlates to the nutritious status of critically ill patient.[14] CRP/Albumin ratio has been shown to correlate with a poor outcome in patients with sepsis.[15]

Hence, we did this study to identify the role of CRP/Albumin ratio as a diagnostic and prognostic marker in sepsis.

METHODOLOGY

2-year prospective survey of 66 septic patients who was admitted to the ED of a tertiary care center in South India. Percentage was used in categorical variables. Mean and standard deviation (SD) was used in numerical variable. Chi square test was done to find the association between categorical variables. Patients more than 18 years with suspected infection along with two or more criteria of sepsis were included in the study. CRP and albumin were analysed from the venous blood sample on admission to the ED itself.

Chi square test was done to find the association between mortality and the different factors. T-test was used to calculate correlation between 2 independent means. Kaplan-Meier method was done to estimate the survival probability. Log-Rank test was done for comparison of survival probabilities w.r.t. the factors.

RESULT

A total of 92 consecutive patients, who presented to the ED with features of sepsis were enrolled. 66 patients who fulfilled the inclusion criteria were included in the study.

In our study population, the mean age was 57.15 ± 16.54 years and 68.2% were males. All the patients were categorised depending on the severity during the presentation into severe sepsis and septic shock. In our study population, 50% patients had severe sepsis and 50% developed septic shock. The mean $\pm$ SD of CRP/Albumin ratio in our patient population was 6.63 ± 4.90. (Table 1)

Table 1 : Descriptive statistics	
Age (years)	57.15 ± 16.54
Male (%)	68.2
Female (%)	31.8
CRP (mg/L)	172.67 ± 117.06
Albumin (g/L)	27.93 ± 6.28
CRP/Albumin ratio (CAR)	6.63 ± 4.90
Length of hospital stay	12.61 ± 10.34

Severity of sepsis

Table 2 : Descriptive statistics severity of sepsis					
Severity of Sepsis		N	Mean	Std. Deviation	Std. Error Mean
CRP/Albumin ratio	Septic shock	33	8.633	5.597	0.974
	Severe sepsis	33	4.631	3.042	0.529

We were able to find a higher mean $\pm$ SD of CRP/Albumin ratio in septic shock patients (8.633 ± 5.597) when compared to severe sepsis patients (4.63 ± 3.042). (Table 2)

Figure 1: ROC Curve for severity

Diagonal segments are produced by ties.

- Area under for curve of CRP for predicting septic shock was 0.677 with sensitivity 0.606, specificity 0.576. (Figure 1)

- Area under for curve of CRP/Albumin ratio for predicting septic shock was 0.705 with sensitivity 0.636, specificity 0.606. (Figure 1)

- The cut off identified from ROC for CRP is ≥139 and cut off identified from ROC for CRP/Albumin is ≥ 5.7.

CRP and Severity of sepsis

Table 3: CRP and Severity of sepsis				
		Severity of Sepsis		P value
		Septic Shock	Severe Sepsis	
CRP	**≥ 139**	58.8%	41.2%	0.139
	< 139	40.6%	59.4%	

Even though majority of the patients (58.8%) above the cut of value of CRP was in the septic shock category, we could not find a statistically significant correlation between
CRP and septic shock (p value = 0.139). (Table 3)

CRP/Albumin ratio and Severity of sepsis

Table 4: CRP/Albumin ratio and Severity of sepsis				
		Severity of Sepsis		P value
		Septic Shock	Severe Sepsis	
CRP/Albumin ratio	**≥5.7**	61.8%	38.2%	**0.049**
	<5.7	37.5%	62.5%	

61.8% patients with CRP/Albumin ratio ≥5.7 were in septic shock. We were able to find a statistically significant correlation between CRP/Albumin and severity of sepsis (p value<0.05). (Table 4)
CRP/Albumin ratio (p value = 0.049) was found to be statistically significant when compared to CRP alone (p value = 0.139) for predicting the severity of sepsis.

Prognosis of Sepsis

In our study, in a 45-day follow up, non-Survivor and survivor were 59.1% and 40.9% respectively (Figure 2). The mortality rate of patients admitted with severe sepsis and septic shock are 30.3% and 87.9%, respectively.
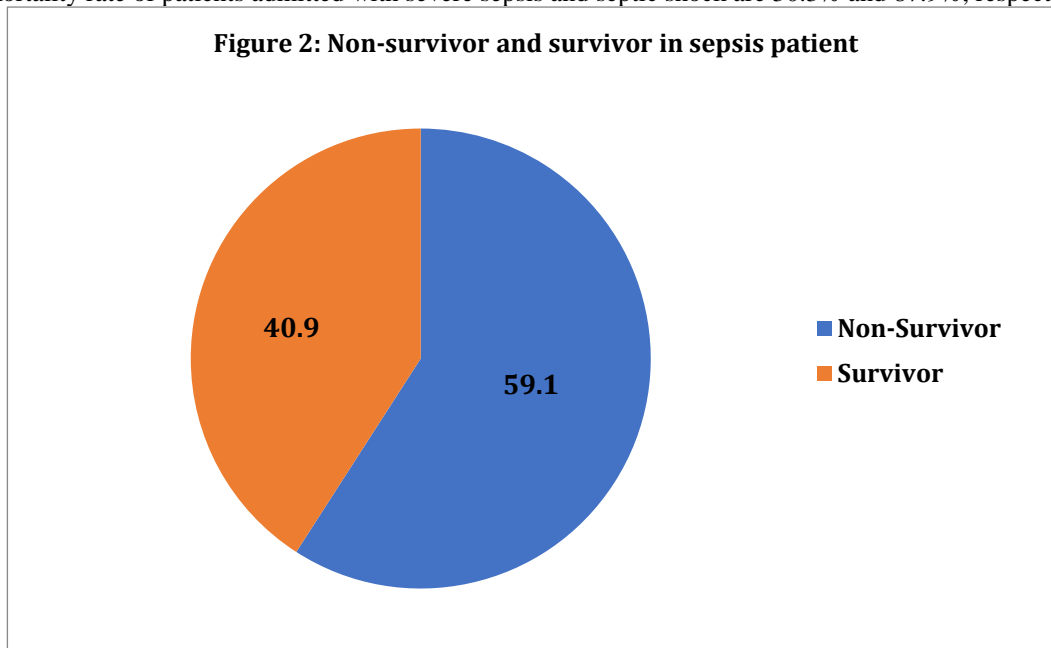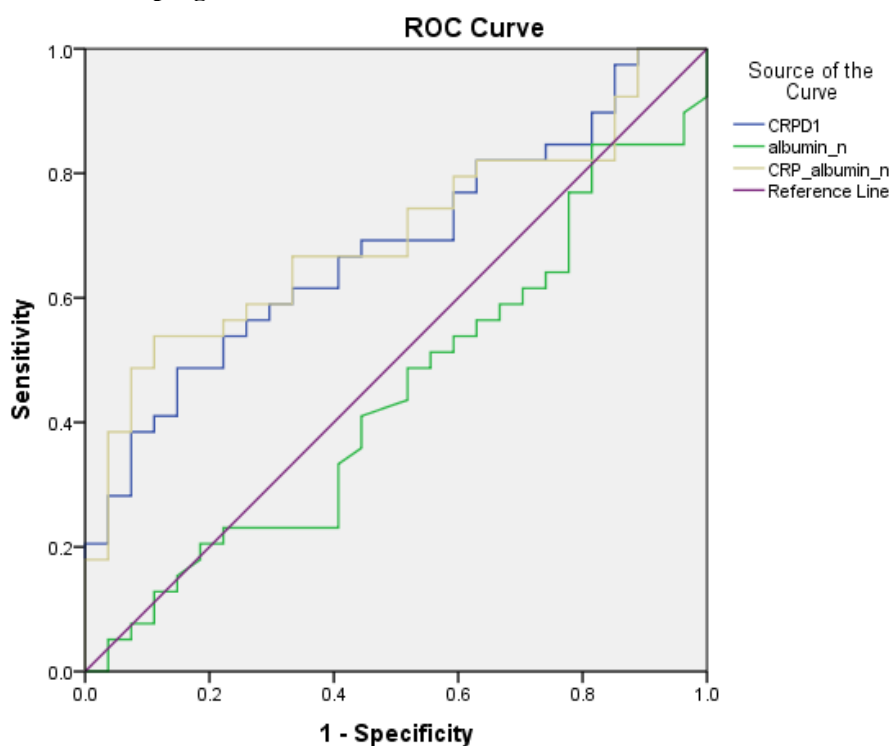
Figure 2: Non-survivor and survivor in sepsis patient

Figure 3: ROC Curve for prognosis

Diagonal segments are produced by ties.

- Area under for curve of CRP for predicting mortality was 0.682 with sensitivity 0.615, specificity 0.630. (Figure 3)

- Area under for curve of CRP/Albumin ratio for predicting mortality was 0.641 with sensitivity 0.636, specificity 0.667. (Figure 3)

CRP and Prognosis

Table 5: CRP and Prognosis				
		Prognosis		**P value**
		Non-survivors	**Survivors**	
CRP	**≥ 139**	70.6 %	29.4 %	0.050
	< 139	46.9 %	53.1 %	

Majority of the patients (70.6%) above the cut of value of CRP were non-survivors. We were able to find a statistically borderline significant correlation between CRP and prognosis (p value = 0.050). (Table 5)

CRP/Albumin ratio and Prognosis

Table 6: CRP/Albumin ratio and Prognosis				
		Prognosis		**P value**
		Non-survivors	**Survivors**	
CRP/Albumin ratio	**≥ 5.4**	74.3 %	25.7 %	0.008
	< 5.4	41.9 %	58.1 %	

Majority of the patients (74.3%) above the cut of value of CRP/albumin ratio were non-survivors. We were able to find a statistically significant correlation between CRP and prognosis (p value = 0.008). (Table 6)
P value CRP/Albumin ratio (p value = 0.008) was found to be statistically more significant when compared to CRP alone (p value = 0.050) for predicting the prognosis.

Severity of sepsis and Prognosis

87.9% of patients in septic shock and 30.3% of patients in severe sepsis were non-survivors. (Figure 4)

Figure 4: Severity of the sepsis and Prognosis

	Severe Sepsis	Septic Shock
■ Survivor	69.70%	12.10%
■ Non-Survivor	30.30%	87.90%
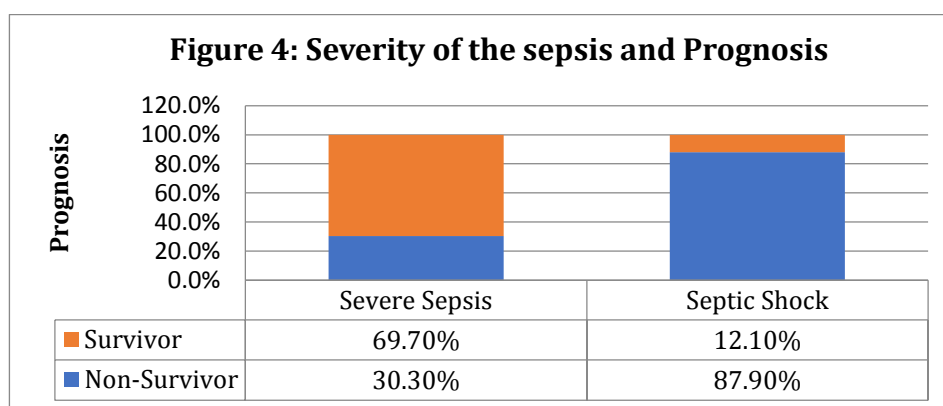
Table 7: Severity of the sepsis and Prognosis			
	Survivor	**Non-Survivor**	**P value**
Severe Sepsis	69.7 %	30.3 %	<0.001
Septic Shock	12.1 %	87.9 %	

In our study, we were able to find a statistical correlation (p < 0.001) between severity of the disease and the prognosis. (Table 7)

Table 8: CRP/Albumin ratio – descriptive statistics			
	Mean	**Median**	**Std. Deviation**
Non-survivors	8.1007	7.7966	5.352
Survivors	4.5111	4.0996	3.214
Septic shock	8.6333	8.9874	5.597
Severe sepsis	4.6312	4.1682	3.042

DISCUSSION

Sepsis is due to dysregulated host response to infection and is a medical emergency.[16] Early diagnosis with prompt and effective treatment is crucial in management of sepsis. All the sepsis cases that came to our ED were categorized clinically into severe sepsis and septic shock. The incidences of severe sepsis and septic shock are less well-described in the developing world.[17]

In our study population, 50% patients had septic shock. Severe sepsis and septic shock were common complications in ICU patients and with high mortality. Similar finding was noted by Jianfang et al in their study.[18] The mortality rate in patients with septic shock was found to be higher than patients with severe sepsis in our study population. Similar finding was noted in Arturo et al in their study were 40-70% mortality in patients with septic shock.[19]

C-reactive protein (CRP) and albumin are measured frequently in the ED and exhibit opposing patterns during inflammation. CRP is a positive acute phase protein whereas albumin is a negative acute phase protein. Both these correlates well with the severity of the inflammatory response that is triggered by an infection.[4,6,7] The use of a ratio between CRP and albumin would provide a variable capable of merging the information provided by CRP and albumin into an index that correlated positively with infection and sepsis as a diagnostic marker, i.e., a higher ratio indicates higher inflammatory status.[15]

In our study, taking into consideration the severity of sepsis, we were able to identify, a higher mean ± SD of CRP/Albumin ratio for patients in septic shock when compared to severe sepsis. This indicates that higher CRP/Albumin ratio at admission to the ED is associated with severity of sepsis. Min et al showed that CRP/Albumin ratio at admission was positively correlated with the severity.[12] However, to our knowledge, not many studies have tried to illustrate the role of CRP/Albumin ratio in diagnostic as well as severity marker in sepsis

Otavio et al in their study showed that CRP/Albumin ratio correlated well with long term prognosis with higher accuracy as well as an independent risk factor for mortality at 90 days in septic patients.[13] They showed that CRP/albumin ratio >2 showed the greatest sensitivity and specificity in predicting mortality at 90 days. An important marker of mortality with improved consistency compared with CRP alone.[12, 15]

We were able to find a higher mean ± SD of CRP/Albumin ratio in non-Survivor (8.1007 ± 5.352) when compared to survivor (4.5111 ± 3.214) (Table 8). CRP/Albumin ratio was found to be statistically more significant when compared to CRP alone for predicting the prognosis. This shows that admission CRP/Albumin ratio can be a good predictor of prognosis of sepsis. In our study, higher CRP/Albumin ratio at admission was associated with a poor prognosis with a lower 45 day survival rate and increased mortality. This is similar to the study published by Yu Y et al.[13] Park et al in their study has determined that higher CRP/albumin ratio was associated with increased mortality in critically ill patients.[21] Hamsa et al also shows similar reports.[22]

We were able to identify that the CRP/Albumin ratio to be statistically more significant when compared to CRP alone for predicting the severity of sepsis as well as the prognosis. This invariably shows that a ratio of positive APR (CRP) to a negative APR (Albumin) resulting in CRP/Albumin ratio, will help to be a diagnostic marker, severity marker as well as a prognostic marker in sepsis.

CONCLUSION

Sepsis is a major cause of morbidity and mortality. Acute phase reactants play a vital role in deciding the severity and prognosis of sepsis. C-reactive protein (CRP) and serum albumin (ALB) are useful markers that can predict morbidity and mortality among critically ill patients. CRP/Albumin ratio is better than CRP alone for predicting the severity of sepsis as well as the prognosis. CRP/Albumin ratio (CAR) is a useful diagnostic marker, severity marker and prognostic marker in sepsis. Timely usage of these could help in early identification and providing a prompt as well as effective treatment for patients in sepsis.

LIMITATION

Serial monitoring of CRP/Albumin ratio will be a good predictor of the prognosis of sepsis.

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