The THAI Journal of SURGERY 2018;39:81-87.
Official Publication of The Royal College of Surgeons of Thailand

Original Article

The Effects of Hypoalbuminemia at Admission on Adverse Outcomes in a Tertiary University Based General Surgical Intensive Care Units

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Abstract

Background: **Although albumin is the marker of nutrition status but the albumin level usually low on acute illness and its level on outcome is controversy. The objective of this study was to determine the effect of serum albumin which on morbidity and mortality in hospitalized surgical patients admitted to general surgical intensive care unit (SICU).**

Method: **We performed an ambispective cohort study between 2011-2013. All patients who admitted to SICU were enrolled to this observation. The albumin level, severity of disease, type of surgery and demographic data were collected on the SICU admission. The outcomes included the length of mechanical ventilator day, hospital and SICU stay, lung complication, septicemia, urine infection, acute kidney injury, surgical site infection, new-onset upper gastrointestinal hemorrhage, delirium, seizure, myocardial infarction and mortality were recorded at patient discharge. We categorized the patient into two group based on admission albumin level as normal group (≥ 3.5 g/dL) and hypoalbuminemia group (< 3.5 g/dL)**

Results: **A total of 893 patients were enrolled and analyzed in this study. Of these, the normal and hypoalbuminemia group were 106 (11.9%) and 787 (88.1%) respectively. After adjusted the adverse outcomes by multivariable analysis, the hypoalbuminemia group had significant higher risk of infective complication [Odds ratio (95% confidence interval): 2.68 (1.35 - 5.30); $p = 0.005$] especially on pulmonary infection [2.08 (1.01 - 4.27); $p = 0.046$], acute kidney injury [4.06 (1.44 - 11.47), $p = 0.008$], and mortality [5.92 (2.12 - 16.54); $p = 0.001$]**

Conclusion: **The incidence of hypoalbuminemia is common in SICU. The hypoalbuminemia patients increase risk of infective complication especially pulmonary infection, acute kidney injury, and mortality.**

Keywords: **Hypoalbuminemia, surgical intensive care unit, mortality, infection, acute kidney injury**

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Introduction

The serum albumin is the majority of protein in human plasma and it is produced by liver. Serum albumin play an important role on physiologic function including regulating blood volume via maintaining the oncotic pressure (colloid osmotic pressure) of the blood compartment, acid base buffering as well as free radical scavenger. In addition, it also has the low water solubility molecules carrying property, such as lipid soluble hormones, bile salts, unconjugated bilirubin, free fatty acids, trace elements (e.g. calcium, iron), and many type of drugs. They also control acid-base balance and having the action like antioxidant[1,2]. Although the morbidity and mortality in intensive care patient could be predicted by severity scoring system such as APACHE II score, SAPS score, and SOFA score. The albumin were no accounting for the variable on these scoring system[3]. These might be arisen from the controversial data. Rady et al reported that the preoperative hypoalbuminemia can predict outcome of cardiovascular patient. Although the incidence of hypoalbuminemia was about < 50%, the cardiac patient undergoing cardiovascular surgery had higher likelihood of postoperative infections, prolong mechanical ventilator day and death[4]. However, Law et al reported the opposite direction of results. They found that the causes of death did not associated with serum albumin level[5]. This evidence was confirmed by the results of Behrouz et al which studying on the subarachnoid hemorrhage patients. The study showed that hypoalbuminemia was also not the predictive factor for hospital mortality[6] . The controversial of this predictive factor, therefore, the objective of this study was to determine the effects of hypoalbuminemia on admission on adverse outcomes which occurred in general surgical intensive care unit (SICU).

Materials and methods

We performed an ambispective cohort study, between 2011 and 2013. All patients who were admitted to general SICU of Maharaj Nakorn Chiang Mai Hospital, Faculty of Medicine, Chiang Mai University on these periods were included. We excluded the patients who no document of admission albumin level, short stay in SICU, moribund patient, and the patient who could not be collected the final outcomes from the study (Figure 1). At admission date, we recorded the baseline of patient characters including albumin level, age, gender, diseases and types of surgery, and severity score using acute physiologic and chronic health evaluation II (APACHE II score). During SICU admission, we collected the adverse outcomes infective complications, acute kidney injury, surgical site infection, upper gastrointestinal hemorrhage, new-onset seizure, delirium, myocardial infarction, and mortality. We also recorded the length of mechanical ventilator usage, SICU and hospital length of stay. The Ethic Committee of Faculty of Medicine, Chiang Mai University was approved this study (Research ID: 1186/ Study code SUR-12-1186-EX).

We categorized the admission albumin into 2 group based on the previous study by Rady et al[4], the normal group was defined as admission albumin more

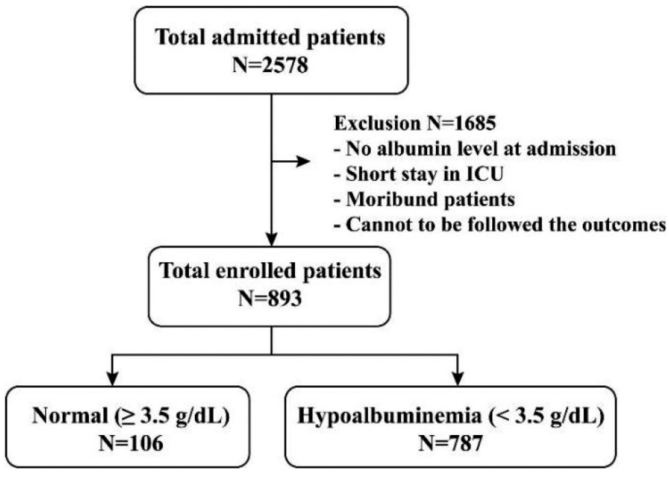

Figure 1 Study flow

than or equal 3.5 g/dl and albumin level less than 3.5 g/dl was defined as hypoalbuminemia group. All the analytic data were analyzed by STATA® version 12.0 software. The continuous variables were reported as mean and standard deviation (SD) or median and interquartile range (IQR) depended on their distribution. The categorical data were reported as number of occurrence and percentage. The difference between groups was analyzed by Chi-square, Mann-Whitney U test and student t test which depended on the type of data. The final adjusted predictive models were analyzed with multivariable regression analysis. The adjusted variables were selected on the difference of baseline characters and reported as coefficient or odds ratio (OR) with 95 percent confidence interval (95%CI) depended on the type of dependence variables. The *p* value less than 0.05 was statistically significant.

Results

During 36 months between 2011 and 2013, a total admitted patients were 2578. We excluded a total number of 1685 patients due to no admission albumin report, short stay in SICU, moribund patients, and cannot to be followed the final results. The total of 893 patients were enrolled and analyzed. The normal value of albumin was found in 106 (11.9%) patients. The hypoalbuminemia at admission in SICU was 787 (88.1%) patients. (Figure 1)

Regarding the demographic data (Table 1), female was the predominant gender on both group and no significant difference. The median age (IQR) of hypoalbuminemia was 62 (52 - 75) years and no difference with normal group. Although there was no statistical significant difference between groups in term of type of disease and type of surgery. The hypoalbuminemia group had a higher proportion in liver diseases when they were compared with normal group [hypoalbuminemia (22.2%) vs. normal (9.4%)]. In contrast, the hypoalbuminemia group had lower proportion in vascular diseases [hypoalbuminemia (17.6%) vs. normal (27.4%)]. Interestingly, the severity score measured by APACHE II score had a significant higher score in hypoalbuminemia [median/IQR: hypoalbuminemia (10/ 7-15) vs. normal (13/9-18); $p < 0.01$]. Therefore, the type of diseases and APACHE II score were the two adjusted variables which were integrated in the multiple regression model.

As Table 2, the univariable analysis demonstrated that hypoalbuminemia had significant longer mechanical ventilator day ($p = 0.014$), hospital length of stay ($p = 0.006$), and SICU length of stay ($p = 0.040$). In addition, hypoalbuminemia increased the

Table 1 Baseline patient characters

Patient characters	Normal* n=106	Hypoalbuminemia** n=787	*P*-value
Gender (Male: Female)	39:67	288:499	0.968
Age [Median (IQR)]	61.5 (46-72)	62 (52-75)	0.110
Type of disease			0.053
Gastro-intestinal	36 (33.96)	243 (30.96)	
Hepato-biliary-pancreas	10 (9.43)	174 (22.17)	
Vascular	29 (27.36)	138 (17.58)	
Trauma	6 (5.66)	35 (4.46)	
Thoracic (non cardiac)	15 (14.15)	110 (14.01)	
Skin and soft tissue	3 (2.83)	23 (2.93)	
Urological	7 (6.60)	53 (6.75)	
Head-neck-breast	0 (0.00)	9 (1.15)	
Type of surgery			0.219
Curative surgery	87 (82.08)	584 (74.49)	
Palliative surgery	6 (5.66)	54 (6.89)	
Without surgical procedure	13 (12.26)	146 (18.62)	
APACHE II score [Median (IQR)]	10 (7-15)	13 (9-18)	< 0.001

Note: *Normal is admission albumin ≥ 3.5 g/dL; **Hypoalbuminemia is admission < 3.5 g/dL

proportion of pulmonary infection ($p = 0.005$) and any infection ($p < 0.001$). They also increased risk of acute kidney injury ($p < 0.001$), myocardial infarction (p = 0.048) and mortality ($p < 0.001$)

Regarding the adjusted value by type of diseases and severity score (APACHE II score) using multivariable analysis model (Table 3), we found that there was statistical significant increase risk of following outcomes including infective complication [OR (95%CI): 2.68 (1.35 - 5.30); $p = 0.05$] especially on the pulmonary infective complication [2.08 (1.01 - 4.27); $p = 0.046$], acute kidney injury [4.06 (1.44 - 11.47); $p = 0.008$], and mortality [5.92 (2.12 - 16.54); $p = 0.01$]. Although the myocardial infarction had significant difference in univariable analysis but we could not analyze on multivariable analysis because there was no occurrence of event in the normal group (Table 2). There was statistical significant difference both of SICU and hospital length of stay between groups in univariable analysis model, but only hospital length of stay had a tendency risk of longer occupation rate in hypoalbuminemia patient in multivariable analysis ($p = 0.088$) (Table 3).

Table 2 Adverse outcomes

Adverse events	Normal n=106	Hypoalbuminemia n=787	*P*-value
Mechanical ventilator day [Median (IQR)]	0.5(0-3)	1(0-4)	0.014
Hospital length of stay [Median (IQR)]	14(9-20)	17(10-28)	0.006
SICU length of stay [Median (IQR)]	3(2-6)	4(3-7)	0.040
Infective complications (%)			
Pulmonary infection	9(8.49)	156(19.82)	0.005
Blood stream	3(2.83)	56(7.12)	0.095
Urinary	5(4.72)	62(7.88)	0.246
Any infection(s)	10(9.43)	207(26.30)	<0.001
Acute kidney injury (%)	4(3.77)	152(19.31)	<0.001
Surgical site infection (%)	3(2.83)	34(4.32)	0.470
Myocardial infarction (%)	0(0.00)	28(3.56)	0.048
Upper gastrointestinal hemorrhage (%)	0(0.00)	21(2.67)	0.089
New-onset stroke (%)	0(0.00)	2(0.25)	0.603
New onset seizure (%)	1(0.95)	11(1.40)	0.710
Delirium (%)	4(3.77)	65(8.26)	0.104
Mortality (%)	4(3.77)	189(24.02)	<0.001

Note: *Normal is admission albumin ≥ 3.5 g/dL; **Hypoalbuminemia is admission < 3.5 g/dL

Table 3 Multivariable analysis of adverse outcomes

Adverse events	Value	Effect size (95% CI)*	*P*-value
Mechanical ventilator day	Coefficient	0.001 (-0.0006 to 0.0027)	0.223
Hospital length of stay	Coefficient	0.001 (-0.0001 to 0.0019)	0.088
ICU length of stay	Coefficient	0.001 (-0.0007 to 0.0027)	0.246
Infective complications			
Pulmonary infection	Odds ratio	2.08 (1.01 - 4.27)	0.046
Blood stream	Odds ratio	1.88 (0.57 - 6.22)	0.300
Urinary	Odds ratio	1.35 (0.52 - 3.50)	0.532
Any infection (s)	Odds ratio	2.68 (1.35 - 5.30)	0.005
Acute kidney injury	Odds ratio	4.06 (1.44 - 11.47)	0.008
Mortality	Odds ratio	5.92 (2.12 - 16.54)	0.001

Abbreviation: 95%CI, 95% confidence interval

* The effect size was adjusted by type of diseases and severity score (APACHE II)

Discussion

The albumin is a complex large protein in human body with molecular weigh between 65 and 70 kilo Dalton[7]. It is synthesized by liver around 9 - 14 g/day in adult and the half-life is 18 - 21 days on normal situation[8]. Currently, circulation albumin has many physiologic function in both healthy and illness including binding and transport of drugs and substances, maintenance of colloid osmotic pressure, free radical scavenger, platelet and thrombotic activity, and vascular permeability effects[7-9]. However, the acute critically ill patient has the potential risk of low serum albumin level by many mechanisms such as resuscitative dilution, interstitial leakage, increase of degradation, and decrease of production[8]. Although a total 65 percent of admitted patients were excluded, the enrolled patient had incidence of hypoalbuminemia as high as 88.1 percent in our study.

Many of previous study showed that hypoalbuminemia increased risk of complications[4,10]. In one meta-analysis, the decreasing serum albumin concentration level on each 1 g/dl significant raised the odds of mortality by 137 percent and morbidity by 89 percent.[10] Our results of study were confirmed of these results that the hypoalbuminemia both of mortality, infective complications, and acute kidney injury. However, the previous results of preoperative hypoalbuminemia increased the likelihood of postoperative prolonged mechanical ventilation,[4] as well as in a meta-analysis of cohort and controlled study demonstrated that each 1 g/dl of decreasing of albumin level increase of ICU and hospital stay by 28 and 71 percent respectively[10], but our results showed no significant effects on these outcomes in multivariable analysis.

The cut off points for defining hypoalbuminemia are difference in range between 3.0 and 3.6 g/dl[4,10,11]. The complication is decreased during the albumin level exceeds 3 g/dl in a meta-analysis.[10] In our study, we select the categorized level at 3.5 g/dl. This level based on the previous report by Rady et al which followed cardiovascular surgical patients. The preoperative albumin level less than 3.5 g/dl increased risk of post-operative organ dysfunction, gastrointestinal hemorrhage, nosocomial infections, length of mechanical day, hospital stay, and ICU stay[4]. In addition, the recent report in elderly trauma patients by Garwe et al, they defined the hypoalbuminemia by emergency department albumin level less than 3.6 g/dl. At this level, the hypoalbuminemia was associated with a 2-fold increase in the risk of 30 day overall hospital complication.[11] Although we categorized the level of hypoalbuminemia higher than the general definition that determine as serum albumin concentration ≥ 3.0 g/dl, but the results of cutoff level in our study showed the unfavorable outcomes both mortality and some morbidity in SICU.

The strength of this study was the large cohort SICU patients that showed the high risk of adverse outcomes in patients who were hypoalbuminemia at admission. However, there were some inevitable limitation in this study. First, the excluded patients were high account for 65 percent of admission patient. However, most of these patients had the extreme prognosis (extreme risk or very low risk of mortality) which might not get the benefit of SICU care and deviate the results. Second, we did not collect the albumin containing fluid treatment during SICU admission in this study. The previous randomized control trial comparison of albumin and saline for resuscitation in ICU (SAFE study) showed no difference of mortality between groups except there were might be benefit in subgroup patient who diagnosed of sepsis[12]. Regarding the hypoalbuminemia in sepsis patients, the ALBIOS study protocol replaced the albumin to severe sepsis and septic shock patient until the concentration more than 3.5 g/dl. Even though the primary outcome of 90 days mortality was not different, but the albumin group had significant of higher mean arterial pressure and lower net fluid balance[13]. The fluid accumulation is one of the predictor of adverse outcomes in ICU. The previous study of fluid accumulation in general SICU demonstrated that threshold of fluid accumulation more than 5 percent of admitted body weight had greater risk of adverse outcome[14]. Of these evidences, the less of fluid accumulation might result in less ICU complications. Although there were many limitations of this cohort, the results of study implied that the hypoalbuminemia patients should be closely monitored and caution. The hypoalbuminemia might be a severity marker that led to the surgeon more early some intervention such as nutrition therapy as well as to choose the appropriate fluid therapy to the critically ill surgical patient.

Conclusion

The incidence of hypoalbuminemia is common in SICU. The hypoalbuminemia patients increase risk of infective complication especially pulmonary infection, acute kidney injury, and mortality.

Acknowledgement

We would like to thanks all the nurse staff to help us for data collection, Miss Kanokkarn Jantaping for data analysis and the surgical research unit for the Ethical Committee submit process.

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บทคัดย่อ **ผลของภาวะอัลบูมินในเลือดต่ำขณะรับเข้ารักษาต่อผลภาวะไม่พึงประสงค์ในหออภิบาลผู้ป่วยหนักศัลยกรรมทั่วไปในโรงพยาบาลมหาวิทยาลัยระดับตติยภูมิ**

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ภูมิหลัง: แม้ว่าอัลบูมินเป็นตัวบ่งชี้ของภาวะโภชนาการแต่ระดับของอัลบูมินมักจะต่ำในภาวะเจ็บป่วยและผลของระดับดังกล่าวยังเป็นที่ถกเถียงกัน วัตถุประสงค์ของการศึกษานี้เพื่อศึกษาผลของระดับอัลบูมินที่มีผลต่อภาวะแทรกซ้อนและการเสียชีวิตในผู้ป่วยศัลยกรรมที่รับเข้ารักษาในหออภิบาลผู้ป่วยหนักศัลยกรรม

วิธีการศึกษา: ผู้วิจัยทำการศึกษาจากระเบียนประวัติในฐานข้อมูลระหว่างปี ค.ศ. 2011 - 2013 ผู้ป่วยที่ที่รับการคัดเลือกจะได้รับการสังเกตการณ์ บันทึกระดับอัลบูมิน ความรุนแรงของโรค ชนิดของการรักษา ลักษณะของผู้ป่วยในขณะเข้ารักษาในไอซียู ผลการรักษาที่ติดตามได้แก่ระยะเวลาที่ใช้เครื่องช่วยหายใจ ระยะเวลาที่นอนโรงพยาบาลและไอซียู ภาวะแทรกซ้อนทางการหายใจ การติดเชื้อ ภาวะไตวายเฉียบพลัน การติดเชื้อของแผลผ่าตัด ภาวะเลือดออกในทางเดินอาหาร ภาวะเพ้อคลั่ง การชัก กล้ามเนื้อหัวใจตาย และการเสียชีวิต ผู้วิจัยได้ทำการแบ่งผู้ป่วยเป็น 2 กลุ่มคือระดับอัลบูมินปกติ (≥ 3.5 กรัม/ดล) และ ภาวะอัลบูมินในเลือดต่ำ (<3.5 กรัม/ดล.)

ผลการศึกษา: ผู้ป่วยจำนวน 893 คน ได้รับการติดตามและวิเคราะห์ในการศึกษานี้ ผู้ป่วยที่มีภาวะปกติและอัลบูมินในเลือดต่ำคือ 106 ราย (ร้อยละ 11.9) และ 787 ราย (ร้อยละ 88.1) ตามลำดับ หลังจากทำการปรับค่าในแบบจำลองพหุถดถอย ภาวะอัลบูมินในเลือดต่ำมีความเสี่ยงสูงอย่างมีนัยสำคัญในความเสี่ยงของการติดเชื้อ [อัตราส่วนความเสี่ยง(ความเชื่อมั่นร้อยละ 95): 2.68 (1.35 - 5.30); $p = 0.005$] โดยเฉพาะการติดเชื้อในระบบทางเดินหายใจ [2.08 (1.01 - 4.27); $p = 0.046$], ภาวะไตวายเฉียบพลัน [4.06 (1.44 - 11.47), $p = 0.008$], และการเสียชีวิต [5.92 (2.12 - 16.54); $p = 0.001$]

สรุปผลการศึกษา: อุบัติการณ์ของภาวะอัลบูมินต่ำในเลือดพบได้บ่อยในไอซียู ภาวะอัลบูมินต่ำในเลือดเพิ่มความเสี่ยงต่อการติดเชื้อโดยเฉพาะอย่างยิ่งในระบบทางเดินหายใจ ภาวะไตวายเฉียบพลันและการเสียชีวิต