The Value of Corrective Effect of Human Serum Albumin For The Mortality of Septic Patients With Hypoproteinemia

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Research Article

Keywords: sepsis, serum albumin, hypoproteinemia, corrective effect, mortality

Posted Date: January 3rd, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1165153/v1>

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Abstract

Timely and accurately evaluating the severity and prognosis of sepsis occupy an important position in septic management. The purpose of the article was to investigate the value of corrective effect of human serum albumin (HSA) in assessment on the mortality of septic patients with hypoproteinemia. A retrospective analysis was carried out. A logistic regression model was adopted to analyze the association between the mortality and related risk factors. Furthermore, the receiver operating characteristic curves (ROC) were utilized to analyze the abilities of potential risk factors in prediction of the mortality of septic patients with hypoproteinemia. The ratio of total dosage of HSA-to-the difference of serum albumin before and after albumin supplement ($T_{HSA}/\Delta ALB$) was significantly increased in non-survivors of septic patients with hypoproteinemia than that in survivors ($P < 0.001$). $T_{HSA}/\Delta ALB$ ($P = 0.018$) was an independent risk factor for the mortality of septic patients with hypoproteinemia. ROC analysis showed that area under curve (AUC) of $T_{HSA}/\Delta ALB$, SOFA score and APACHE II score were 0.800, 0.802 and 0.766, respectively. The data demonstrated that $T_{HSA}/\Delta ALB$ could be an independent risk factor in predicting the mortality of septic patients with hypoproteinemia.

Introduction

Sepsis is defined as dysregulation of host response to infection, which may lead to life-threatening organ dysfunction¹. It is featured by critical illness, high mortality and heavy economic burden that has attracted much attention to. According to statistics, sepsis is the second leading causes of death among patients in intensive care unit (ICU) due to the extremely complex etiology, with a mortality rate of 15%-20% and 30%-50% in those with septic shock². It's known that timely and accurately evaluating the severity and prognosis of sepsis are critical components for effective septic management. Sequential Organ Failure Assessment (SOFA) score, Acute Physiology and Chronic Health Evaluation II (APACHE II) score and 'quick' SOFA (qSOFA) are common choice for evaluation in the clinical setting, which, however, have their own shortages. qSOFA allows a rapid bedside assessment yet with relatively low accuracy. SOFA and APACHE II scores are scoring system involving vital signs, biomedical indicators, Glasgow score and other multiple aspects, which are comprehensive in evaluation and have good sensitivity and specificity, yet accompanied by insufficient timeliness and easier to be affected by the assessor bias³⁻⁶. In addition, C-reactive protein (CRP) and procalcitonin (PCT) are recognized to be valuable in predicting the severity of sepsis, but their roles in prognosis still remain controversial^{7,8}. Consequently, it is of special interest to find a biological indicator with sufficient timeliness and high accuracy to evaluate the mortality of patients with sepsis.

Serum albumin is one of the most crucial biological macromolecules in vivo. It plays important roles in regulating plasma osmotic pressure, binding and transportation of fatty acid, calcium ion, steroid hormones, thyroid hormone, bilirubin and various drugs, scavenging of free radicals (reactive oxygen and nitrogen species), etc.⁹. Numerous studies have indicated that hypoproteinemia was an independent risk factor for high mortality in critically ill patients including sepsis¹⁰⁻¹⁴. For instance, Artero et al. suggested

that hypoproteinemia was the most important risk factor in predicting the prognosis of sepsis caused by community-acquired bloodstream infection¹⁵. Furukawa et al. pointed out that hypoproteinemia might act as a key biomarker identifying the high mortality risk of sepsis¹⁶. However, this is still disputed since some researchers thought that hypoproteinemia might have no prognostic value although it might aggravate the condition of patients with sepsis¹⁷⁻¹⁹. In view of the above, our study was carried out to explore the relationship between serum albumin level on admission and mortality of sepsis, corresponding results revealed that there was no statistical significance in serum albumin level on admission in the survivors of sepsis than that in the non-survivors (supplementary Table 1-3). A meta-analysis including nine prospectively controlled trials have showed that the rate of complications decreased with the level of human serum albumin (HSA) reaching 30g/L or more after supplement in critically ill patients²⁰, and recent expert consensus concluded that the HSA infusion could be terminated while the septic patients' hemodynamics were stable with the level of serum albumin higher than 30g/L²¹. It is expected to determine the value of corrective effect of HSA in assessment on the mortality of sepsis with hypoproteinemia.

Results

A total of 98 adult septic patients with hypoproteinemia were included in our study. Statistically significant difference was found in the length of stay in hospital (10.3 days vs. 7.4 days; $P = 0.017$) between the survivors and non-survivors of septic patients with hypoproteinemia. (Table 1)

Compared with survivors of septic patients with hypoproteinemia, there were significant increase in the total dosage of HAS/ the difference of serum albumin before and after albumin supplement ($T_{HSA}/\Delta ALB$) (35.2 vs. 17.9; $P < 0.001$), SOFA score (9.0 vs. 4.0; $P < 0.001$) and APACHE II score (15.0 vs. 10.0; $P < 0.001$) in non-survivors. (Table 2)

$T_{HSA}/\Delta ALB$ (OR, 1.032; 95% CI, 1.005-1.058; $P = 0.018$), SOFA score (OR, 1.205; 95% CI, 1.037-1.399; $P = 0.015$) and APACHE II score (OR, 1.103; 95% CI, 1.007-1.208; $P = 0.035$) were independent risk factors for the mortality of septic patients with hypoproteinemia. (Table 3)

ROC analysis showed that areas under curve (AUCs) of $T_{HSA}/\Delta ALB$, SOFA score and APACHE II score were 0.800 (95% CI, 0.712-0.887), 0.802 (95% CI, 0.703-0.900) and 0.766 (95% CI, 0.666-0.865), respectively. The Youden index were 0.554, 0.532 and 0.413, respectively. The optimum cutoffs were 20.3, 6.5 and 10.5, respectively. The sensitivities were 93.1%, 79.3% and 86.2%, respectively, while the specificities were 62.3%, 73.9% and 55.1%, respectively. (Table 4, Figure 1)

Discussion

In our study, $T_{HSA}/\Delta ALB$ was an independent risk factor in predicting the prognosis of septic patients with hypoproteinemia. Additionally, $T_{HSA}/\Delta ALB$ had similar AUC as SOFA score in predicting the mortality

of septic patients with hypoproteinemia, which was higher than APACHE II score. Besides, $T_{HSA}/\Delta ALB$ also had better sensitivity and higher Youden index when compared with SOFA and APACHE II scores.

Sepsis is a common clinical disease that may induce hypoproteinemia via diverse pathophysiological mechanisms¹². The combined occurrence of sepsis with hypoproteinemia can be explained by the following causes. The first is the increased leakage of albumin. Human capillary endothelial cell is 60 kDa in width and albumin has a molecular weight of 69 kDa. In general, the width of the former is insufficient for the passage of albumin under normal conditions. While under the condition of sepsis, there may be increased expressions of inflammatory mediators such as cytokines, leukotrienes, interleukin and oxygen free radicals, which may promote the contraction of vascular endothelial cell to elevate vascular permeability. Albumin with small molecular weight may be the first to pass through capillary wall, which may in turn result in the formation of hypoproteinemia^{22,23}. The second is the decreased synthesis of albumin. The liver is not only responsible for albumin synthesis but also one of the most vulnerable target organs during sepsis. According to previous research, 34%-46% of septic patients had liver dysfunction and 1.3%-22% of which progressed to liver failure, during which albumin synthesis was attenuated along with the impairment of liver function²⁴. In addition, the liver preferentially synthesized acute phase proteins CRP, complement and globulin under stress, which would further aggravate hypoproteinemia⁹. The third reason may be the increased catabolism of albumin. In case of acute infection, the catabolism of albumin can be accelerated to provide substrate for the synthesis of acute phase proteins; moreover, increased amount of albumin may be decomposed to meet the increased demand of energy consumption in vivo⁹.

Afterwards, the progression of hypoproteinemia may aggravate the condition of sepsis. It shall be noted that serum albumin possesses multiple functions. To be specific, serum albumin is an important factor in maintaining plasma osmotic pressure. In case of an increased capillary leakage resulted from inflammatory mediator release in septic patients, there may be reduced serum albumin level that may induce a decrease in plasma colloid osmotic pressure, which may be the pathological basis of sepsis shock²⁵. Furthermore, serum albumin is of great significance to balance the redox state of plasma scavenging reactive oxygen and nitrogen radicals, which will be weakened if albumin decreases²⁶. Decline in serum albumin can produce negative effect on the innate immunity, which renders the risk of infection⁴. Besides, it is a carrier protein integrating with various exogenous and endogenous ligands. In addition to transporting molecules (e.g., fatty acid, calcium ion, steroid and thyroid hormones), it can also promote the transport of multiple drugs such as antibiotics, non-steroidal anti-inflammatory drugs and warfarin²⁷⁻²⁹. When there was a decreased serum albumin, as reported previously, hypoproteinemia could increase the free fraction of drug to increase the incidence of toxic side effects, shorten the half-life and drug effectiveness, and accelerate the clearance, eventually reducing the treatment effect²⁹.

HAS has been widely used in fluid resuscitation and correction of hypoproteinemia in trauma, infection, surgery and other diseases since the Second World War³⁰⁻³². In recent decades, the utility of HSA in sepsis have been studied extensively^{22,33,34}. For instance, Gatta et al. reported that decreased serum

albumin might aggravate sepsis, yet without significant impact on the outcome¹². While Aguayo et al. implied that the mortality of burn patients whose albumin was $\leq 2\text{g/dl}$ was as high as 80%, much higher than those with normal levels of albumin³⁵. Delgado et al. also argued that hypoproteinemia was a predictor of high incidence and high mortality³⁶. In our study, there was no statistical significance in serum albumin level on admission in the survivors of sepsis when compared to the non-survivors, which was in accordance with the research findings reported by Godinez et al.³⁷. In our opinion, hypoproteinemia in some septic patients could be corrected through intravenous injection of HSA, which thus might have positive effect on the early stage of sepsis and no such influence in the prognosis of sepsis. Patients with the failure of serum albumin correction might generally have poor prognosis. In a study performed by Wang et al., based on the duration of low albumin, corresponding mortality was 46% and 15.4% in patients with persistent hypoproteinemia and temporary hypoproteinemia, respectively³⁸. It indicated that patients might experience an aggravated prognosis with the prolongation of lower albumin. Therefore, our study was carried out to evaluate the value of corrective effect of HSA for the mortality of septic patients with hypoproteinemia.

In order to reduce the bias of dosage, frequency and the supplement time of HSA on the results, our research proposed the concept of “corrective effect of hypoproteinemia”. In other words, the intravenous injection dosage of HSA for every 1g increase in serum albumin level could also be translated to an algorithm “ $T_{\text{HSA}}/\Delta\text{ALB}$ ”. In our study, serum albumin increased by 1g/L required 17.9g of HSA infused in the survivors but 35.2g in non-survivors. In addition, $T_{\text{HSA}}/\Delta\text{ALB}$ was an independent risk factor in predicting the prognosis of septic patients with hypoproteinemia. Furthermore, $T_{\text{HSA}}/\Delta\text{ALB}$ had similar AUC as SOFA score when compared with SOFA and APACHE II scores while higher AUC than APACHE II score. Besides, $T_{\text{HSA}}/\Delta\text{ALB}$ had higher sensitivity and Youden index than SOFA and APACHE II scores. The value of $T_{\text{HSA}}/\Delta\text{ALB}$ have several advantages. Specifically, serum albumin is one of the routine clinical test items, which can be tested in almost all patients on admission, and the result can be obtained quickly with a good timeliness. Besides the bias of dosage, frequency and the supplement time of HSA, $T_{\text{HSA}}/\Delta\text{ALB}$ is also independent of the subjective assessment with good objectivity. The only requirement is the dynamic monitoring of serum albumin, highlighting the superiority of $T_{\text{HSA}}/\Delta\text{ALB}$ in patient compliance and economic benefits. Thus, we proposed the feasibility of “corrective effect of hypoproteinemia” in our study, which is expected to become a new biomarker in evaluating the mortality of septic patients with hypoproteinemia.

The study still has several limitations, such as the design of a single-center retrospective study with possible presence of selection bias, and the relatively small sample size. In the future, a prospective, multicenter and randomized controlled study can be performed based on large sample size if possible to provide more convincing results.

Conclusion

In summary, $T_{HSA}/\Delta ALB$ was an independent risk factor in predicting the mortality of septic patients with hypoproteinemia. It was expected to be a new biomarker in evaluating the mortality of septic patients with hypoproteinemia.

Methods

Study Design and Participants

This retrospective study was conducted focusing on patients with sepsis admitted to emergency intensive care unit (EICU) and ICU from January 2016 to October 2019 in the Second Xiangya Hospital of Central South University. An outcome-based grouping was performed and enrolled patients were divided into two groups of survivors and non-survivors. Exclusion criteria were listed as follows: patients younger than 18 years or older than 80 years; patients who were admitted to the hospital within 24 hours; patients with incomplete hospitalization data; patients with autoimmune diseases and long-term use of immunosuppressant; patients with acquired immunodeficiency syndrome; patients with nephrotic syndrome; patients with cardiac, kidney or liver failure; patients with malignant tumor; as well as pregnant and lactating women.

Data Collection

All medical records and data of the included patients were collected individually and reviewed carefully by two members of our research group. Blood samples were drawn from each patient within 24 hours after admission. Data recording involved the following parameters, including the worst scores of APACHE II and SOFA within 24 hours on admission, detailed information on demographic data, source of infection, related blood test, the level of serum albumin which was $<30\text{g/L}$ before albumin supplement, the level of serum albumin which was $\geq 30\text{g/L}$ after albumin supplement (if it was $<30\text{g/L}$ at the last monitoring before discharge, the value was considered as the post-supplement level), the difference of serum albumin before and after albumin supplement (ΔALB), total dosage of HAS (T_{HSA}) (interruption of HAS supplement in case of a $\geq 30\text{g/L}$ level of serum albumin when hemodynamics are stable). This case series was subjected to approval by the Ethics Committee of the Second Xiangya Hospital of Central South University (KY-LJX2015), and patient consent was waived due to the retrospective study.

Statistical Analysis

Statistical analyses and figure plotting were generated by using Medcalc software version 18.0 (Medcalc) and IBM SPSS version 26 software. Statistical significance was set at $P < 0.05$. Categorical variables were presented as numbers and percentages. Normally distributed continuous data were expressed as mean $\pm$ standard deviation. Non-normally distributed variables were expressed as medians and interquartile ranges. Differences in clinical and laboratory findings were assessed using unpaired t-test, Mann-Whitney U test and chi-square test or exact Fisher's test when appropriate. Independent predictors of mortality were analyzed by Logistic regression. Receiver operating characteristic (ROC) curves were

constructed to compare prognostic performance of the evaluated biomarkers. All methods were carried out in accordance with relevant guidelines and regulations.

Abbreviations

ICU: intensive care unit; SOFA: Sequential Organ Failure Assessment; APACHE II: Acute Physiology and Chronic Health Evaluation II; qSOFA: 'quick' SOFA; CRP: C-reactive protein; PCT: procalcitonin; HSA: human serum albumin; EICU: emergency intensive care unit; Δ ALB: the difference of serum albumin before and after albumin supplement; THSA: total dosage of HAS; ROC: Receiver operating characteristic; THSA/DALB: the total dosage of HAS/ the difference of serum albumin before and after albumin supplement; AUCs: areas under curve.

Declarations

DATA AVAILABILITY STATEMENT

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

ETHICS STATMENT

The study was approved by the Ethics Committee of Second Xiangya Hospital of Central South University (KY-LJX2015). Patient consent was waived due to the retrospective study.

CONSENT FOR PUBLICATION

Not applicable.

COMPETING INTERESTS

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHORS' CONTRIBUTIONS

YZ and SW contributed to the study design, implementation, and critical revision. HZ contributed to the study design. FP contributed to methodology, software, and writing original draft preparation. SL, JJ, and QZ collected and interpreted the data. All authors read and approved the final manuscript.

FUNDING

This study was funded by the Natural Science Foundation of Hunan Province, China: 2021JJ40896.

ACKNOWLEDGEMENTS

Not applicable.

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Tables

Due to technical limitations, tables 1-4 are only available as a download in the Supplemental Files section.

Figures

Figure 1

ROC curves of the biomarkers for predicting the prognosis of septic patients with hypoproteinemia. $T_{HSA}/\Delta ALB$ had similar AUC as SOFA score when compared with SOFA and APACHE II scores while higher AUC than APACHE II score.

Supplementary Files

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