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Evaluation of serum albumin as a prognostic marker in traumatic brain injury

Sivaa Rajendran[1,*], Thiagarajan Govindan[2], Meenakshi Vedavyasan[3], Kalaiselvi Selvaraj[4]

[1,3]Assistant Professor, Dept. of Biochemistry, [2]Professor & HOD, Dept. of Neurosurgery, [4]Assistant Professor, Dept. of Community Medicine, Pondicherry Institute of Medical Sciences, Puducherry

***Corresponding Author:**
Email: drsivaar@gmail.com

Abstract

Introduction: Traumatic Brain Injury (TBI) due to road traffic accidents is one of the leading causes of mortality and morbidity in India. Since albumin is associated with the patho-physiological events following TBI, we aimed to estimate the same in these patients and to find whether it can be used as biomarker.

Materials and Method: Fifty four consecutive patients admitted to our emergency intensive care with varying degrees of head injuries, were grouped into 3 categories based on the admission time Glasgow Coma Scale (GCS) as mild (13 to 15), moderate (9-12), and severe brain injury(8 or less) and their serum albumin were estimated.

Results: Out of 54 patients, 15 had hypoalbuminemia (albumin <3.5g/dL), while for the rest the levels were normal. In the normal albumin group 87% patients showed good outcome and only 13% showed poor outcome. With Kaplan-Meier survival curves, patients with normal albumin levels showed a significantly higher chance to survive than patients with hypoalbuminemia. Further stratification of our cohort into groups according to the interquartile range of serum albumin and comparing it with their clinical outcome by Cox regression indicated that the probability of mortality increased with the decrease in serum albumin (hazard ratio[HR] = 0.15; 95% CI = 0.03- 0.6) with a significant p value of <0.05.

Conclusion: Serum albumin can be used as a prognostic markers in predicting the adverse outcome in TBI patients.

Keywords: Albumin, Traumatic Brain Injury (TBI).

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Introduction

Traumatic brain injury (TBI) is fast emerging as one of the major causes of death globally. In Asian countries the rapid urbanization has increased the risk of TBI.(1) India remains in the leading position in the world in fatalities due to road accidents.(2) Even if people survive, the concomitant physical disabilities, long-term cognitive and psychological damage pose a major threat. With the subsequent secondary damage setting insidiously, the pathological sequelae warrants a multidisciplinary approach for management and longer period of stay in the ICU setting. It takes a heavy toll on both financial status of the patients and the hospital's available resources. In order to mitigate the misery of the patients and to judiciously allocate the hospital resources, it becomes mandate to predict the favourable outcome earlier in order to take decision whether to continue aggressive therapeutic measures or not.(3) This will guide the clinicians immensely in deciding the mode of patient management. But predicting the prognosis of TBI remains a challenge for clinicians. Early intensive rehabilitation increases the survival rate and helps in restoration of functional capacity of the patients.

There are different systems available to evaluate the extent of brain injury. Neuro- psychological examination like Glasgow Coma Scale (GCS) and pupil response are widely used for the assessment of the severity of brain injury.(4) The neuroimaging techniques, such as computed tomographic scanning (CT scan) and magnetic resonance imaging (MRI) have emerged as the choice of investigation. But all these have limitations such as poor sensitivity and failure to detect secondary pathological events.(5) Hence exhaustive research has been carried out for identifying better prognostic marker, preferably a serum bio marker. These efforts to identify an ideal biomarker which could reflect the pathology of TBI and secondary injury have yielded meagre success. This is evident from the finding that the markers released from the brain cells are also elevated in non- brain pathological conditions and are non-specific.(6)

Acute Inflammation following the primary injury remains central to the pathogenesis of secondary injury that influences the outcome of the patients.(5) A repertoire of inflammatory molecules are pressed into service, the key player being cytokines as part of local and systemic acute phase response. Few studies explored the utility of using the circulating inflammatory mediators as the predictors of outcome in injury.(7) The acute inflammatory response, designed to be protective mechanisms, can override at times, leading to unfavourable outcome. Considerable attention has been directed towards the utility of acute phase reactants as prognostic marker for predicting outcome. Among the acute phase reactants albumin is ideally a candidate for research as the measurement is easily available and routinely done.

Albumin (69Kda) is the major protein of the human plasma accounting to about 60% of the total plasma protein.(4) Albumin is produced by the liver at a rate of 9 to 12 g/day. Its hepatic synthesis is primarily affected by

osmotic colloid pressure and inflammatory states, but also, and to a lesser degree, by nutritional status and hormones. It is one of the negative acute phase reactants and its level tend to fall in the plasma as a result of injury or infection independent of the nutritional status.[8] Many studies had highlighted the role of albumin as a prognostic marker in life threatening illnesses, various types of cancer such as colorectal, lung and breast cancer.[9-13] It has also been studied to determine the clinical outcome following cardiac surgery.[14] Du Chen, Long Ba, et al, have studied the use of serum albumin along with pre-albumin to predict the poor outcome in TBI and observed serum albumin serve as a better marker.[15] Most of the studies are retrospective in nature. Hence we have taken up a prospective study to establish the prognostic value of serum albumin in TBI.

Materials and Method

This study was conducted in a Tertiary care hospital and was approved by the Institutional Ethical Committee. We have included 54 consecutive patients admitted to our emergency intensive care department between 2011- 2012 with varying degrees of head injuries. Standard medical treatment and care was administered to all patients and consent was obtained from each of the patient's attender. The inclusion criteria was TBI patients admitted within 24 hours with Glasgow Coma Scale (GCS) score from 3 to 14. Exclusion criteria were Patients below 18 years of age and pregnant women.

The patients were grouped into 3 categories based on the GCS score at the time of admission. GCS score of 13 to 15 were considered as mild injury, 9 to 12 were considered as moderate injury, and of 8 or less as severe traumatic brain injury.

Serum albumin was measured within 24 hours of admission and on the day of discharge. Serum albumin was measured by BCG (Bromocresol Green) method using Roche Integra 400 auto-analyser. Hypo-albuminemia is defined as a serum albumin value less than 3.5 g/dL. The within run and in-between run precision, expressed as CV were 1.5% and 2.8% respectively. Clinical follow up of the patients were made till discharge or death. An improvement in the discharge day GCS score when compared to the admission day score is considered as good outcome. While a death or fall in the GCS score during follow up of the patients is considered as a bad outcome.

Continuous data were presented as median value with corresponding IQR or mean with corresponding SD. Further, patients were stratified as per their admission day GCS score and serum albumin, expressed as quartiles. Clinical outcome between groups were compared using Chi-square test. Multivariate analysis was performed by Cox regression analysis to identify the independent prognostic factors, using the SPSS software version 17.0 after adjusting for age and sex. A p-value of less than 0.05 is considered as statistically significant. Confident intervals (CIs) were calculated at 95% level.

Results

The demographic and clinical characteristics of the patients included in the study were described (Table 1). A total of 54 patients with severe traumatic brain injury (49 males and 5 females) were included in the study. The mean age of the patients was 40.6 ± 11 years. The mean duration of the hospital stay was 8.0 ± 4.6 days. The mean albumin was observed to be 3.8 ± 0.5 g/dL at the time of admission. We have initially divided the patients into 2 groups according to serum albumin levels as normal albumin group and hypoalbuminemia group. A total of 39 patients (72%) had normal serum albumin level ≥ 3.5 g/dL and 15 patients had hypoalbuminemia with albumin less than <3.5g/dL. The overall mortality was 27.7% (15 out of 54). (Table 1)

In the normal albumin group 87% patients showed good outcome(34 out of 39) and only 13% (5 out of 39) showed poor outcome (Fig. 1).

Increase in the levels of the admission day albumin significantly improved the clinical outcome of the patients (Table 2). In the Univariate analysis, the GCS scores ($p<0.001$) and the admission day serum albumin levels ($p<0.001$) emerged as significant predictors of overall mortality (Table 3).

Kaplan-Meier survival curves comparing the percentages of patients who survived according to their serum albumin levels measured at the time of admission is shown (Fig. 2). Patients with serum albumin ≥ 3.5 g/dL showed a significantly higher chance to survive than patients with hypoalbuminemia. The progression – free survival rate was significantly worse in the hypoalbuminemia group (log-rank test, $p < 0.001$). (Fig. 2)

Then Multivariate Cox regression analysis was performed using the variables identified as prognostic factors for overall survival in the Univariate analysis. The Multivariate analysis showed admission day serum albumin as an independent predictor of survival with an adjusted hazard ratio(HR) of 0.15 with a 95% CI of 0.03 – 0.6 for survival. This indicates that an increment of 0.15 g/dL in albumin increased the survival of the patient (Table 4).

Table 1: General characteristics of the subjects

Characteristics	
Age (years)	40.6 ± 11.0
Gender Male Female	 49 (90.7%) 5 (9.3%)
Mean duration of hospital stay (days)	8.0 ± 4.6
Serum albumin at the time of admission (g/dL) Proportion of hypoalbuminemia Proportion of normal albuminemia	3.8 ± 0.5 27.8%(15) 72.2% (39)
Total no of cases with unfavourable outcome	27.7%

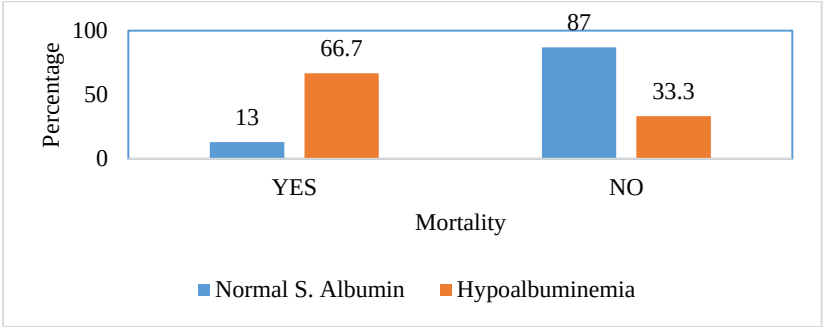

Fig. 1: Admission day serum albumin levels and clinical outcome

Table 2: Comparison of outcome with Interquartile ranges of serum albumin at the time of admission

Quartile	S. albumin(g/dL)	Good prognosis	Poor prognosis	Total
I	≤ 3.4	5(33.3%)	10(66.7%)	15
II	3.41-3.95	9(75%)	3(25%)	12
III	3.96-4.2	17(94.4%)	1(5.6%)	18
IV	>4.2	8(88.9%)	1(11.1%)	9

Table 3: Univariate analysis of prognostic factors for mortality

Variable	Unfavourable Outcome	Favourable Outcome	P Value
Age (year)	42.9 ±12.9	39.7±10.3	0.2
GCS	Min 3 max 13	Min 7 Max 13	<0.001*
Days in hospital (median, IQR)	4 (2, 8)	8 (5, 11)	0.1
Albumin mean ±SD (g/dL)	3.38±0.5	4.0±0.5	<0.001*

*p-value < 0.05 statistically significant

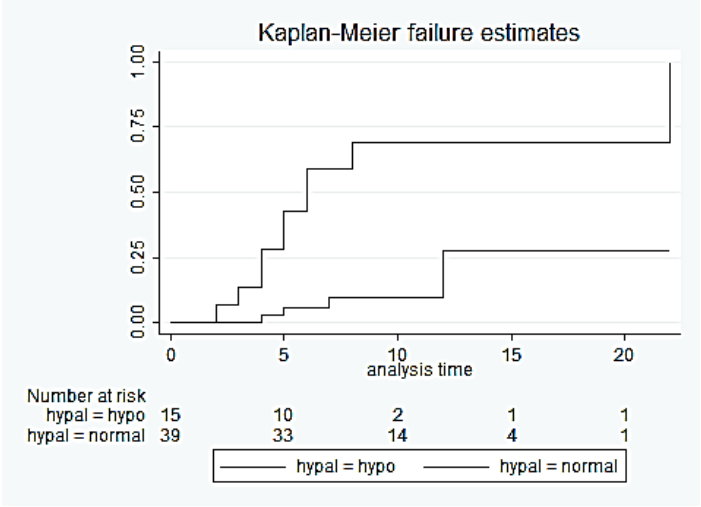

Fig. 2: Survival analysis of TBI patients

Table 4: Multivariate Cox regression analysis of prognostic factors for overall survival

Variable	Hazard Ratio (HR)	95% confidence interval	p value
sex	3.0	0.5 – 17	0.2
Albumin	0.15	0.03 -0.6	<0.01*
Age			
18- 35 yrs	4.5	0.3 – 6.4	0.26
35 – 43 yrs	3.1	0.3 – 3.8	0.38
Above 43 yrs	6.9	0.5 – 9.1	0.14

*p-value < 0.05 statistically significant.

Discussion

In our prospective cohort study of TBI patients admitted in the ICU care, the Univariate analysis indicated the patients with low GCS score had low albumin levels and the mortality was higher. Hypoalbuminemia was associated with unfavourable outcome. By hazard ratio(HR), we have demonstrated that serum albumin levels on admission day can be used as an independent marker for predicting the clinical outcome in TBI. Out findings agrees well with previous retrospective studies.

The injury resulting in trauma to brain has two components namely primary and secondary. The primary injury is caused by mechanical forces generated by direct physical assault. These forces being disruptive, damage blood vessels, axons or entire nerve cells and glia at a multiple foci or covering a large area. But the secondary injury has an insidious onset occurring over a time span of minutes to days. They bring about the cellular, neurochemical and metabolic changes.[16-17] Inflammation plays a major role in mediating secondary injury, as it directly damages the cells and unleash the other injury factors such as oxidative stress and edema formation.[18-21] The mainstay of management in TBI is targeted at prevention of secondary insults to the brain, following the initial brain injury. The secondary injury results largely from the neuro-inflammation. Huge repertoire of pro-inflammatory molecules such as cytokines, chemokines, interleukines, tumor necrosis factor (TNF) and immune cells are cells are enlisted to promote this process.[22-24] Serum albumin is a negative acute phase protein whose level decreases in response to any acute inflammation. In critically ill patients, hypoalbuminemia is commonly observed and it reflects the extent of inflammatory response to the insult.[25-27]

Serum albumin plays a wide variety of roles. It is the chief determinant of plasma oncotic pressure. It has antioxidant property. A substantial number of studies have been carried out to evaluate the prognostic significance of serum albumin in diseases which has inflammation as an integral component of pathology. The conditions include non-cardiac surgery, various types of cancers, acute trauma where the admission day serum albumin were measured.[28-32] All these studies documented association between serum albumin and increased risk of adverse outcome such as mortality.

The prognostic significance of serum albumin stems from its merit of being a marker of nutritional status too besides its immune modulatory properties. Thus systemic inflammatory response and nutritional status play key roles in chronic debilitating conditions and critically ill patients.[33-37] In acutely ill patients hypoalbuminemia has been associated with increased risk of infectious complications, prolonged hospital stay and mortality.[38] Few mathematical scores are designed including albumin as one of the component in assessing the outcome in diseases involving inflammation.[39,40]

Traumatic brain injury is also an acute condition, where outcome prediction is impeded by a reliable marker. Hence we explored the possibility of using serum albumin to predict the poor outcome in TBI which is a stressful condition. The Chi-square test revealed that low albumin is associated with unfavourable outcome. Our earlier study reported increased serum cortisol, as an indicator of stress.

From the Cox regression analysis, the serum albumin on admission is statistically significant with the hazard ratio of 0.15, 95% CI (0.03-0.6) after adjusting for the variables such as age and sex. Exhaustion of serum albumin during stress conditions, loss of albumin in case of massive haemorrhage, less intake or suppression of synthesis of albumin by liver and being an effective antioxidant, used up while clearing the reactive oxygen species are the possible mechanisms explaining hypoalbuminemia in TBI.[15]

As serum albumin levels more than 3.4 g/dL predicts good favourable prognosis, maintaining serum albumin levels above 3.5g/dL is a pathway for speedy recovery. Maintaining a good nutritional support and preventing calorific deficit can definitely can accelerate good outcome. Hence in this study we tried to confirm the predictive role of serum albumin as hypoalbuminemia in TBI results in poor prognosis. The measurement of serum albumin is very simple, cost effective and it is always requested as a part of liver function tests routinely. Serial evaluations can be done rapidly. This feature confers additional advantage in support of use of serum albumin as a prognostic marker.

The strength of our study is, it is a prospective study whereas many of the previous studies are findings from retrospective studies. Sample size, absence of other markers of TBI and failed to make out long term follow up of discharged patients for any possible complications are the limitations of our study.

Conclusion

Serum albumin can be used as a prognostic marker in predicting the adverse outcome in patients with TBI.

References

1. Shekhar C, Gupta LN, Premsagar IC, Sinha M, Kishore J. An epidemiological study of traumatic brain injury cases in a trauma centre of New Delhi (India). J Emerg Trauma Shock. 2015 Jul-Sep;8(3):131–139.
2. Puvanachandra P, Hyder AA. The burden of traumatic brain injury in Asia: A call for Research. Pak J Neurol Sci. 2009;4:27–32.
3. Finfer SR, Cohen J. Severe traumatic brain injury. Resuscitation. 2001;48(1):77-90.
4. Turgeon AF, Lauzier F, Zarychanski R, Fergusson DA, Léger C, McIntyre LA, et al. TBI-Prognosis Study Team and the Canadian Critical Care Trials Group. Prognostication in critically ill patients with severe traumatic brain injury: the TBI-Prognosis multicentre feasibility study. BMJ Open. 2017; 7(4):e013779.
5. Papa L, Ramia MM, Edwards D, Johnson BD, Slobounov SM. Systematic review of clinical studies examining biomarkers of brain Injury in athletes after sports-related concussion. Journal of Neurotrauma. 2015;32:661–673.
6. Arsalan S. Haqqani, James S. Hutchison, Roxanne Ward, Danica B. Stanimirovic, For The Canadian Critical Care Translational Biology Group. Protein Biomarkers in Serum of pediatric patients with SevereTraumatic Brain Injury Identified by ICAT–LC-MS/MS. Journal of Neurotrauma. 2007;24(1):54–74.
7. Adrian H, Marten K, Salla N, Lasse V. Biomarkers of Traumatic Brain Injury: Temporal Changes in Body Fluids. eNeuro. 2016 Nov-Dec; 3(6): ENEURO.0294-16.2016.
8. Burtis CA, Ashwood ER, Bruns DE. Teitz text book of clinical chemistry and molecular diagnosis. 4th ed. New Delhi: Elsevier Saunders; p 546.
9. Chen Z, Shao Y, Wang k, Cao W, Xiong Y, Rongzu Wu, Shicheng Luo, et al. Onco Targets and Therapy. 2016;9:6701–6710.
10. Boonpipattanapong T, Chewatanakornkul S. Preoperative carcinoembryonic antigen and albumin in predicting survival in patients with colon and rectal carcinomas. J Clin Gastroenterol. 2006;40:592-595.
11. Cengiz O, Kocer B, Surmeli S, Santicky MJ, Soran A. Are pretreatment serum albumin and cholesterol levels prognostic tools in patients with colorectal carcinoma? Med Sci Monit. 2006;12(6):240-247.
12. Mohri T, Mohri Y, Shigemori T, Takeuchi K, Itoh Y,Kato T. Impact of prognostic nutritional index on long-term outcomes in patients with breast cancer. World J Surg Oncol. 2016;14:170.
13. Tanriverdi O, Avci N, Oktay E, Kalemci S, Pilanci KN, Cokmert S, et al. Pretreatment Serum Albumin Level is anIndependent Prognostic Factor in Patients with Stage IIIB Non-Small Cell Lung Cancer: A Study of the Turkish Descriptive Oncological Researches Group. Asian Pac J Cancer Prev. 2015;16(14):5971-5976.
14. M Koertzen, PP Punjabi, and GG Lockwood. Pre-operative serum albumin concentration as a predictor of mortality and morbidity following cardiac surgery. Perfusion. 2013;28(5):390–394.
15. Chen D, Bao L, Lu SQ, Xu F. Serum albumin and prealbumin predict the poor outcome of traumatic brain injury. PLoS One. 2014 ;9(3):e93167.
16. Hall ED, Gibson TR, Pavel KM. Lack of a gender difference in post-traumatic neurodegeneration in the mouse controlled cortical impact injury model. J Neurotrauma. 2005;22:669–79.
17. Saatman KE, Bozyczko-Coyne D, Marcy V, Siman R, McIntosh TK. Prolonged calpain-mediated spectrin breakdown occurs regionally following experimental brain injury in the rat. J Neuropathol Exp Neurol. 1996;55:850–60.
18. Finnie JW, Blumbergs PC. Traumatic brain injury. Vet Pathol. 2002;39:679–89.
19. Maas AI, Stocchetti N, Bullock R. Moderate and severe traumatic brain injury in adults. Lancet Neurol. 2008;7:728–741.
20. Gaetz M. The neurophysiology of brain injury. Clin Neurophysiol. 2004;115:4–18.
21. Smith DH, Meaney DF, Shull WH. Diffuse axonal injury in head trauma. Head Trauma Rehabil. 2003;18:307–316.
22. Woodcock T, Morganti-Kossmann MC. The role of markers of inflammation in traumatic brain injury. Front Neurol. 2013;4:18.

23. Corps KN, Roth TL, McGavern DB. Inflammation and neuroprotection in traumatic brain injury. JAMA Neurol. 2015;72:355–362.
24. Bergold PJ. Treatment of traumatic brain injury with anti-inflammatory drugs. Exp Neurol. 2016;275:367–80.
25. Al-Subaie N, Reynolds T, Myers A et al: C-reactive protein as a predictor of outcome after discharge from the intensive care: a prospective observational study. Br J Anaesth.2010;105:318–25.
26. Hedlund JU, Ortqvist AB, Kalin ME, Granath F: Factors of importance for the long term prognosis after hospital treated pneumonia. Thorax, 1993;48:785–789.
27. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. N Engl J Med. 1999;340(6):448–454.
28. 8. McMillan DC, Watson WS, O'Gorman P, Preston T, Scott HR, McArdle CS. Albumin concentrations are primarily determined by the body cell mass and the systemic inflammatory response in cancer patients with weight loss. Nutr Cancer. 2001;39(2):210–213.
29. Lai CC, You JF, Yeh CY, et al. Low preoperative serum albumin in colon cancer: a risk factor for poor outcome. Int J Colorectal Dis. 2011;26(4):473–481.
30. Tanriverdi O, Avci N, Oktay E, et al. Pretreatment serum albumin level is an independent prognostic factor in patients with stage IIIB non-small cell lung cancer: a study of the Turkish descriptive oncological researches group. Asian Pac J Cancer Prev. 2015;16(14):5971–5976.
31. Han S, Huang Y, Li Z, Hou H, Wu A. The prognostic role of preoperative serum albumin levels in glioblastoma patients. BMC Cancer. 2015;15:108.
32. Gibbs J, Cull W, Henderson W, et al. Preoperative serum albumin level as a predictor of operative mortality and morbidity: results from the National VA Surgical Risk Study. Arch Surg.1999;134:36–42.
33. Bauer J, Capra S. Comparison of a malnutrition screening tool with subjective global assessment in hospitalised patients with cancer – sensitivity and specificity. Asia Pac J Clin Nutr. 2003;12(3):257–260.
34. Fuhrman MP, Charney P, Mueller CM. Hepatic proteins and nutrition assessment. J Am Diet Assoc. 2004;104(8):1258–1264.
35. McMillan DC. Systemic inflammation, nutritional status and survival in patients with cancer. Curr Opin Clin Nutr Metab Care. 2009;12:223–26.
36. Roxburgh CS, McMillan DC. Role of systemic inflammatory response in predicting survival in patients with primary operable cancer. Future Oncol. 2010;6:149–163.
37. Brookes GB. Nutritional status – a prognostic indicator in head and neck cancer. Otolaryngol Head Neck Surg.1985;93:69–74.
38. JL Vincent, MJ Dubois, RJ Navickis. Hypoalbuminemia in acute illness: Is there a rationale for intervention? A meta-analysis of cohort studies and controlled trials Annals of Surgery.2003 March;237(3).319-334.
39. Pang S, Zhou Z, Yu X, Wei S, Chen Q, Nie S, Liang X, Liu L. The predictive value of integrated inflammation scores in the survival of patients with resected hepatocellular carcinoma: A Retrospective Cohort Study. Int J Surg. 2017;42:170-177.
40. Jiang H, Li AJ, Tang J, Xu D, Chen Y, Zhang Y, et al. Prognostic Value of the Combination of Preoperative Hemoglobin, Lymphocyte, Albumin, and Neutrophil in Patients with Locally Advanced Colorectal Cancer. Med Sci Monit. 2016;22:4986-4991.