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ORIGINAL ARTICLE

Albumin supplementation may have limited effects on prolonged hypoalbuminemia in major burn patients: An outcome and prognostic factor analysis

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Abstract

Background: Burns that affect ≥20% of the total body surface area (TBSA) trigger a major inflammatory response in addition to capillary leakage and loss of serum proteins including albumin. Persistent hypoalbuminemia is therefore common in major burn patients. The purpose of this study was to determine whether human albumin solutions can benefit major burn patients with persistent hypoalbuminemia.

Methods: We conducted a retrospective review of major burn patients with ≥20% of TBSA involved at Taipei Veterans General Hospital between January 2007 and December 2018. Thirty-eight patients were enrolled. Patient demographics, burn characteristics, fluid balance, laboratory results, and outcomes were recorded through chart review.

Result: No significant differences were found in the baseline characteristics of patients who received <25 mg/kg/%TBSA/day of human albumin solutions and those who received more than this amount. Renal replacement therapy, duration of mechanical ventilation, length of stay in the burn unit, and in-hospital mortality rate were not statistically different between the two groups. The serum C-reactive protein/albumin ratio was associated with in-hospital mortality (p = 0.036).

Conclusion: The administration of large amounts of albumin supplements for the correction of prolonged hypoalbuminemia in major burn patients had no significant benefits on mortality.

Keywords: Albumin supplementation; Major burn; Mortality

1. INTRODUCTION

Burns that affect ≥20% of the total body surface area (TBSA) trigger a major inflammatory response and lead to capillary leakage.[1] Leakage in the capillaries can result in systemic inflammatory response syndrome, disseminated intravascular coagulation, or catabolism due to the loss of serum proteins.[2] A major loss of extracellular fluids induces shock, potentially leading to a vicious cycle.[3] Of the serum proteins, albumin plays an important role in oncotic pressure maintenance and several other physiological effects, including binding of endogenous and exogenous substances, antioxidant and scavenger activities, and protective effects on microcirculation.[4,5] Hypoalbuminemia is therefore associated with symptoms related to increased extravascular fluid, including delayed wound healing due to soft tissue edema, respiratory insufficiency due to pulmonary edema, and gut malabsorption due to intestinal edema.[6]

Major burn patients lose a considerable amount of the intravascular albumin and become hypoalbuminemic. This hypoalbuminemic state may persist for weeks after the injury. Hypoalbuminemia is commonly seen in critically ill patients and has been demonstrated to be associated with poor clinical outcomes.[7–9] However, this issue remains controversial for major burn patients. One study showed that an initial serum albumin level <25 g/L is an independent predictor of mortality in multivariate analysis.[10] Another showed that hypoalbuminemia (≤30 g/L) in the first 24 hours was associated with organ dysfunction independent of age, TBSA, and inhalation injury, but failed to demonstrate a relationship with mortality.[11]

Human albumin solutions[12] have long been used to treat patients with burn injuries. HAS can be administered either for fluid resuscitation or for the correction of persistent hypoalbuminemia in the post-resuscitation phase. Most previous studies focused on the former application for burn patients, and a meta-analysis conducted by Eljaiek et al. showed a neutral effect on organ failure, hospital length of stay, and mortality.[13] On the other hand, after the immediate postburn period, intensive care in the post-resuscitation phase plays an important role in determining the outcome.[14,15] However, only one study examined the latter application in adult burn patients. The study concluded that maintaining the serum albumin level is unnecessary.[16]

The purpose of this study is to determine whether HAS improves outcomes in the post-resuscitation phase and if serum

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albumin or other biochemical variables can be used as a predictor of mortality in adult burn patients.

2. METHODS

Taipei Veteran General Hospital is a tertiary medical center in Taiwan. After approval by the Research Ethics Board of our institution (VGHIRB No.: 2019-05-004BC), a retrospective chart review was performed for all patients diagnosed with burn injury between January 2011 and June 2018. Adult patients (age ≥ 18 years) with burns of ≥20% TBSA were selected for this study. Once the patients were identified from the hospital database, their electronic medical records were reviewed. Exclusion criteria included inadequate data, admission after >24 hours following the burn episode, chronic diseases such as end-stage kidney disease, nephrotic syndrome, hepatitis, inflammatory bowel disease, chronic obstructive pulmonary disease, and hematological malignancy.

Patient demographics (age, gender, and body weight), burn characteristics (cause, inhalation, full-thickness area), abbreviated burn severity index (ABSI), fluid balance, laboratory results, and outcomes were evaluated.

Major burn was defined as burn (thermal, electrical or chemical) injury with ≥20% TBSA which resuscitation within 24 hours of injury was necessary. The etiology of the burn was recorded. TBSA was calculated based on the Lund and Browder chart. Full-thickness burns were defined as third-degree burns, which involve the destruction of the entire epidermis and dermis. Inhalation injury was diagnosed using bronchoscopy.

The resuscitation phase was defined as the first 24 hours (D0) following the burn injury. The amount of crystalloid and colloid fluids received and the urine output during the resuscitation and post-resuscitation phases (D1–D7) were all collected. The precise amount of albumin supplement from HAS and fresh frozen plasma was calculated as the daily albumin intake (mg/kg/%TBSA/day). The patients were separated into groups according to the albumin supplement amount using the cutoff value of 25 mg/kg/%TBSA/day. Daily urine output was recorded from D0 to D7 (mL/kg/day).

The laboratory data, including C-reactive protein (CRP) and albumin, from D0 to D7 were all recorded. Each patient had at least three laboratory data records, one on D0, one on D3 or D4, and one on D7. Serum albumin levels were considered an ordinal variable and were divided into two groups: ≤25 g/L and >25 g/L.

The primary outcome measure was in-hospital mortality. Secondary outcome measures included the need for renal replacement therapy, duration of mechanical ventilation (defined as the time from initial intubation to 48 consecutive hours without any mechanical ventilator support), and length of stay in the burn unit.

Statistical analysis was performed using Statistical Product and Service Solution version 25.0 (IBM, Armonk, NY). Univariate analysis was performed with the χ^2 test or Fisher's exact test and the independent *t*-test. Multivariate analysis was performed using multiple logistic regression to assess the predictor of mortality and the effect of albumin supplementation on outcomes. A *p*-value of <0.05 was considered to indicate statistical significance. To our best knowledge, no previous report discussed about the CRP/albumin ratio in major burn patients. To fully explore the role of the CRP/albumin ratio as a predictor of mortality in major burn patients, the ratio was also assessed as a binary variable using the cutoff value. Prediction accuracy was assessed using the area under the receiver operating characteristic curve. The cutoff values showing the greatest accuracy were determined using the Youden's index.

3. RESULTS

Between January 2011 and June 2018, 48 patients with burns of TBSA ≥ 20% were admitted to our institution. Ten patients were excluded due to inadequate data (n = 1), age < 18 years (n = 2), delayed admission (n = 6), and chronic heart failure (n = 1). Therefore, 38 patients met the criteria for analysis. Patients with initial serum albumin levels ≤ 25 g/L suffered from a more severe burn injury and tended to stay in the burn unit for a longer period. The overall in-hospital mortality rate was 18.4%, but the mortality rate for patients with lower initial serum albumin levels was not statistically higher (Table 1).

There were no significant differences in baseline characteristics between patients who received different amounts of HAS (Table 2). The serum albumin level on D7 and the average serum albumin level in the first week (W1) were significantly higher in patients who received more HAS, but the other outcome parameters, including the requirement of renal replacement therapy, duration of MV, length of stay in burn unit, and in-hospital mortality rate were not statistically different (Table 3).

On multivariable logistic regression analysis, serum albumin and CRP level on D0 failed to predict mortality (Table 4). CRP/albumin ratio, however, was an independent predictor for mortality using the cutoff value of 0.6 (p = 0.036). The prediction of mortality was assessed using the ROC curve (Figure 1). The area under curve (AUC) for the CRP/albumin ratio was 0.890 (p = 0.002). The most sensitive and specific cutoff value for CRP/albumin ratio was 0.6, with the sensitivity and specificity being 85.7% and 84.6%, respectively.

4. DISCUSSION

Burns are a common cause of traumatic injury. In Taiwan, ~120 patients die from burn injuries each year. Although modern advancements in burn care have greatly increased the survival of major burn patients, many aspects remain controversial.

Hypoalbuminemia is frequently seen in major burn patients and may persist for weeks. In the initial phase after a burn injury, a strong inflammatory response is induced, and the release of vasoactive substances increases the skin's permeability to water, albumin, and even larger protein molecules. Leakage of albumin across the hyperpermeable capillary membranes into

Table 1.

Initial serum albumin and baseline characteristics and outcomes in major burn patients

	≤25 g/L	>25 g/L	*p*
Number (%)	21 (55.3%)	17 (44.7%)	
Age (year)	25 ± 11	35 ± 20	0.083
Gender, male	12 (57.1%)	12 (70.6%)	0.506
Cause			0.193
Flame	21 (100.0%)	15 (88.2%)	
Scald	0 (0.0%)	2 (11.8%)	
Inhalation	18 (85.7%)	6 (35.3%)	0.002
Total TBSA	64.2 ± 20.1	41.1 ± 18.5	0.001
Full-thickness TBSA	38.1 ± 23.5	16.5 ± 16.9	0.003
ABSI	7.3 ± 3.0	5.1 ± 1.7	0.008
Serum albumin (g/L) (day 0)	19.8 ± 5.5	32.1 ± 6.3	<0.001
Serum CRP (mg/dL) (day 0)	3.56 ± 4.87	1.12 ± 2.00	0.101
Duration of MV (days)	23.8 ± 29.9	5.3 ± 10.8	0.032
LOS—in BU (days)	44.4 ± 31.4	19.0 ± 14.3	0.006
In hospital mortality	5 (23.8%)	2 (11.8%)	0.427

TBSA = total body surface area; ABSI = abbreviated burn severity index; CRP = C-reactive protein; MV = mechanical ventilation; LOS = length of stay; BU = burn unit.

Table 2.

Amount of HAS-supplement and baseline characteristics in major burn patients albumin supplement (mg/kg/%TBSA/day)

	≤25	>25	p
Number	19	19	
Age (year)	34 ± 15	26 ± 17	0.139
Gender			
Male	14 (73.7%)	10 (52.6%)	0.313
Female	5 (26.3%)	9 (47.4%)	
Etiology			
Flame	18 (94.7%)	18 (94.7%)	1.000
Scald	1 (2.6%)	1 (2.6%)	
Inhalation	10 (41.7%)	14 (58.3%)	0.313
TBSA (%)	49.1 ± 26.4	58.7 ± 17.0	0.190
Full-thickness TBSA (%)	24.4 ± 24.5	32.4 ± 21.9	0.298
ABSI	6 ± 3	6 ± 2	0.772
Serum albumin (g/L) (day 0)	25.4 ± 8.6	24.1 ± 9.3	0.671
Serum CRP (mg/dL) (day 0)	3.44 ± 5.00	1.71 ± 2.86	0.320

HAS = human albumin solution; TBSA = total body surface area; ABSI = abbreviated burn severity index; CRP = C-reactive protein.

Table 3.

Albumin supplement and outcome of burn patients albumin supplement (mg/kg/%TBSA/day)

	≤25	>25	p
Albumin supplement (mg/kg/%/day)	12.2 ± 9.2	33.0 ± 4.4	<0.001
Serum albumin (g/L) (day 7)	33.2 ± 9.4	39.1 ± 4.9	0.023
Serum albumin (g/L) (week 1)	29.5 ± 6.8	35.3 ± 5.0	0.007
Serum CRP (mg/dL) (day 7)	18.65 ± 7.05	12.61 ± 7.75	0.022
Urine output (mL/kg/day)	43.0 ± 18.2	53.1 ± 18.4	0.102
Renal replacement therapy	6 (31.6%)	1 (5.3%)	0.090
Temporary	3 (15.8%)	0 (0.0%)	0.090
Permanant	3 (15.8%)	1 (5.3%)	
Duration of MV (days)	15 ± 33	15 ± 16	0.992
LOS—in BU (days)	23 ± 34	40 ± 20	0.096
In-hospital mortality	6 (47.4%)	1 (14.3%)	0.090

TBSA = total body surface area; CRP = C-reactive protein; MV = mechanical ventilation; LOS = length of stay; BU = burn unit.

Table 4.

Multivariate predictors of mortality in major burn patients mortality

Characteristic	OR (95% CI)	p
ABSI		
1-increase	1.73 (1.03–3.50)	0.040
Serum albumin (day 0)		
>25g/L	1	
≤25g/L	4.74 (0.11–201.68)	0.416
CRP (day 0)		
1-increase (mg/dL)	1.16 (0.88–1.53)	0.300
CRP/Alb ratio		
<0.6	1	
≥0.6	96.03 (1.35–685.68)	0.036

OR = odds ratio; CI = confidence interval; ABSI = abbreviated burn severity index; CRP = C-reactive protein; Alb = albumin.

the extravascular space is thought to be the primary cause of hypoalbuminemia in this phase.[2] Afterward, hypoalbuminemia persists due to the loss of albumin through open wounds and diminished synthesis.[17,18]

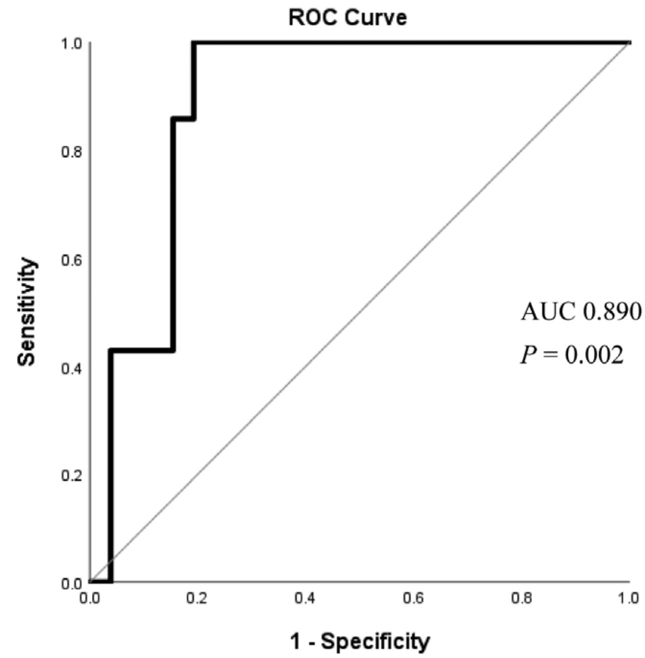

Fig. 1 Receiver operating characteristic (ROC) curve of CRP/albumin ratio in predicting mortality of major burn patients. The area under curve (AUC) for the CRP/albumin ratio is 0.890. CRP, C-reactive protein.

We evaluated serum albumin level in the initial resuscitation phase (D0) and post-resuscitation phase (D7), which both failed to predict mortality in our study. A retrospective cross-sectional study established that serum albumin level ≤ 20 g/L is a predictor of mortality.[19] However, only 16.9% of patients in that study had a TBSA > 30%; therefore, generalizing the results to major burn patients is difficult. Another retrospective study found that hypoalbuminemia (≤30 g/L) in the first 24 hours of admission was an independent predictor of organ dysfunction using the sequential organ failure assessment score but was not associated with mortality.[11] The authors assumed that HAS can correct hypoalbuminemia and subsequently reduce organ failure. However, this theory lacked strong evidence-based support.

The two different phases of hypoalbuminemia lead to two clearly distinct clinical indications for albumin administration in burn patients: for fluid resuscitation or for the correction of hypoalbuminemia. Our study focused on the latter indication, and we found that while a larger amount of albumin supplements can result in higher serum albumin levels, and the mortality rate tends to be lower, it did not reach a statistically significant difference. This is compatible with the only two studies reported on the issue. In 1995, Greenhalgh et al. demonstrated that albumin supplementation to maintain normal serum levels did not appear to be warranted in previously healthy children who suffered severe burns and who received adequate nutrition.[20] A more recent study concluded that routine supplementation to maintain a serum albumin level ≥ 20 g/L in adult burn patients is expensive and provides no benefits in wound healing, hospital length of stay, or in-hospital mortality.[16] This study did not quantify the amount of albumin supplementation and had a baseline difference in the incidence of inhalation injury between the two groups. In contrast, we calculated the precise amount of HAS by mg/kg/%TBSA/day in our study and had similar baseline characteristics between the two groups.

One possible explanation for this finding is that serum albumin is a good prognostic marker correlated with morbidity and mortality, but a poor nutritional marker.[21] Hypoalbuminemia results from lower liver synthesis in the post-resuscitation phase in burn patients and reflects the severity of the underlying disease. Intravenous infusion of HAS may correct the serum albumin level, but may only have a small effect on the disease itself.

CRP is a widely used inflammatory marker, and its value as a prognostic marker has been proven in septic patients.[22] Many studies have investigated the use of inflammatory markers, such as CRP or procalcitonin, to predict different outcomes in burn patients, but neither CRP nor procalcitonin showed an adequate operative capability to detect an infection or a fatal outcome in pediatric burn patients.[23]

Albumin levels are associated with the chronic nature of disease and represent the inflammatory status in burn patients,[12] and the value of albumin levels was demonstrated in predicting mortality in severe sepsis and septic shock patients.[24] On the other hand, hypoalbuminemia was associated with organ dysfunction but not mortality in burned patients.[11]

The combination of CRP and albumin resulted in a stronger predictor. The CRP/albumin ratio was shown to be an independent predictor for 90-day mortality in septic patients[25] and for 180-day mortality in patients with severe sepsis or septic shock.[26] To our knowledge, no previous study have evaluated the prognostic significance of the CRP/albumin ratio in major burn patients. Our study showed that although serum CRP and albumin levels failed to predict mortality, the CRP/albumin ratio could be an independent predictor for mortality in major burn patients. A CRP/albumin ratio of 0.6 and above is highly predictive of mortality, with 85.7% sensitivity and 84.6% specificity (84.6%), and an AUC of 0.890 represent an acceptable accuracy. Together with other existing model, including revised Baux score and ABSI, major burn patients can be stratified according to the severity more precisely.

Our study has limitations. The sample size was relatively small. Nevertheless, the only previous study on albumin administration for hypoalbuminemia correction included a sample of 43 patients, and related randomized clinical trials for fluid resuscitation included a mean patient number of 35.[27–30] The retrospective nature of our study also introduces some general weaknesses. Patients were not randomized and, therefore, selection bias cannot be ruled out. In addition, we compared patients using HAS because almost every burn patient with hypoalbuminemia can receive some amount of HAS due to our national health insurance. Ideally, a well-designed prospective randomized controlled trial comparing patients with HAS to patients without HAS can improve these limitations.

In conclusion, larger amounts of albumin supplementation for the correction of hypoalbuminemia in major burn patients had no significant benefits to mortality. Serum CRP/albumin ratio is a significant predictor for mortality in major burn patients.

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