International Journal of Basic and Applied Medical Sciences ISSN: 2277-2103 (Online)
An Open Access, Online International Journal Available at http://www.cibtech.org/jms.htm
2015 Vol. 5 (1) January-April, pp. 228-234/Nirmala et al.
Research Article

A STUDY OF SERIAL ESTIMATIONS OF SERUM ALBUMIN AS A PROGONOSTIC MARKER

***Nirmala A.C., Namratha and Avinash B.H.**
Department of Internal Medicine, BMCRI, Bangalore
**Author for Correspondence*

ABSTRACT
Critical illnesses have many prognostic markers & scoring systems for risk stratification. They are required for utilization of more aggressive treatment strategies & for taking decisions regarding further management. Serial serum albumin levels have been described in numerous studies as to be having good predictive value in prognostication. So our objective was to determine the effectiveness of monitoring of serial serum albumin levels in the prognostication of patients with critical illness. 50 patients suffering from critical illnesses admitted in emergency wards and intensive care units were selected serum albumin levels were monitored serially in them on days 1,3,5,7 and 10. Duration of study was 2 years. The incidence of critical illnesses was higher in the age group of 50 to 60 years and males. Most patients in the study had primarily neurologic illnesses and APACHE II scores of most patients were in the range of 6 to 15. Day 1 serum albumin in the two groups of survivors and non survivor had no significant difference. Day 3, and 5 and day 7 serum albumin levels showed a decline in non survivors which correlated with mortality later. Decline of day 3 serum albumin was proved to be a good prognostic marker with a very good predictive value of mortality, slightly better than day 5 serum albumin levels. Also, in this study it was found that day 3 serum albumin level is a better prognostic marker than APACHE II score. Gross decline of serum albumin level to the extent of <3g /dl On day 3 implied universal mortality in this study. Monitoring of serum albumin levels in critically ill patients is simple, cost effective and has a good prognostic value and should be encouraged. Critical illnesses have high mortality rates. There are numerous prediction parameters and complex scoring methods for prognostication. Early recognition of probable outcome can prompt more vigorous treatment and for risk stratification. Recognition of an age accredited, simple, cost effective parameter is of paramount importance in prognosticating critically ill patients. Serum albumin on day 3 & 5 has promisingly excellent predictive values & should be routinely utilized in resource poor settings.

Keywords: *Serum Albumin, Human Plasma, Mortality*

INTRODUCTION
Human serum albumin is the most abundant protein in human plasma. It is produced in the liver. Albumin constitutes about half of the serum protein. It is soluble & monomeric. The reference range for albumin concentrations in blood is 4-5 g/dl. It has a serum half life of approximately 20 days. It has a molecular mass of 67kDa.

In critically ill patient, nutritional status as estimated by serum albumin levels tends to deteriorate during the hospital stay. In comparison to serum albumin levels at presentation, those done later are better predictors of mortality (Amit and Khilnani, 2007).

This underscores the importance of measurements of serial albumin levels. The function of circulating albumin in critical illness is not fully understood. It may differ significantly from that in healthy subjects. A low serum albumin concentration in critical illness is associated with a poor outcome (Gosling, 1995; Nicholson, 2000).

Serum albumin (SA) is a useful marker of nutritional status (Amit and Khilnani, 2007). Apart from being a negative acute phase protein and the main determinant of osmotic pressure; albumin also mirrors the nutritional status of a person. Thus, estimation of serial albumin levels will logically show the direction in which physiology is being successful in combating pathology.

MATERIALS AND METHODS

Method of Collection

(a) *Study design:* cross sectional with short term prospective
(b) *Study period:* From November 2011 to May 2013
(c) *Sample size:* 50
(d) *Inclusion criteria:*
(i) Critically ill patients suffering from medical illness requiring admissions to Intensive Care Units or Emergency Wards in Victoria Hospital and Bowring and Lady Curzon Hospital.
(ii) Patients who have given written informed amount.
(e) *Exclusion criteria:*
(i) Chronic liver disease
(ii) Acute and chronic kidney disease with proteinuria
(iii) Malnutrition
(iv) Protein losing enteropathy
(v) Patients who have not given written informed consent

Statistical Analysis: Statistical methods: Descriptive and inferential statistical analysis has been carried out. Results on continuous measurements are presented on Mean $\pm$ SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5% level of significance. The following assumptions on data are made,

Assumptions

(1) Dependent variables should be normally distributed,
(2) Samples drawn from the population should be random,
(3) Cases of the samples should be independent

Analysis of variance (ANOVA) has been used to find the significance of study parameters between three or more groups of patients; student t test has been used to find the significance of study parameters on continuous scale between two groups on metric parameters and to find the significance of study parameters on continuous scale with each group. Chi-square/ Fisher exact test has been used to find the significance of study parameters on categorical scale between two or more groups Logistic Regression analysis has been used to predict the mortality based on fall in albumin levels at day 3 and at day 5.

Significant Figure

- Suggestive significations (P value: $0.05<P<0.10$)
- Moderately significant (P value: $0.01<P\leq0.05$)
- Strongly significant (P value: $P\leq0.01$)

Methodology

Serum albumin levels in critically ill patients were estimated on days 1,3,5,7 and 10 and correlated with prognosis of the condition.

RESULTS AND DISCUSSION

Results

Table 1: Etiological diagnosis or systems involved

Etiological diagnosis	No. of Patients	%
1.*Cardiovascular*	6	12.0
2.*Endocrine*	4	8.0
3.*Gastrointenstinal*	2	4.0
4.*Metabolic*	6	12.0
5.*Miscellaneous*	2	4.0
6.*Neurological*	18	36.0
7.*Respiratory*	12	24.0
Total	**50**	**100.0**

Mean age of patients in this observational study was 50.52 ± 17.05 years. Majority of patients were in the age group of 50 to 60 years. 30 patients (60%) were males and 20 patients (40%) were females. Majority of the patients had neurological diagnosis-18 patients (36%). They included neuroinfections, seizure disorders, status epilepticus and cerebrovascular accidents. The next important group of diagnosis was of respiratory system-12 patients (24%) and the diagnosis included various types of pneumonia and acute exacerbations of chronic obstructive pulmonary disease.
Most of the patients-24 patients (48%) in our study had an APACHE II score between 11 and 15. Only 13 patients (25%) had the score of more than 15. Thus inferring that all the patients included in the study were critically ill as per the APACHE II Score (Dan *et al.*,).

Table 2: APACHE II score in patients studied

APACHE II	No. of Patients	%
1-5	2	4.0
6-10	11	22.0
11-15	24	48.0
>15	13	26.0
Total	**50**	**100.0**

Mean serum albumin showed a falls on day 3 followed by a constant raise irrespective of the outcome.

Table 3: Evaluation based on serial serum albumin

Serum Albumin	Min-max	Mean+- SD	difference	t value	p value
Day 1	2.90-4.30	3.45±0.28	-	-	-
Day 3	1.80-4.20	3.21±0.49	0.242	3.592	0.001**
Day 5	2.70-4.10	3.27±0.28	0.188	3.816	<0.001**
Day 7	1.80-4.30	3.33±0.49	0.194	1.961	0.067+
Day 10	3.20-3.70	3.46±0.18	-0.020	-0.272	0.799

The average length of stay was 6.42 ± 2.11 days. The maximum length of the stay was 12 days and the minimum was 3 days. Majority of the patients in the study were treated in emergency wards (72%) followed by intensive care units (28%). 30 patients (60%) recovered and 20 patients (40%) died.
In another study by Namendys *et al.*, (2011) the crude mortality rate was 22.5%. Majority of the survivors were in the age group of 50-60 years. But, there was no specific age group where the number of deaths was high. Age was not statistically associated with outcome with P=0.880. 43.3% males and 35% of females died; but gender was not statistically associated with P=0.556. Mean length of stay was higher among survivor group-7.47 day and it was 4.85 days among non survivors. With p value being <0.001, it is significantly different between two groups; the difference probably can be attributed to deaths during the study.

Table 4: Length of stay in days and its relation to outcome

	Outcome Recover(n=30)	Death(n=20)	p value
Length of stay in days	7.47+1.96	4.85+1.14	<0.001**

Among both survivors and non survivors, majority of patients had neurological illnesses.
There was a small difference in serum albumin levels with non survivors having higher day 1 mean serum albumin, but the difference was statistically insignificant with the P value being 0.840.
Mean serum albumin on day 3 in non survivor group was much lesser than that in survivor group and the difference was significant.

Mean serum albumin on day 5 in non survivor group showed a paradoxical rise when compared to day 3 mean serum albumin level, but it was less than mean serum albumin in the same group on day 1 and also than that in the survivor group of the same day i.e. day 5. Difference of serum albumin on day 5 was statistically significant but less significant than the difference on the day 3 albumin levels. Similar significance was noted in day 7 mean serum albumin level. Sample size was insufficient for calculation of significance of day 10 mean serum albumin level.

Table 5: Serum albumin levels and its relation to outcome

Serum Albumin levels	Outcome Recovery (n=30)	Death (n=20)	p value
Day 1	3.44 ± 0.30	3.46 ± 0.25	0.840
Day 3	3.46 ± 0.29	2.83 ± 0.51	0.001**
Day 5	3.35 ± 0.26	3.07 ± 0.22	<0.003**
Day 7	3.46 ±0.29	2.35 ±0.78	0.001**
Day 10	3.46 ±0.18	-	-

Among the 20 patients who died on our study, only one did not have fall in serum albumin level an day 3, whereas 19 patients had. Among the 30 patients who recovered in our study, only 5 patients had a fall of serum albumin, whereas the rest of 25 patients had no fall.

Maximum fall in serum albumin on day 3 was observed in the set of patients with endocrine and metabolic disorders. Maximum fall in serum albumin on day 5 was observed in the set of patients with metabolic disorders.

Fall in albumin on day 3 predicts mortality better than fall on day 5 with the odds ratio being 95 for day 3 albumin decline.

Till an APACHE II score of 15, the score associated well with mortality and is comparable with fall in day 3 albumin levels. But in patients with scores of more than 15, it shows paradoxical results of lesser mortality with higher scores. This is probably because of lesser number of patients in that range (>15) of score. Overall, APACHE score did not associate statistically with mortality with P value being 0.882.

100% if patient who had serum albumin of less than 3g/dl on day 3 succumbed to death. Thereby a quantitative correlation between the level of fall of serum albumin and mortality risk was established.

Table 6: Risk assessment of mortality according to serum albumin levels on day 3 and day 5

Serum albumin levels	Day 3 risk assessment		Day 5 risk assessment	
	No of cases	**Mortality risk**	**No of cases**	**Mortality risk**
2.2 – 2.6	5	5 (100%)	-	-
2.6-3.0	7	7 (100%)	7	4 (57.1%)
3.0-3.4	22	7 (31.8%)	26	8 (30.8%)
3.4-3.8	13	1 (7.7%)	8	0
3.8-4.2	3	0	1	0

Discussion

Critically ill patients are those who by dysfunction or failure of one or more organs/system depend on survival from advanced instruments of monitoring & therapy (Waydhays, 1999). Critically ill patients after have reduced albumin levels due to malnutrition or the metabolic stress or both (Irwin and Rippe, 2008). serum albumin appears to be a reliable prognostic indicator in various contexts. A recent review suggests that serum albumin could be an independent predictor of mortality in a wide range of clinical & research settings (Goldwasser and Feldman, 1997). Large community bared studies have shown a link between low serum albumin and an increase in morbidity and mortality (Klonoff *et al.*, 1992l; Phillips and Shaper, 1982). The prognostic value of serum albumin extends to critically ill patients (Aplegren and

Rombeau, 1982; Ching *et al.,* 1980; Golub *et al.,* 1994). A low serum albumin concentration correlates with increased length of stay in the intensive care unit and with complication rates, such as ventilator depending and the development of new infection (Murray *et al.,* 1988). The daily trend of serum albumin can be a useful tool and predicting the capability of patients needing mechanical ventilation (Sapijaszko *et al.,* 1996).

In our study, mean serum albumin on day 1 was 3.45 ± 0.28 g/dl (range: 2.90-4.30); on day 3, 3.21± 0.49 g/dl (range; 1.80-4.20); on day 5, 3.27± 0.28 g/dl (range: 2.70-4.10); on day 7, 3.33 ±0.49 g/dl (range: 1.80-4.30); on day 10,3.46± 0.18g/dl(range 3.20-3.70). There is a fall of mean serum albumin on day 3 followed by consistent small rises on subsequent days.

Further, the difference of 0.242 mg/dl between mean serum albumin of days 1 & 3 was statistically significant with the P value being <0.01, the difference of 0.188 mg /dl between mean serum albumins of day 1&5 was also statistically significant with P value being <0.194 and was just suggestive of significance. Mean serum albumin of day 10 was higher than day 1 albumin in our study.

Mean serum albumin levels showed consistent fall during hospital stay (mean serum albumin on day 1, 3, 5, 10&15 were 3.2± 0.7 gm%, 2.9± 0.6gms%, 2.9±0.6gm%, 2.8±0.6gm%, 2.7±0.65gm% respectively) in the study by Amit Bange (Amit and Khilnani, 2007).

In our study, mean serum albumin on day 1 of survivors was 3.44 ± 0.30 g/dl and of non survivors was 3.46±0.25 g/dl. There was a marginal difference with non survivors having higher day 1 mean serum albumin, but the difference was statistically insignificant with P value being 0.840.

In the study by (Amit and Khilnani, 2007) there was no statistically significant difference between day 1 mean serum albumin levels for survivors and non-survivors.

Study by Yap *et al.,* (2002) showed that serum albumin at admission was lower in non-survivors than in survivors, but albumin concentrations poorly differentiated the two groups. Similar results were found in another study by Mccluskey *et al.,* (1996). It is very minor and also not statistically significant to be implicated to the outcome of the illnesses.

In our study, mean serum albumin on day 3 in survivor group was 3.46±0.29 g/dl, whereas in non survivor group it was 2.83±0.51 g/dl. The difference was large and the p value was <0.001, which suggests that fall in serum albumin on day 3 was strongly associated with mortality among patients with critical illness over and above that could be attributed to chance factor.

In our study, mean serum albumin on day 5 in survivor group was 3.35±0.26g/dl, whereas in non survivor group it was 3.07±0.22 g/dl. With the p value being 0.003, fall of day 5 albumin also showed statistically significant correlation with bad prognosis that is death. The statistical correlation though significant is slightly lesser when compared with that of day 3 albumin.

In our study, mean serum albumin on day 7 in survivor group was 3.46±0.29 g/dl, whereas in non survivor group it was 2.35±0.78 g/dl. Even this showed a very significant correlation to outcome, comparable to that of day 3 albumin, though sample size was lesser than that for day 3 albumin due to deaths in between days 3 and 7.

Significance of day 10 serum albumin could not be calculated because of insufficient sample size due to deaths and recovery.

In a study by (Amit and Khilnani, 2007) mean serum albumin levels showed consistent fall during hospital stay (mean serum albumin on day 1,3,5,10 & 15 were 3.2±0.7 gm%, 2.9±0.6 gm%, 2.9±0.6 gm%, 2.8±0.6 gm%, 2.7±0.65 gm% respectively). The difference between the groups became statistically significant on day 3 onwards and remained so subsequently.

In another study by McCluskey (1996), the admission serum albumin concentration was found to be an insensitive prognostic indicator. However, serum albumin measured after 24 h was as accurate as the admission APACHE II score in correctly classifying patients according to outcome. There was a good correlation between the admission APACHE II score and serum albumin measured after 24 hr.

Decline of Serum Albumin Levels at Day 3 and Day 5 and its Relation to Outcome

Among the 20 patients who died in our study, only one did not have a fall in serum albumin level on day 3, whereas 19 patients had. Among the 30 patients who recovered in our study, only 5 patients had a fall

of serum albumin, whereas the rest of 25 patients had no fall. This is statistically significant with the p value being <0.001.

Similarly, day 5 serum albumin of 11 of 20 patients who died showed a fall, whereas it fell in 15 of 30 patients who survived. This is also statistically significant with the p value being <0.001.

Thus inferring from this, is that any falling of serum albumin on days 3 and 5 of admission correlates with poor prognosis.

This result is similar to the results produced in the aforementioned studies.

Serum Albumiin Levels on Day 1 and Day 3 and their Difference / Comparison of Apache Ii Score in Patients in Relation to Outcome

In our study, mortality increased with increase of APACHE II score. In the scores ranging from 15 to 19, mortality was somehow underestimated and survival also in addition showed a consistent rise with increase in APACHE II scores. Thus, probably with the p value being 0.882, the increased occurrence of deaths with increased APACHE II scores may not be statistically significant. This is unlike the results obtained in the study by McCluskey, where APACHE II score showed comparability with serum albumin done after 24 hours at all APACHE II scores. In our study, APACHE II scores at admission in the range of 5 to 14 are comparable with day 3 and 5 serum albumin levels.

Overall, serum albumin levels on day 3 and 5 were proved to be better predictors of outcome than APACHE II score.

Risk Assessment of Mortality According to Quantitative Serum Albumin Levels on Day 3 and Day 5

In our study, 100% of patients who had serum albumin of less than 3 g/dl on day 3 succumbed to death and 31.8% of patients who had serum albumin between 3 and 3.4g/dl on day 3 had the outcome as death. Thus our study inferred a mortality risk of 100% for a day 3 serum albumin of less than 3 g/dl.

Patients who had a day 5 serum albumin of less than 5 g/dl had a mortality risk of 57.1% and a serum albumin between 3 and 3.4 g/dl had a mortality risk of 31.8%.

In a study by Atousa Tabrizian, the mortality rate for albumin>3g/dl vs<3g/dl was 10.3% vs 29.1% respectively, similar to the results obtained in our study.

Results of Logistic Regression Analysis and Odds Ratio in Prediction of Mortality

In our study, it was found that fall in serum albumin on day 3 can predict mortality around 95 times better than no fall in albumin with odds ratio being 95.08 and fall in serum albumin on day 5 can predict mortality around 11 times better than no fall in serum albumin.

Conclusion

Critical illnesses have high mortality rates. There are numerous prediction parameters and complex scoring methods to prognosticate patients. Early recognition of probable outcome can prompt more vigorous treatment and risk stratifies patients. Recognition of an age accredited, simple, cost effective parameter is of paramount importance in prognosticating critically ill patients.

Serum albumin assessment serially is a cheap and effective method of prognosticating patients. Serum albumin on day 3 and 5 have promisingly excellent predictive values and should be routinely utilized in resource poor settings as it is not a compromise with accuracy of prediction of outcome.

REFERENCES

Amit Banga FCCP and Khilnani GC (2007). Serial estimations of serum albumin levels in critically ill patients. *Chest* **132**(4) 551.

Aplegren KN and Rombeau JL (1982). Comparision of nutritional indices and outcomes in critically ill patients. *Critical Care Medicine* **10** 305-7.

Ching N, Grossei CE and Angers J *et al.*, (1980). The outcome of surgical treatment as related to the response of the serum albumin level to nutritional support. *Surgery, gynecology & Obstetrics* **151** 199-202.

Dan L Longo *et al.*, (No Date). Harrisons Principles of Internal Medicine, 18th edition.

Goldwasser P and Feldman J (1997). Association of serum albumin and mortatity risk. *Journal of Clinical Epidemiology* **50** 693-703.

Golub R, Sorrento JJ and Cantu RJ (1994). Efficacy of albumin supplementation in the surgical intensive care unit; a prospective, randomized study. *Critical Care Medicine* **22** 613-9.
Gosling P (1995). Albumin and critically ill. *Critical Care* **III**(11) 57-61.
Irwin and Rippe (2008). *Intensive Care Medicine,* 6th edition 982, 1283.
Klonoff Cohen H, Barrett Connor EL and Edelstein SL (1992). Albumin levels as a predictor of mortality in the elderly. *Journal of Clinical Epidemiology* **45** 207-12.
McCluskeyA, Thomas AN, Bowles BJM and Kishen R (1996). The prognostic value of serial measurements of serum albumin in patients admitted to an intensive care unit. *Anaesthesia* **51** 724-7.
Murray MJ, Marsh HM and Wochos DN *et al.*, (1988). Nutritional assessment of intensive care unit patients. *Mayo Clinic Proceedings* **63** 1106-15.
Namendys-Silva SA, Gonzalez-Herrera MO, Texocano-Becerra J and Herrera-Gomez A (2011). Hypoalbuminemia in critically ill patients with cancer: incidence and mortality. *American Journal of Hospice & Palliative Care* **28**(4) 253.
Nicholson JP (2000). The role of albumin in critical illness, *British Journal of Anaesthesia* **85**(4) 599-610.
Phillips A and Shaper AG (1982). Association between serum albumin and mortality from cardiovascular disease, cancer, and other causes. *Lancet* **2** 1434-6.
Sapijaszko MJA, Brant R and Sandham D (1996). Non respiratory predictor of mechanical ventilation dependency in intensive care unit patients. *Critical Care Medicine* **24** 601-7.
Waydhays C (1999). Equipment review: Intrahospital transport of critically ill patients. *Critical Care Medicine* **5** 83-9.
Yap FH, Joynt GM, Buckley TA and Wong EL (2002). Association of serum albumin concentration and mortality risk in critically ill patients. *Anaesth Intensive Care* **30** 202-205.