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Original Research Article

Serial Serum Albumin and C-Reactive Protein Levels as Predictors of Mortality in Critically Ill Patients

Suhena Patel[1], Rahul Gambhir[2], Hiren Makwana[3], Pankaj Patil[4]

[1]Senior Resident, P.D.U. Medical College, Rajkot, Gujarat, India
[2]HOD and Professor, P.D.U. Medical College, Rajkot, Gujarat, India
[3]Assistant Professor, P.D.U. Medical College, Rajkot, Gujarat, India
[4]Assistant Professor, P.D.U. Medical College, Rajkot, Gujarat, India

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Corresponding author: Dr. Pankaj Patil
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Abstract

Background: It's important to identify those ICU admitted patients at the time of admission who are likely to have a poor outcome for their better management. Serum Albumin (SA) & CRP (C-reactive protein) levels can act as potential predictor of prognosis. Objectives of the study are: (1) to evaluate the CRP and albumin as prognostic markers in critically ill patients (2) to assess for correlation of S. Albumin & CRP levels with mortality (3) the association between duration of stay and mortality in critically ill patients.

Patients & Methods: Prospective observational study involved 100 critical admitted patients.

Results: SA (<3.5 g/dl) on Day 1, Day 3 & Day 5 or CRP levels (>11 g/dl) on Day 1, Day 3 & Day 10 is a suggestive of bad prognosis (in terms of survival). Decrease in albumin level >0.9 g/dl from day 1 to day 10 or rise of mean CRP level to >12 on days 1,3 & day 10 is a suggestive of bad prognosis. Equation obtained in study correctly predicts survival with 82% accuracy. A steady increase in CRP / albumin ratio or a higher score in APACHE-II indicates a poor prognosis.

Conclusion: Equation obtained in study can predict survival with accuracy of 82%. CRP level (>11g/dl) on Day 1, Day 3 and Day 10 or decrease in albumin level of more than 0.9 g/dl from day 1 to day 10 is a suggestive of bad prognosis. Average duration of ICU stay was higher in non-survivors than survivors.

Highlights: Serial serum albumin and c-reactive protein levels can act as predictors of mortality in critically ill patients. Equation obtained from this study can determine prognosis accurately using both these predictors in 82% of cases.

Keywords: CRP, Albumin, Predictor, critically ill.

Introduction

Albumin is the most abundant plasma protein in humans. We now know the amino acid sequences of albumin, the complete gene sequence of human albumin, and the location of mutations in the gene sequence.[1] It helps maintain the colloid oncotic pressures, acts as a carrier protein, and is involved in metabolic, antioxidant and various other functions.

Patients who are admitted in the Intensive Care Unit (ICU) are at an increased risk of mortality due to the severity of their illness. It

is, thus, important to identify patients at the time of admission who are likely to have a poor outcome so that such patients can be managed aggressively.[2] Serum Albumin (SA) appears to be one such prognostic indicator. Its utility as a prognostic indicator has been studied in various contexts, including critically ill patients. A low serum albumin (SA) concentration correlates with increased length of stay in ICU, increasing the risk of death and readmission to the hospital sooner and more frequently. The daily trend of SA can be useful inpredicting the weaning capability of patients needing mechanical ventilation. Many investigators have used it as an index of the nutritional and metabolic status of the patients. Hypoalbuminemia has been associated with increased hospital mortality and morbidity. It is known that serum albumin concentrations may decrease rapidly in critically ill patients with septic shock and after major surgery as well as in other illnesses.[3] Hypoalbuminemia is also a potent dose-dependent, independent predictor of poor outcomes. Each 10gm/litre decrease in SA concentration significantly increased the odds of mortality by 137%, morbidity by 89%, prolonged ICU stay by 28%, hospital stay by 71% and increased resource utilization by 66%.[4]

For the direction of treatment, it is important to determine the prognosis of patients who require critical care. Several studies have evaluated parameters or biomarkers used forthe prognosis of critically ill patients. However, these factors are difficult to determine, and the application of such prognostic information is difficult when dealing with unstable patients.[5]

C-reactive protein(CRP) is an acute-phase protein that is produced by various cytokines in response to infection, ischemia, trauma, and other inflammatory conditions. High CRP levels have been studied in relation to prognosis and mortality in critically ill patients.[6] On the other hand, low serum albumin is associated with poor prognosis and mortality.Based on the above information,we speculated that the ratio of CRP to albumin could be used as a predictive marker for mortality.

A simple, accessible, quick parameter is needed to confirm treatment response and predict mortality in critically ill patients. This study has following objectives: (1) to evaluate the CRP and albumin as prognostic markers in critically ill patients (2) to assess for correlation of S. Albumin & CRP levels with mortality and (3) the association between duration of stay and mortality in critically ill patients.

Patients and Methods

The present study is a prospective observational study. The sample size was calculated using the formula Sample size n= $4pq/L^2$where p= average percentages of last 3 years of admission of critically ill patients in the emergency department of Pandit Dindayal Upadhyay Medical College and Hospital, Rajkot=80%, q=100-p=20% and L=allowable error=10% of p =8. By using this formula, the total sample size came to 100.

The study duration was 7 months during March 2021 to September 2021, to get the required sample size. All patients admitted in the institute's emergency ward who needed ventilatory support for atleast 5 days and whose relatives were ready to give informed written consent were included in the study. Any patient admitted to the emergency department of the institute and on the ventilator support was excluded from the study if dies within 5 days of ventilator support or was weaned off from ventilator support within 5 days of being put on ventilator support. The treating physician decided to put on mechanical ventilation.

A pre-tested semi-structured questionnaire was prepared. This questionnaire contained information about patients' clinical and demographic profiles at the time of admission to MICU, including age, sex, smoking status, history of previous hospital admissions, and associated chronic illnesses like hypertension, diabetes mellitus, and chronic obstructive pulmonary disease. A careful and detailed history was taken, and a thorough clinical examination was conducted. Findings of Investigations like Total blood counts, renal functions, liver functions, and serum albumin(SA) done at the time of admission, Chest X-ray, arterial blood gas analysis, and some other information like days on the ventilator, days of ICU stay and days of hospital stay were recorded for all the patients. For patients who were included in the study, serum albumin and CRP estimation were done on the day of admission when they were put on a mechanical ventilator and subsequently on day three,day five and day10 of their hospital stay. Serum albumin was assayed using a bromocresol green (BCG) method, and CRP was assayed using an immune turbimetry(IT) method Calibrations were performed according to manufacturer'sguidelines. The patient's outcome was recorded either as a discharge from the hospital (survivor) or patient's death in the hospital(non-survivor).

Ethical permission of the study was obtained from the institutional ethical committee. All data entry was done in MS Excel 2010 version. Statistical analysis was done using the student's unpaired 't' test and Mann-Whitney's 'U' test. Fitting the logistic regression analysis, with the outcome as the dependent variable and serum albumin/ CRP levels on day one, day three, day five and day ten as an independent variable, the following equation was obtained: Outcome = 11.9447– (4.2028 X SA / CRP day1) + (3.9706 X SA / CRP day3) – (1.4891 X SA / CRP day5) – (2.8210 X SA / CRP day10). Values 0 or less than 0 were considered to be suggestive of likely survival and values more than 0 were considered to be suggestive of likely death of the patient.

Results

Table 1 shows that highest number of participants in our study were from 61-70 years age group. Highest survival was seen in younger age group (<30 years). Male to female ratio was 7:3 in our study.

Table 2 shows that two most common etiological diagnosis of the patients at admission to Emergency ward were Respiratory and neurological disorders. Most common reason for initiation of mechanical ventilation was Acute respiratory failure with acute respiratory distress syndrome.

We can see from table 3 that lower serum albumin levels(<3.5 g/dl) on day1, day 3 and day 5 is seen more commonly in the non-survived group as compared to the survived group and this association is statistically significant. This shows that lower S. albumin on Day 1, Day 3 and Day 5 is a suggestive of bad prognosis (in terms of survival of pts) in such patients.

Table 3 also showed that higher CRP levels(>11.0 g/dl) on day1, day 3 and day 10 is seen more commonly in the non-survived group than inthe survived group and this association is statistically significant. This shows that higher CRP levels on Day 1, Day 3 and Day 10 is suggestive of a bad prognosis in such patients.

We can see from table 4 that the decrease in mean serum albumin between Day 1 & Day 10 is 0.86 in the survived group and its 1.09 in the non-survived group, which is a statistically significant association. So we can roughly say that decrease in albumin level between day 1 and day 10 is <0.9 in the survived group, while in the non-survived group it's>0.9. So decrease in albumin level >0.9 g/dl from day 1 to day 10 is a suggestive

of bad prognosis (in terms of survival of pts) in such patients.

Table 4 also shows that on days 1, 3 and 10, the difference between mean CRP levels is statistically significant. So from observation, we can say that in the Survived group, the mean CRP on days 1,3 and 10 ranges between 11-12 (excluding 11 and 12) g/dl, while the same in the non-survived group is >12 g/dl. So rising of mean CRP level to >12 on days 1,3 and day 10 is a suggestive of bad prognosis (in terms of survival of pts) in such patients.

As shown in table 5, using the logistic regression equation, it was found that 26 patients were correctly identified as survivors but 5 patients who were predicted to die actually survived. This indicates that this equation is perfectly able to predict survival in 83.87% of patients. Similarly, 15 patients were correctly identified as non-survivors, but four patients who were predicted to survive actually died. This indicates that this equation can correctly predict the patient's death in 78.95% of cases. Overall, it was able to correctly predict the outcome of the patients in 82% of the cases.

As shown in table 6, in the study group, the mean duration of mechanical ventilation was 8.8 days (± 2.8 days). The average number of days of survivors on mechanical ventilation was 8.2 days (± 2.6 days); in non-survivors, this duration was 9.7 days (±2.9 days). The duration of mechanical ventilation was significantly more (p=0.049) in non-survivors.

As seen from table 7 that the average number of days of ICU stay was 12.6 days (± 3.5 days) for the study group. It was 11.4 days(± 3.4 days) for survivors and 14.6 days (± 3.0 days) for non-survivors. The average duration for which patients were in ICU was significantly higher (p=0.0317) in non-survivors.

As it can be seen from table 8 that the total incline in CRP / albumin ratio in the survivors from Day 1 to day 10 is 1.74, while that in non-survivors is 2.72.It suggests that the high CRP / albumin ratio has a bad effect on the patient's prognosis in terms of mortality. A steady increase in CRP / albumin ratio indicates a poor prognosis.

As shown in table 9 that the mean APACHE-II score among survivors decreased by 0.8 units from day 1 to day 10, while it increased for non-survivors by 0.3 units. This result shows that as the APACHE-II score increases, the chances of mortality increases. Further, there were significant differences of APACHE-II scores between the two groups. A higher score in APACHE-II indicates a poor prognosis of the patient.

Table 1: Demographic Profile of participants

Parameter	sub-group of parameter	Survived (n=62)	Non-survived (n=38)	Total
Age in yrs	≤ 30	20 (32.2%)	2 (5.2%)	22(22%)
	31 – 40	8(12.9%)	0 (0%)	8(8%)
	41 – 50	6(9.6%)	4 (10.5%)	10(10%)
	51 – 60	6 (9.6%)	10 (26.3%)	16(16%)
	61 – 70	12 (19.3%)	12 (31.5%)	24(24%)
	> 70	10 (16.1%)	10 (26.3%)	20(20%)
Sex	Male	42 (60.0%)	28 (40.0%)	70 (70%)
	Female	20 (66.67%)	10 (33.3%)	30 (30%)

Table 2: Etiological diagnosis of the patients at admission to Emergency ward & Reason for initiation of Mechanical ventilation

Diagnosis	Number	Percentage
Neurological Disorders	25	25%
Respiratory Disorders	30	30%
Organophosphorus Compound Poisoning	22	22%
Infective Causes	5	5%
Renal Disorders	1	1%
Metabolic Disorders	2	2%
Miscellaneous	15	15%
Reason for initiation of mechanical ventilation	Number	Percentage
Acute Respiratory Failure with Acute Respiratory Distress Syndrome	69	69%
Acute Respiratory Failure with Coma	15	15%
Acute Respiratory Failure on Chronic Pulmonary Disease (COPD)	10	10%
Acute Respiratory Failure with Neuromuscular Disease	6	6%

Table 3: Comparison of S. Albumin (g/dl) and CRP levels (g/dl) at different days of admission

Parameter	sub-group of parameter	Survived (n=62)	Non survived (n=38)	Test Value (X^2/Fiser Exact)	P value
Serum albumin					
Day 1	< 3.5	32 (51.6%)	30 (78.9 %)	7.4717	0.006
	≥ 3.5	30 (48.4%)	8 (21.1%)		
Day 3	< 3.5	42 (67.7%)	38 (100%)	0.0003	0.001
	≥ 3.5	20 (32.3%)	0 (0 %)		
Day 5	< 3.5	52 (83.9%)	38 (100%)	0.047	<0.001
	≥ 3.5	10 (16.1%)	0 (0 %)		
Day 10	< 3.5	58 (93.6%)	38 (100%)	0.6462	0.089
	≥ 3.5	4 (6.4%)	0 (0 %)		
CRP					
Day 1	< 11.0	29 (46.78%)	3 (7.89%)	0.002	<0.001
	≥ 11.0	33 (53.22%)	35 (92.11%)		
Day 3	< 11.0	20 (32.25%)	2 (5.26%)	0.0012	0.001
	≥ 11.0	42 (67.75%)	36 (94.74%)		
Day 5	< 11.0	17 (27.42%)	11 (28.95%)	1.0	0.089
	≥ 11.0	45 (72.58%)	27 (71.05%)		
Day 10	< 11.0	20 (32.26%)	3 (7.89%)	0.0063	0.008
	≥ 11.0	42 (67.74%)	35 (92.11%)		

Table 4: Comparison of mean serum albumin & mean CRP levels on different days between the two groups

Day of estimation	Mean Serum albumin levels in g/dl		Student's T-test	p-value
	Survivors (n=62)	Non-survivors(n=38)		
Day 1	3.43	3.12	1.983	0.025
Day 3	3.04	2.75	-1.812	0.036
Day 5	2.76	2.37	2.558	0.012
Day 10	2.57	2.03	-4.283	<0.001
Day of estimation	**Mean Serum CRP levels in mg/dL**		**Student's T- test**	**p-value**
	Survivors (n=62)	**Non-survivors (n=38)**		
Day 1	11.1	12.5	-3.952	<0.001
Day 3	11.4	13.1	3.021	0.003
Day 5	12.1	12.9	-0.22	0.825
Day 10	11.9	13.6	2.733	0.007

Table 5: Result of Logistic Regression Equation to predict the outcome

Actual Outcome	Predicted Outcome		% Correct
	Survivors	Non-Survivors	
Survivors	52	10	83.87%
Non-Survivors	8	30	78.95%
% of cases correctly classified			82.00%

Table 6: No. of days of ventilation in two groups

No. of days	Survivors (n=62)	Non survivors (n=38)	Total (n=100)
5–7	28(45.1%)	12(31.5%)	40 (40%)
8–10	22(35.4%)	8(21.0%)	30 (30%)
11–13	10(16.1%)	14(36.8%)	24 (24%)
>13	2(3.2%)	4(10.5%)	6 (6%)

Table 7: No. of days of ICU stay in two groups

No. of days	Survivors(n=62)	Non survivors(n=38)	Total(n=100)
5–7	4(6.4%)	0 (0%)	4 (4%)
8–10	26(41.9%)	4(10.5%)	30 (30%)
11–13	18(29.0%)	18(47.3%)	36 (36%)
>13	14(22.5%)	16(42.1%)	30 (30%)

Table 8: Day-wise comparison of CRP/ albumin levels between two groups

Day of estimation	Mean CRP/albumin levels		Student's T-test	P value
	Survivors(n=62)	Non-survivors(n=38)		
Day1	3.21	4.23	-8.3872	<0.00001
Day3	4.16	5.05	-3.4183	<0.000916
Day5	5.01	6.48	-1.091	0.2781
Day10	4.95	6.95	-4.9938	<0.00001

Table 9: Comparison of APACHE-II scores between two groups

Day of estimation	APACHE-II score		Student's T-test	p-value
	Survivors (n=62)	Non-survivors (n=38)		
Day1	22.7±8.3	29.2±9.5	-5.7778	<0.001
Day3	22.5±8.2	29.3±9.1	-6.8868	<0.001
Day5	22.3±8.0	29.3±9.4	-7.0934	<0.001
Day10	21.9±8.1	29.5±9.2	-6.7306	<0.001

Discussion

In our study proportion of male patients were 68% while the same were 57.4% and 62.6% in the studies conducted by Anibal Basile-Filho *et al* and Tak Kyu Oh *et al* respectively. [7,8] In our study, two most common groups of etiological diagnosis of patients were Respiratory and Neurological disorders while the same were Respiratory and Cardiovascular disorders in the study conducted by Anibal Basile-Filho *et al*.[7] In the study conducted by Ji Eun Park *et al* , two most common groups of etiological diagnosis were infective and renal disorders while the same were neoplastic disorders and vascular disorders in the study conducted by Tak Kyu *et al*. [9,8] So it can be said that etiological diagnosis varies in critically ill patients in different studies but broadly it involves Respiratory, cardiovascular, infective, renal and neoplastic disorders.

Mean albumin level within first 24 hours of admission was higher in survivors group (3.43 g/dl) than non-survivors (3.12 g/dl) in our study. A study conducted by Anibal Basile-Filho *et al* showed that mean albumin level 3.3 g/dl in survivors group while it was 2.7 g/dl in non-survivors group.[7] Mean albumin levels in survivors and non survivors groups were 2.6 g/dl and 2.4 g/dl respectively in the study by Ji Eun Park *et al*.[9] So a generalized statement can be made from above studies that mean albumin level is significantly higher in survivors group than non-survivors group.

The average number of days of ICU stay was 12.6 days (± 3.5 days) in total patients in the present study while the same was 4.8 days (± 9.6 days) in the study conducted by Tak Kyu Oh *et al*.[8] The average days of ICU stay was 11.4 days (± 3.4 days) for survivors and 14.6 days (± 3.0 days) for non-survivors and this difference was statistically significant. In the study by Anibal Basile-Filho *et al*, average days of ICU stay in survivors group was 2.5 days and in non survivors group was 5 days and this difference was also statistically significant [7]. Both studies showed that average days of ICU stay were higher in non survivors group than survivors group.

Mean CRP/albumin levels in survivors group was 3.21 while it was 4.23 in non-survivors group and this difference was statistically significant in our study. Mean CRP/albumin levels in survivors group was 0.9 while it was 11.5 in non-survivors group and this difference was statistically significant in study by Anibal Basile-Filho *et al*.[7] Mean CRP/albumin levels in survivors group was 43.9 while it was 50.9 in non-survivors group and this difference was statistically significant in study by Ji Eun Park *et al*.[9] So it can be said from above studies that Mean CRP/albumin levels was higher in non survivors group than survivors group.

APACHE-II score in survivors and non-survivors group was 22.7 and 29.2 respectively in our study while the same was 12 and 21 in survivors and non-survivors group respectively as found in the study by Anibal Basile-Filho *et al*.[7] 22.7 and 29.2 were the APACHE-II score in survivors and

non-survivors group respectively in the study conducted by Ji Eun Park *et al*.[9] So it can be said from above studies that APACHE-II score was higher in non-survivors than survivors and this association was statistically significant in all of the above studies.

Conclusion

The formula for outcome [outcome = 11.9447– (4.2028 X SA / CRP day1) + (3.9706 X SA / CRP day3) – (1.4891 X SA / CRP day5) – (2.8210 X SA / CRP day10)] can predict survival with accuracy of 82%. Values 0 or less than 0 were considered to be suggestive of likely survival and values more than 0 were considered to be suggestive of likely death of the patient. Higher CRP level (>11g/dl) on Day 1, Day 3 and Day 10 is suggestive of a bad prognosis in such patients (in terms of survival of pts). Decrease in albumin level of more than 0.9 g/dl from day 1 to day 10 is a suggestive of bad prognosis. The average duration for which patients were in ICU was significantly higher in non-survivors as compared to survivors.

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