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Role of first day levels and subsequent trends of serum proteins in acute burns

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ABSTRACT

Objective: To explore the role of first day levels and subsequent trends of serum proteins as prognostic indicators in acute burns. **Methods:** This prospective observational study was carried on 100 burn patients (18-60 years with 20% to 60% total burned body surface area). Serum albumin, globulin and total protein were estimated on alternate days starting from first day of burn. The first day value and the trend of serial values throughout the clinical course were compared between survivor and non-survivor groups. **Results:** Mean day 1 serum values of albumin, globulin, and total protein were significantly higher in the survivors compared to non-survivors ($P < 0.0001$). Univariate logistic regression showed that increase in day one value of serum albumin, globulin and total protein by 10g /L each, significantly decreased risk of mortality by 99.4%, 98.3% and 96.6%, respectively. The serial serum values of albumin, globulin and total protein showed rising and declining trends in survivors and non-survivor respectively. Based on the ROC curve, the cut off values at any point during the course below which the prognosis was poor were 16.0 g/L, 18.0 g/L and 39.0 g/L for albumin globulin and total protein, respectively. **Conclusions:** The study highlights the prognostic importance of day one value and trend of serum albumin, serum globulin and total protein in acute burns. The trend of serum proteins over the course of burns should be monitored for better patient management.

1. Introduction

Burn injury is a global public health problem. In India over 100 0000 people are moderately or severely burnt every year. According to WHO report of 2014, burn injury accounted for over 300 000 deaths annually. Majority of these occur in low and middle income countries and nearly 50% occur in the South-East Asia

Region[1,2]. Realtime monitoring of mortality risk in burn patients is essential all through the clinical course for selecting and guiding the appropriate management protocol[3,4]. Various mortality scales with varied prognostic factors such as sex, age, total burned body surface area (TBSA), percentage of full-thickness injuries, inhalation injury

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have been proposed[5]. The protein loss through leaking capillaries during acute burn is compounded by subsequent hyper-catabolism and hepatic dysfunction leading to hypo-proteinemia throughout the clinical course[6-8]. Serum albumin as a marker for prognosis has been studied previously but the results are conflicting[9]. The physiological and metabolic derangements in burns are dynamic over the whole clinical course. Since most of the literatures dwell upon first day of burn serum protein values only, the dynamics of trend of serum proteins levels through the clinical course of burns needed evaluation.

2. Material and methods

This prospective observational study was carried out in Department of Burns, Plastic and Maxillofacial Surgery, and Department of Biochemistry from November 2015 to March 2017. A total of 100 patients in the age group of 18-60 years with 20% to 60% TBSA burn injury were included in the study. Relevant approvals had been obtained from the Institutional Review Board and the Ethics Committee [reference number: No.T.P (DM/MCh) (18/2015)/IEC/9633]. Burn admission delayed by more than 24 h, electrical or chemical burn and patients with associated injury were excluded from the study. All patients were treated conservatively with regular dressing till wound healing or delayed skin grafting after eschar separation. The patients were divided into survivors (Group A) and non-survivors (Group B). There were 83 survivors (Group A) who were discharged in stable condition and 17 patients non-survivors (Group B) who expired during the course. Average age of the patients in the survivor group ($n=83$) was 41 years and in non survivor group ($n=17$) it was 49 years. The average hospital stay in the non-survivor group was 21 days whereas it was 13 days in survivor group. Average TBSA of burns in the non-survivor group was $(50.00\pm 5.59)\%$ and in survivor group it was $(34.76\pm 8.76)\%$. Serum albumin, globulin and total protein were estimated on alternate days starting from day one of admission. For this 4-5 mL of whole blood sample was collected from each patient in serum separator gel tubes. Serum was separated by centrifuging at 3500 rpm for 10 min and serum proteins estimation was done on Fully Automated Dry Clinical Chemistry Analyzer, Vitros, 5,1 by Ortho Clinical Diagnostics. A drop of patient sample was deposited on the respective slides for estimation of total protein and albumin. Protein in the sample formed a complex with cupric

ion and the decrease of the copper-azo dye complex, measured by reflectance spectrophotometry was proportional to the concentration of proteins in the sample. Serum albumin levels were measured by the bromocresol green method. The dye binds to albumin from the sample and the colour complex formed was proportional to the concentration of albumin in the sample. Within lab imprecision for total protein was 4.9% and for albumin was 1.7%. The first day value and the trend of serial values of total protein, albumin and globulin throughout the clinical course were compared in the two groups.

The value of each predictor variable in relation to time, in predicting mortality was evaluated by Pearson correlation coefficient for every patient. Trend of variables over time in survivor and non survivor groups was tested by one sample t test of the Pearson correlation with the reference value of zero and difference between survivors and non survivors was tested by Two samples t test. The risk of increasing or decreasing values of variables on survival was assessed with the proportional hazard regression model of Cox. Univariate and Multivariate Logistic regression analysis was used to assess predictability of mortality by different risk factors by considering their day 1 value. Receiver Operating Characteristic Curve was used to find out cut-off point of different risk factors in predicting mortality. The results were considered significant with P value less than 0.05.

3. Results

Mean serum values of albumin, globulin, total protein on first day of burns in survivor group was (24.3 ± 3.4) g/L, (25.3 ± 4.1) g/L, (49.6 ± 6.6) g/L, respectively. In the non-survivor group, the average serum albumin, globulin and total protein were (18.5 ± 3.2) g/L, (19.9 ± 3.2) g/L and (38.4 ± 5.5) g/L, respectively. This difference was statistically significant with lower levels of each parameter in non survivor group.

Receiver Operating Characteristic Curve was used to deduce the cut-off value of day 1 level of serum albumin, globulin and total protein in predicting mortality (Table 1).

Serum albumin levels equal to or less than 21.0 g/L on first day of burns was considered as a poor prognostic factor ($P<0.0001$) with sensitivity of 88.24 and specificity of 78.31, and area under the ROC curve (AUC) of 0.89. Serum globulin levels equal to or less than 22.0 g/L on first day of burns was considered as a poor prognostic factor ($P<0.0001$) with sensitivity of 76.47 and specificity of 77.11

Table 1
ROC curve for initial prognostication on first day of burns.

Serum level at Day 1	AUC	Standard error	95% confidence interval	P value	Cut off value (g/L)	Sensitivity	Specificity
Albumin	0.89	0.0410	0.811877 - 0.943901	<0.0001	21.0	88.24	78.31
Globulin	0.85	0.0482	0.762366 - 0.911967	<0.0001	22.0	76.47	77.11
Total protein	0.91	0.0404	0.832086 - 0.955793	<0.0001	42.0	82.35	86.75

and AUC of 0.85. Serum levels of total protein equal to or less than 42.0 g/L on first day of burns was considered a poor prognostic factor ($P<0.0001$) with sensitivity of 82.35 and specificity of 86.75, and AUC of 0.91.

Univariate logistic regression was used taking mortality as dependent variable for the variables taken on day 1 (Table 2). With the increase in serum levels of albumin, globulin and total protein at first day of burns by 10.0 g/L each, risk of mortality significantly decreased by 99.4%, 98.3% and 96.6%, respectively.

Table 2

Univariate logistic regression for values at first day of burns taking mortality as dependent variable.

Level at 1st day of burns	B	SE	P value	Odds ratio	95% CI for odds ratio	
					Lower	Upper
Albumin	-5.160	1.200	<0.0001	0.006	0.001	0.060
Globulin	-4.073	1.041	0.0001	0.017	0.002	0.131
Total protein	-3.384	0.816	<0.0001	0.034	0.007	0.168

The trend in the serum values of albumin, globulin and total protein in survivor group was significantly positive with Pearson correlation coefficient of +0.64, +0.39 and +0.65 respectively. In the non-survivor group there was significant declining trend in the serum levels with Pearson correlation coefficient of -0.63, -0.57 and -0.80, respectively (Figure 1).

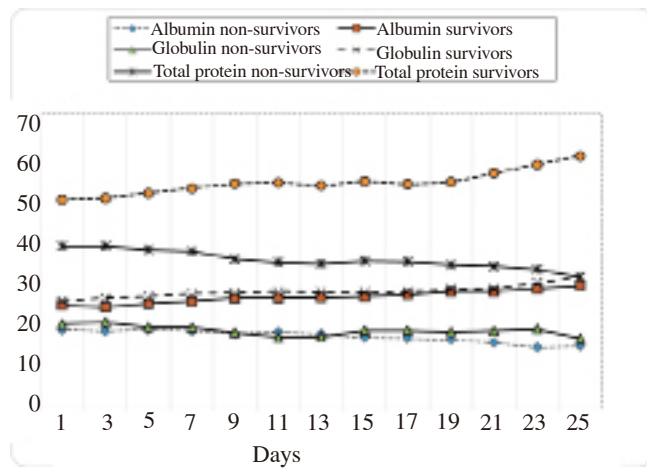


Figure 1. Serum albumin, globulin and total protein trend over time.

The mortality risk of increasing or decreasing values of albumin, globulin and total protein was assessed using the proportional hazard

regression model of Cox. Increase in value of serum albumin with time significantly decreases the risk of mortality by 90.37%. Increase in value of serum globulin with time significantly decreases the risk of mortality by 95.20%. Increase in value of serum total protein with time significantly decreases the risk of mortality by 97.99% (Table 3).

Table 3

Univariate cox regression for assessment of mortality risk of increasing or decreasing values of albumin, globulin and total protein.

Serum level trend	B	SE	P value	Odds ratio	95% CI for odds ratio	
					Lower	Upper
Albumin	-2.340	0.780	0.003	0.096	0.021	0.444
Globulin	-3.037	1.094	0.006	0.048	0.006	0.410
Total protein	-3.909	1.827	0.032	0.020	0.001	0.720

During the clinical course when the cut off value of albumin levels was taken as 16.0 g/L, area under the ROC curve was 1.00, the chances of mortality of the patients having serum albumin value below this at any point of time was proved to be almost certain with 100.00% sensitivity and specificity ($P<0.0001$). When the cut off value of globulin levels during the course was taken as 18.0 g/L, area under the ROC curve was 0.97 and the chances of mortality of the patients having serum globulin value below this at any point of time were very high with 88% sensitivity and 95% specificity with $P<0.0001$. Similarly when the cut off value of total protein levels during the course was taken as 39.0 g/L, area under the ROC curve was 0.96 and the chances of mortality of the patients having serum total protein value below this at any point of time were very high with 100.00% sensitivity and 86.75% specificity with $P<0.0001$ (Table 4).

4. Discussion

Improvement in critical care and wound care has reduced mortality in burns and prolonged its clinical course. Hence it is important to monitor the prognosis of burns throughout the treatment phase. The major factors associated with mortality in burn patients are age and percentage of total body surface area burned[10-14]. The presence of inhalation injury, other associated injuries and comorbidity are also significant contributors in mortality[11-13]. Various clinical scores like Abbreviated Burn Severity Index and Acute Physiology And Chronic

Table 4

Predicting mortality according to lowest values (Cut-off values) of serum albumin, globulin and total protein (g/L) based on ROC Curve.

Minimum level	AUC	Standard error	95% confidence interval	P value	Cut off value (g/L)	Sensitivity	Specificity
Albumin	1.00	0.0000	0.963783 - 1.000000	<0.0001	16.0	100.00	100.00
Globulin	0.97	0.0224	0.914651 - 0.993717	<0.0001	18.0	88.24	95.18
Total protein	0.96	0.0188	0.902154 - 0.989517	<0.0001	39.0	100.00	86.75

Health Evaluation have been introduced which includes variables such as sex, age, percentage of TBSA, full-thickness injuries, and inhalation injury[15]. But in addition to these factors the hyper-catabolism associated with burns also affects the prognosis. The hyper-catabolism is due to combined effect of heat loss, increased adrenergic and adrenocortical activity and increased cellular activity leading to release of paracrine peptides. The hypermetabolic response associated with major burn is accompanied by increased body temperature, oxygen consumption, carbon dioxide production, glycogenolysis, proteolysis and lipolysis[16]. This leads to erosion of lean body mass, muscle weakness, immunodepression and poor wound healing which is unmatched in severity to any other disease or trauma[17]. Studies have also shown that the hepatic hyper-metabolic response in burn patients resulted in increased protein turnover, degradation and negative nitrogen balance[17]. In addition, during the acute phase of burns (>20% of the body surface area) there is major loss of protein rich intravascular fluid to the third space owing to increased vascular permeability. Subsequently throughout the whole clinical course there is loss of plasma proteins from the wound exudations. Therefore hypo-proteinemia in burns is the manifestation of heightened protein loss and hyper-catabolism[18]. With this premise, this study was undertaken with the hypothesis that, the base line protein level recorded at day one of burns and the trend of daily protein values throughout the course of treatment have bearing on prognosis. In our study serum albumin on first day of burn was significantly lower in non survivor group (18.5 vs. 24.3 g/L) with a cut-off value was 21 g/L, below which prognosis was poor. We also found that with an increment of albumin value at first day of burn by 10 g/L reduced mortality by 99.4 %. Hence the baseline serum albumin value recorded at day one of burns, reflecting the nutritional status, has prognostic value. The serum albumin, globulin and total protein as prognostic markers have been evaluated in many previous studies with conflicting results. A similar study reported that serum albumin value of less than 20 g/L at first day of burn had a mortality risk of >80%. Although this study reported 84% sensitivity and 83% specificity compared to our value of 88% sensitivity and 73% specificity[19]. Association of serum albumin and mortality risk in burns and other acute illness is also reported[20,21]. Demling *et al* correlated wound sepsis, delayed wound healing and higher mortality in patients with protein energy malnutrition[22]. Pérez-Guisado *et al* studied the association of serum albumin level with total burn surface area and length of hospital stay but not with burn mortality or morbidity[23]. Similar to albumin levels, globulin level at first day of burn was also lower in non survivor group (1.99 vs. 2.53), and the cut off value was 22 g/L below which prognosis was considered poor but the sensitivity of 76.47% and specificity of 77.11% which was lower than albumin.

The hyper-catabolic state in burns is dynamic, continues through the clinical course of burns and is known to parallel the extent of

burns, sepsis and dietary intake. Hence we envisaged to study the trend of values of serum albumin, globulin and total protein through the treatment course till the final outcome. In our study there was a significant positive trend with gradual increase in serum albumin levels in the patients who survived. On the other hand, in non-survivors, the serum albumin levels showed a consistent decline over the clinical course signifying a negative trend in the patients who expired. Increase in value with time decreases the mortality by 90.37%. We could also deduce that at albumin value of less than 16.0 g/L, the mortality was almost certain with 100.00% sensitivity and specificity. Similar positive trend in survivors and negative trend in non-survivors was also seen in serial globulin and total protein levels. The cut off values below which there was high mortality were 18.0 g/L and 39.0 g/L for globulin and total protein respectively. The sensitivity of total protein cut-off value was as good as serum albumin but specificity of both globulin and total protein cut-off values were lower than albumin. Similarly when albumin and globulin were compared with each other, it was seen that day one value of albumin is a better predictor than globulin but both could be used in prognostication.

In our research it was seen that there is significant reduction in mortality chances with 10 g/L increase in albumin, globulin and total protein level at day one of burns. Similarly in the serial trend, increment in the value of albumin, globulin and total protein at any point of time also reduced the chances of mortality. As a corollary Goldswasser *et al* reported that during the course, there is 24% to 56% increase in mortality chance for each 25 g/L decrement in serum albumin concentration[20]. Ramos *et al* also reported a cut off value of 20 g/L below which mortality chance increased by 33 % [24]. On the other hand Miquet-Romero *et al* didn't find any association of mortality with albumin level, which can be explained due to small sample size of their study[25]. Most of the studies evaluated the day one levels of serum albumin, globulin and proteins as prognostic marker only and the trends of serial values were not studied throughout the course. In our research we found significant difference in trend of serum albumin, globulin and total protein in both the groups. This was in spite of the fact that there was regular par-enteral administration of albumin and plasma as per the standard of care during the treatment course of the patient in both the groups. Since the study points towards the role of proteins as prognostic factor in burns, protein levels can be included in the prognostic scores.

The study underscores the prognostic value of metabolic parameters like serum albumin, serum globulin and total protein. From the results of the study it is quite evident that apart from physical parameters, biochemical parameters also play a pivotal role in prognosticating the patients and merit inclusion in prognostic index scales. It is prudent not to look at only the absolute values of serum proteins levels, but also the trend of serum proteins over the

course of the disease for better patient management. The results pointedly indicate that prompt intervention is warranted when serum albumin level < 16.0 g/L, serum globulin level < 18.0 g/L and serum total protein level < 39.0 g/L to improve the prognosis. The results of the study have a possible translatory value as serum proteins can be included as a parameter in the existing burn prognostic scores and can also pave the way to the development of “metabolic burn prognosis score”.

Conflict of interest statement

The authors declare that they do not have any conflict of interest.

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