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THE SIGNIFICANCE OF LEVELS OF SERUM PROTEINS AND THEIR TRENDS AS PROGNOSTIC INDICATORS OF BURN MORTALITY

Plastic Surgery

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ABSTRACT

Introduction: In severe burns, there is a profound systemic response that persists till the wounds heal. Since these physiological and metabolic derangements are dynamic over the clinical course of burns, it is expected that both trend of change and absolute values of the proteins, to have a bearing on the prognosis and the ultimate outcome. Hence, this study evaluates the prognostic value of this metabolic variable in burn patients.
Materials and Methods: The study conducted on 100 adult patients of thermal burn (20% and 60% total body surface area). Serum albumin, globulin and total proteins were estimated on alternate days starting from day of admission till discharge or death. The 1st-day value and the trend of serial values throughout the clinical course were compared among expired and survivors. Results: Mean serum values of albumin, globulin, and total protein on first-day of burns in survivor group were higher. Serum albumin levels of ≤2.1 g/dl at day one was a poor prognostic factor. The trend in the serum values of albumin, globulin and total protein in survivor group was significantly positive and was negative in expired. Among the biochemical markers evaluated, most significant prognostic parameter was serum albumin, with maximum sensitivity and specificity. Conclusion: The cutoff values of proteins and trend of subsequent serial values can guide metabolic manipulations, albumin infusion, and dietary intake. In addition, these biochemical parameters merit inclusion in burn prognostic index scales. Keywords: Albumin, burns, prognosis, total protein, trends

KEYWORDS

INTRODUCTION

Burn is defined as an injury to the skin and underlying tissues primarily caused by heat, electricity, friction, or contact with chemicals.[1] However, its manifestations are systemic especially if burn surface area exceeds 15% total body surface area (TBSA).[2] Burn mortality becomes significant due to its metabolic and physiological derangements than due to the actual injury. Many burn mortality prediction models have been developed over time, which have been important for quality control, assessment, planning of treatment, explaining prognosis, and as research tools to compare efficacy of different therapeutic modalities. Virtually, all burn mortality models include three variables: age, percentage TBSA burn, and inhalation injury in their analysis of burn outcomes. Although metabolic derangements are not accounted in most of the prognostic scoring systems and hence do not include any of the biochemical parameters[3-6]

Severe burn injury is followed by a profound systemic response that persists till the wounds heal.[7-9] These metabolic and physiological reactions include hepatic dysfunction, increase in vascular permeability, catabolism, and heightened inflammatory response.[10-14]

These ultimately affect serum protein and lipid levels in burn patients. The physiological and metabolic derangements in burns are dynamic over the clinical course. Hence, it is expected that the trend of change rather than the absolute values of the protein levels, to have a bearing on the prognosis and the ultimate outcome in these patients. There are various studies in the literature citing the relationship between serum proteins and lipids with the prognosis of burn patients; however, results are conflicting.[12,15-28]. This study was carried out to observe the effects of all these factors/variables on burn patients for determining and improving the prognosis.

MATERIALS AND METHODS

The study was carried out in the Department of Burns and Plastic Surgery in collaboration with Department of Biochemistry from November 2018 to November 2019. This was a prospective, observational study conducted on 100 patients in the age group of 18–60 years suffering from thermal burn injury ranging between 20% and 60% TBSA. Relevant approvals had been obtained from the Institutional Review Board and the Ethics Committee. Burn patients admitted after 24 h of injury, electrical or chemical burns, or patients with inhalation injury or associated injury were excluded from the study. Preexisting hepatic and renal ailments and abnormalities of lipid metabolism were ruled by liver function test, kidney function test, and lipid profile respectively. All patients were treated conservatively as per the department protocol, i.e., daily dressing with 1% silver sulfadiazine cream till eschar separation or complete healing. Raw area after eschar separation was skin grafted when the patient was optimized for anesthesia and wound fit for grafting. Patients with hypoalbuminemia were treated with albumin infusions and plasma. All patients were put on enteral diet of at least 2500 KCal rich in carbohydrates and protein, and parenteral nutrition was reserved for patients in sepsis and ileus. The patients were grouped into Expired (Group A) and survivors (Group B). Serum albumin, globulin and total proteins were estimated on alternate days starting from day 1 of admission till discharge or death. The first sample was collected immediately on admission, and patient reporting after 24 h of burn were not recruited. For this 4–5 ml of whole blood sample was collected from each patient in serum separator vauettes. The first-day value and the trend of serial values throughout the clinical course were compared in the two groups. Normal serum concentration, which will be taken as a reference value will be as follows:[18]

Serum total protein: 6.7–8.2 g/dl
Serum albumin: 3.2–5.5 g/dl
Serum globulin: 1.8–3.4 g/dl

Sample size calculation

Serum albumin level as a risk factor for mortality in burn patients has been studied earlier and observed that the risk of mortality was significantly higher among patients with serum albumin 2 g/dL (odds ratio [OR] = 25.8, $P < 0.0001$). Taking this value as reference, the minimum required sample size with 5% level of significance and 90% power of study is 22. To reduce the margin of error, sample size taken is 50. Moreover, we have done the study on 100 patients. Formula used is: $n \geq 4(Z\alpha + Z\beta)^2 / (\log[OR])^2$ Where $Z\alpha$ is the value of Z at two-sided alpha error of 5% and $Z\beta$ is value of Z at power of 90% and OR is odds ratio.

Following statistical tests were applied:

1. Dependence of every predictor variable on time from admission to discharge/death will be evaluated by the Pearson's correlation coefficient for every patient
2. A trend of variables over time of survivors and expired will be tested by one sample t-test of the Pearson correlation with the reference value of 0, and difference between survivors and expired will be tested by two samples t-test
3. The risk of increasing or decreasing values of variables on survival will be assessed with the proportional hazard regression model of Cox
4. Univariate and multivariate logistic regression analysis will be used to assess predictability of mortality by different risk factors

by considering their day 1 value

5. Receiver operating characteristic (ROC) curve will be used to find out the cutoff point of different risk factors in predicting mortality.

The value of each predictor variable in relation to time, in predicting mortality was evaluated by the Pearson correlation coefficient for every patient. Trend of variables over time in survivor and expired groups was tested by one sample t-test of the Pearson correlation with the reference value of 0 and the difference between survivors and expired 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 the predictability of mortality by different risk factors by considering their day 1 value. ROC curve was used to find out cutoff point of different risk factors in predicting mortality. The results were considered significant with $P < 0.05$. $P < 0.05$ will be considered statistically significant. Analysis will be done using SPSS Statistics for windows. The study was conducted on 100 burn patients, and there were 83 survivors who were discharged in stable condition and 17 patients who expired during the course. Demography Average age of the patients in the survivor group was 42 years, and in the expired group, it was 49 years. The average hospital stay in the expired group was 22 days whereas it was 13 days in survivor group. Average TBSA in the expired group was 55% ±5.59%, and in the survivor group, it was 35.76% ±8.76% [Table 1].

In the survivor group (n = 83), there were 46 female patients and 37 male patients, and in expired group (n = 17), there were 11 female patients and 6 male patients. There were more number of female patients in both the groups; however, the sex ratio was similar in both the groups statistically with $P = 0.48$.

First-day values

Mean serum values of albumin, globulin, total protein on first-day of burns in survivor group was 2.53, 2.64, and 4.98 g/dl, respectively. In the expired group, the average serum albumin, globulin, and total protein were 1.83, 1.89, and 3.54 g/dl, respectively. This difference was statistically significant with lower levels of each parameter in expired group.

Cutoff value for day 1

Serum albumin levels of ≤2.1 g/dl at day 1 was considered as a poor prognostic factor with $P < 0.0001$ with sensitivity of 89.24 and specificity of 79.31, and area under the ROC curve (AUC) of 0.89. Serum globulin levels of ≤2.2 g/dl at day 1 was considered as a poor prognostic factor with $P < 0.0001$ with sensitivity of 75.47 and specificity of 78.11, and AUC of 0.85. Similarly,serum levels of total protein on day 1 ≤4.2 g/dl was considered as a poor prognostic factor with $P < 0.0001$ with sensitivity of 83.35 and specificity of 86.55, and AUC of 0.91. With the increase in serum levels of albumin, globulin, and total proteins at day one by 1 g/dl each, risk of mortality significantly decreases by 99.4%, 98.3%, and 96.6%, respectively.

Trend comparison

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 expired group, there was a significant declining trend in the serum levels with Pearson correlation coefficient of −0.63, −0.57 and −0.8 respectively. The mortality risk was assessed by increasing or decreasing values of albumin, globulin and total proteins. 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%.

Predicting mortality according to the serum values during the course

The cutoff point of albumin levels during the course was found to be 1.6 g/dl at which area under the ROC curve was 1, signifying mortality chance of 100% with 100% sensitivity and specificity and $P < 0.0001$. Similar cutoff value of globulin levels during the course was 1.8 g/dl at which area under the ROC curve was 0.96 signifying very high chances of mortality with 88% sensitivity and 95% specificity and $P < 0.0001$. The cutoff point of total protein levels during the course was 3.9 g/dl with area under the ROC curve was 0.96 implying very chances of mortality with 100% sensitivity and 86.75% specificity and $P < 0.0001$.

DISCUSSION

Objective and real-time evaluation of prognosis in burns throughout the clinical course of patients is important to improve outcome. The earliest and simplest score predicting burn mortality included age and percentage TBSA.[3] Subsequently, the Abbreviated Burn Severity Index was proposed, which is a five-variable scale including sex, age, inhalation injury, percentage of full-thickness burn, and percentage of TBSA.[3] Chances of mortality in burns are also governed by many physiological and metabolic derangements which happen during the clinical course of the patients. It is a fact that the clinical course of burn injury is in constant flux owing to the physiological, metabolic, and inflammatory responses. Hence, metabolic parameters are expected to reflect the status of pathology and ultimately the prognosis of burn patients. However, none of the existing burn prognostic scales included any metabolic parameter. In extensive burns, the hypermetabolic state continues for more than 2 years post trauma.[8] The response is characterized by increased metabolic rates, hypercatabolism, insulin resistance, multiorgan dysfunction, muscle protein degradation, and increased risk for infection.[9] Hypoproteinemia during acute phase of burn is because of loss of protein-rich plasma to third space owing to increased capillary permeability and increase of free-radical oxidation of serum oxidatively modified proteins. Subsequently, the reduction in serum protein level in burn are because of various factors which include oxidation of albumin which causes an increase of platelet and erythrocyte aggregation and reduction of protein levels, loss from wound exudation, and acute phase response of plasma protein synthesis in the liver.[11-13] The hypercatabolic state in burns is dynamic, continues throughout the clinical course and is known to parallel the extent of burns, sepsis, and dietary intake. With these facts in mind, this study was undertakenwith the hypothesis that, the baseline protein recorded at day 1 of burns and the subsequent trend of daily serum values throughout the course of treatment have tangible bearing on prognosis. In the study, it was hypothesized that day 1 values reflected the basal nutritional level of the patient and the magnitude of third space sequestration of protein-rich plasma during acute phase. In the study, it was observed that patients who survived had a higher initial serum protein and the statistically initial level serum protein was significant . Hence, it can be deduced that the baseline serum proteins values recorded at day 1 of burns, reflecting the nutritional status, has prognostic value. In our research, we could also deduce a cutoff value of 2.1, 2.2, and 4.2 g/dl of albumin, globulin, and total protein, respectively, below which the prognosis was very poor. The corollary was also proved, as there was reduction in mortality chance by 99.4% with 1 g/dl increase in albumin level at day 1. Comparing albumin and globulin, it was seen that day 1 value of albumin was a better predictor than globulin, but both could be used in prognostication. In a similar study, there was 24%–56% increase in burn mortality for each 2.5 g/dl decrement in serum albumin concentration.[16]

CONCLUSION

In the study, among the biochemical markers evaluated, most important prognostic parameter was found to be serum albumin, whose day 1 value and subsequent trend during the course were significantly different among survivors and expired groups, with maximum sensitivity and specificity. The findings of the study, pertaining to protein levels, are in-spite of regular plasma, albumin, and amino acid infusion as per the standard of care. Hence, the cutoff values of proteins open an objective indication for intervention in the form of more aggressive parenteral protein and albumin infusion. The cutoff values of proteins at day 1 can be an early warning to initiate plasma and albumin infusion. Similarly, trend of subsequent serial values can guide metabolic manipulations, albumin/amino acid infusion, and dietary intake of patients. In addition, apart from physical parameters, biochemical parameters such as serum albumin levels merit inclusion in burn prognostic index scales.

Conflicts of interest

There are no conflicts of interest.

Table 1 Patient charactaristics

Parameter	Expired	Survivors
Age (mean±SD)	49.14±7.36	42.11±13
Hospital stay (mean±SD	21.65±4.85	15.18±4.7
TBSA (mean±SD)	55±5.59	35.76±8.76

Table 2 Serum levels on day 1

Parameter	Expired	Survivors	P - value
Serum albumin (mean±SD) (g/dl)	1.83±0.35	2.53±0.34	<0.0001
Serum globulin (mean±SD) (g/dl)	1.89±0.32	2.64±0.41	
Serum total protein (mean±SD) (g/dl)	3.54±0.55	4.98±0.65	

Table 3 Receiver operating characteristic curve for initial prognostication

Parameter	AUC	Cut off point	sensitivity	specificity
Albumin at day 1	0.890150	≤2.1 (g/dl)	89.24	79.31
Globulin at day 1	0.85798	≤2.2 (g/dl)	75.47	78.11
Total protein at day 1	0.916804	≤4.1 (g/dl)	83.35	86.55

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