

Hypoalbuminemia: a risk factor for acute kidney injury development and progression to chronic kidney disease in critically ill patients

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Abstract

Purpose The increased likelihood of poor outcomes in critically ill patients with hypoalbuminemia is well recognized. However, hypoalbuminemia remains poorly defined as an independent predictor of acute kidney injury (AKI) and stage 4 chronic kidney diseases (CKD₄). The aim of this study was to assess the role of hypoalbuminemia as an independent risk factor for AKI and CKD₄ in critically ill patients.

Design A retrospective cohort study.

Setting General intensive care unit (ICU) at Anhui Provincial Hospital, PR China.

Intervention None.

Measurements and main results We screened patients admitted to the ICU at Anhui Provincial Hospital between January 1, 2008, and October 31, 2011, and included those aged >18 years with available records of serum albumin (SA), baseline serum creatinine, and outcome data. The

exclusion criteria were: (1) patients with known AKI and CKD stage 4, 5 before ICU admission; (2) patients lost to follow-up; and (3) patients without research authorization. A total of 588 patients with available data were enrolled in the study, and 62 patients with preexisting CKD stage 4 and CKD stage 5 and 115 with preexisting AKI were excluded. Thirty patients were lost to follow-up. Ultimately, 381 patients were analyzed, 233 (61.2%) of whom developed AKI. Patients with low SA were significantly more likely than those with normal SA ($p = 0.0003$) to develop AKI, and to progress from AKI to CKD₄ ($p = 0.0229$). More patients in the AKI group than in the non-AKI group had risk factors such as hypotension, mechanical ventilation (MV), proteinuria, sepsis, nephrotoxin exposure, and high-risk surgery ($p < 0.01$). The difference in duration of MV, ICU days, ICU mortality, hospital days, and hospital mortality between the AKI and non-AKI groups was also significant ($p < 0.01$). Logistic regression showed that hypoalbuminemia was significantly associated with AKI and CKD₄ [odds ratio (OR) 1.810, 95% confidence interval (CI) 1.102–2.992, and OR 2.494, 95% CI 1.231–5.295, respectively]. After 4 years of follow-up, Kaplan–Meier analysis showed that survival in hypoalbuminemia patients was significantly shorter than in patients with normal SA ($p = 0.0393$). In the Cox proportional hazard model, hypoalbuminemia was an independent predictor of long-term mortality (hazard ratio 1.5, 95% CI 1.042–2.183, $p = 0.0291$).

Conclusion Hypoalbuminemia in critically ill patients is independently associated with an increased risk of development of AKI and AKI progressing to CKD₄.

Keywords Acute kidney injury · Chronic kidney disease (stage 4) · Hypoalbuminemia · Predictor · Survival time · Serum albumin

Min Shao and Shengyu Wang have contributed equally to this work.

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Introduction

Acute kidney injury (AKI) is a well-recognized clinical disorder in intensive care units (ICU), occurring as a complication secondary to circulatory overload, metabolic acidosis, hyperkalemia, and neurological complications [1, 2]. Studies have shown its association with increased mortality, risk of chronic kidney disease (CKD), length of hospital stay, and healthcare costs [3]. It is reported that 2147 subjects per million population per year develop AKI in the USA [4]. Furthermore, the incidence of AKI is increasing and is expected to double over the next decade with the increase in population.

Critically ill patients develop AKI at a higher rate than the general population, as they are more likely to have high-risk factors. The incidence of ICU-acquired AKI is higher than that of community-acquired kidney injury and is increasing at an alarming rate [5, 6]. Thus, early identification of risk factors is vital in improving prognosis of critically ill patients. To date, some independent risk factors for AKI have been identified, such as age, body mass index, baseline renal function, acute circulatory or respiratory failure, liver disease, infection, peripheral vascular occlusive disease, chronic obstructive pulmonary disease, chronic heart failure, lymphoma or leukemia, prior invasive procedures, and higher-risk surgery [6, 7].

Hypoalbuminemia, despite being a common laboratory finding in critically ill patients, remains a poorly defined predictor of AKI. Albumin functions as a plasma protein, binding to and transporting a wide range of endogenous and exogenous substances. It therefore plays a key role in the metabolism and also in clearance of many drugs [8]. Hypoalbuminemia is defined as a serum albumin concentration of less than 35 g/L. The reported frequency of hypoalbuminemia was 21% at the time of admission in adult hospitalized patients [9]. After admission, worsening of existing hypoalbuminemia and development of de novo hypoalbuminemia are both frequently encountered [10]. The increased likelihood of poor outcomes such as mortality, morbidity, and prolonged ICU and hospital stay in acutely ill patients with hypoalbuminemia is well recognized [11]. However, the relation between serum albumin (SA) concentration and AKI in the ICU requires further study.

Patients who survive an episode of AKI are still at high risk of progressing to advanced stages of CKD [12, 13]. About 20% of patients with an in-patient diagnosis of acute tubular necrosis progress to CKD stage 4 or greater within 18–24 months [12]. The continuity of disease from AKI to CKD to end-stage renal disease (ESRD) has been recognized by most clinicians. Nevertheless, few studies explore whether patients with hypoalbuminemia are at greater risk of CKD. The aim of this study was therefore to assess whether hypoalbuminemia is an independent factor of AKI

and CKD₄ in critically ill patients and to compare survival time between patients with hypoalbuminemia and those with normal SA.

Materials and methods

Study population

This was a retrospective study. We screened patients admitted to the ICU at Anhui Provincial Hospital between January 1, 2008, and October 31, 2011. The inclusion criteria were: (1) adult patients older than 18 years and (2) all enrolled patients with available records of serum albumin, baseline serum creatinine, and outcome data. The exclusion criteria were: (1) patients with known AKI and CKD stage 4 or CKD stage 5 before ICU admission; (2) patients lost to follow-up; and (3) patients without research authorization. A total of 588 patients with available data were enrolled. Sixty-two patients with preexisting CKD stage 4 and CKD stage 5, 115 with AKI before admission, and 30 patients lost to follow-up were excluded. Ultimately, 381 patients were analyzed (Fig. 1). This study was approved by the Ethics Committee of Anhui Provincial Hospital.

Data collection

SA was measured using the photometric method within the first 72 h of admission to the ICU. The severity of illness was estimated according to the sequential organ failure assessment (SOFA) score. Baseline demographic parameters, creatinine level during ICU, and other clinic data including comorbidities, laboratory data, length of mechanical ventilation, length of stay in ICU, and mortality were obtained from Anhui Provincial Hospital Patient Database.

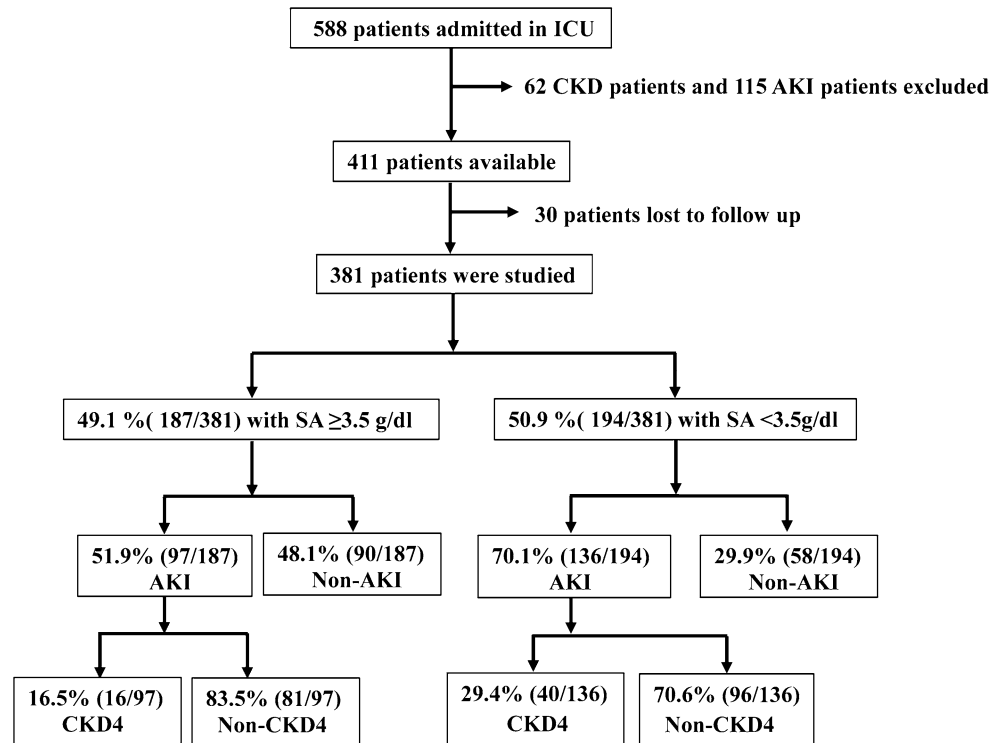
Outcomes

The primary outcome was incidence of AKI and CKD₄. AKI was defined by the Acute Kidney Injury Network criteria [14], and CKD by the Kidney Disease: Improving Global Outcomes CKD Work Group [15]. CKD₄ was defined as the first date on which estimated glomerular filtration rate decreased below 30 mL/min per 1.73 m² without increasing above 30 mL/min per 1.73 m² again [15]. The secondary outcome was survival duration of patients with low versus normal SA.

Long-term follow-up

The long-term follow-up (4 years) data for these patients were obtained from Anhui Provincial Hospital Patient Database.

Fig. 1 An overall flow diagram of the study. *AKI* acute kidney injury, *CKD* chronic kidney disease, *SA* serum albumin



Statistical analysis

The data were analyzed using JMP™ version 10 (SAS Inc., Cary, NC, USA). Chi-square test was used for the analysis of categorical variables. Student's *t* test or Mann–Whitney test was utilized to compare measurement variables. Logistic regression was used to identify variables that predict AKI and CKD₄. Kaplan–Meier method was used to compare survival time of patients with low and normal SA. Cox proportional hazard regression model was utilized to identify the independent predictors for AKI mortality. A two-sided *p* value <0.05 was considered to indicate statistical significance.

Results

Baseline demographic, clinical characteristics, and clinical outcomes between the two groups (SA \geq 3.5 g/dL and SA < 3.5 g/dL) are summarized in Table 1. Of the 381 patients included, 233 (61.2%) developed AKI, 76 (32.6%) of whom required hemodialysis or renal replacement therapy. Of patients with normal SA, 51.9% (97/187) developed AKI, compared with 70.1% (136/194) of patients with low SA. The difference was found to be statistically significant ($p = 0.0003$). The differences between groups in age, gender, BMI, serum creatinine, and comorbidities were not significant. Patients with low SA were found to have increased incidences of chronic liver disease, MV, and sepsis, and

significantly higher SOFA scores ($p < 0.001$) compared to those with normal SA. Furthermore, duration of MV in patients with low SA was longer than in those with normal SA ($p = 0.0011$), as was the duration of ICU and hospital stay ($p < 0.0001$). Hospital mortality in patients with low SA was significantly higher compared with normal SA ($p = 0.033$), while no difference was found in ICU mortality ($p = 0.065$). After 4 years of follow-up, 56/233 (24.0%) AKI patients progressed to CKD₄, including 16 in the normal-SA group and 40 in the low-SA group ($p = 0.0229$).

Table 2 shows baseline demographics, clinical characteristics, and outcomes in the AKI and non-AKI groups. Compared with patients without AKI, those with AKI were older; had more comorbidities including diabetes, hypertension, chronic liver disease, chronic lung disease, CKD ($p < 0.05$); and more high-risk factors such as hypotension, MV, proteinuria, sepsis, nephrotoxin exposure, and high-risk surgery ($p < 0.01$). The AKI patients had higher SOFA scores and serum creatinine levels than non-AKI patients. In addition, the difference in length of MV, ICU days, ICU mortality, hospital days, and hospital mortality between the two groups was significant ($p < 0.01$).

Logistic regression was used to analyze independent risk factors for AKI (Table 3). Hypoalbuminemia [odds ratio (OR) 1.810, 95% confidence interval (CI) 1.102–2.992], male sex (OR 0.409, 95% CI 0.241–0.686), nephrotoxin exposure (OR 7.642, 95% CI 2.091–38.210), mechanical ventilation (OR 1.919, 95% CI 1.148–3.234), high-risk surgery (OR 2.177, 95% CI 1.184–4.105), hypotension

Table 1 Demographic and clinical characteristics between two serum albumin levels

Variable	Serum albumin		<i>p</i> value
	≥3.5 g/dL (<i>N</i> = 187)	<3.5 g/dL (<i>N</i> = 194)	
<i>ICU admission [n (%)]</i>			
Medical	143 (76.5)	148 (76.3)	0.967
Sepsis	40 (28.0)	44 (22.7)	
MODS	28 (19.6)	27 (13.9)	
Shock	22 (15.4)	25 (12.9)	
Cardiac arrest	10 (7.0)	11 (5.7)	
Poisoning	14 (9.8)	10 (5.2)	
Other	29 (20.3)	31 (16)	0.955
Surgery	31 (16.6)	30 (15.5)	0.767
Trauma	13 (6.9)	16 (8.2)	0.634
			0.8676
<i>Demographic characteristics</i>			
Age (years)	61.8 ± 19.7	63.6 ± 18.1	0.3634
Male	124 (66.3)	124 (63.9)	0.6243
BMI [mean (SD)] (kg/m ²)	26.2 ± 6.5	25.5 ± 7.7	0.3892
<i>Comorbidities [n (%)]</i>			
Age >65 years	86 (46)	98 (50.5)	0.3768
Diabetes	53 (28.3)	49 (25.3)	0.4966
Hypertension	114 (61.0)	120 (61.9)	0.8579
Chronic liver disease	15 (8.0)	40 (20.6)	0.0005
Congestive heart failure	32 (17.1)	28 (14.4)	0.4729
Chronic lung disease	68 (36.4)	83 (42.8)	0.2003
Chronic kidney disease	60 (32.1)	58 (29.9)	0.6442
<i>Acute risk factors [n (%)] (<48 h of ICU admission)</i>			
Hypotension	14 (7.5)	22 (11.3)	0.1986
Mechanical ventilation	70 (37.4)	94 (48.5)	0.0299
Proteinuria	14 (7.5)	22 (11.3)	0.2104
Severe infection/sepsis	35 (18.7)	71 (36.6)	<0.0001
Nephrotoxin exposure	10 (5.4)	16 (8.2)	0.2737
High-risk surgery	47 (25.3)	48 (24.6)	0.8828
<i>Lab test</i>			
Serum albumin (g/dL)	4.1 ± 1.8	2.8 ± 0.4	<0.0001
Scr at ICU admission [mean (SD)] (mg/dL)	1.8 ± 1.9	1.8 ± 1.6	0.4058
<i>Score</i>			
SOFA	4.7 ± 3.5	6.6 ± 4.3	<0.0001
<i>Outcomes</i>			
Incidence of AKI [n (%)]	97 (51.9)	136 (70.1)	0.0003
Need for RRT [n (%)]	5 (2.7)	11 (5.7)	0.1510
Need for HD [n (%)]	33 (17.8)	27 (13.9)	0.2960
The length of mechanical ventilation	1.9 ± 4.4	4.5 ± 5.7	0.0011
ICU mortality [n (%)]	7 (3.7)	16 (8.3)	0.0650
ICU stay [mean (SD)] (days)	2.4 ± 4.5	4.6 ± 5.9	<0.0001
Hospital mortality [n (%)]	12 (6.4)	25 (12.9)	0.0330
Hospital stay [mean (SD)] (days)	7.7 ± 9.6	14.3 ± 16.5	<0.0001
4 years later CKD ₄ /AKI [n (%)]	16/97 (16.5)	40/136 (29.4)	0.0229

AKI acute kidney injury, BMI body mass index, CKD₄ chronic kidney disease (stage 4), RRT renal replacement therapy, Scr serum creatinine

Table 2 Clinical characteristics and outcomes between AKI and non-AKI subjects

Variable	Non-AKI (<i>N</i> = 148)	AKI (<i>N</i> = 233)	<i>p</i> value
<i>ICU admission [n (%)]</i>			
Medical	122 (82.4)	169 (72.5)	0.0698
Surgery	19 (12.9)	42 (18.0)	
Trauma	7 (4.7)	22 (9.5)	
<i>Demographic characteristics</i>			
Age (years)	58.8 ± 20.0	65.2 ± 17.7	0.0016
Male	96 (64.9)	152 (65.2)	0.9409
BMI [mean (SD)] (kg/m ²)	25.1 ± 6.1	26.4 ± 7.7	0.1012
<i>Co-morbidities [n (%)]</i>			
Age >65 years	63 (42.6)	121 (51.9)	0.0746
Diabetes	28 (18.9)	74 (31.8)	0.0058
Hypertension	70 (47.3)	164 (70.4)	<0.0001
Chronic liver disease	12 (8.1)	43 (18.5)	0.0051
Congestive heart failure	17 (11.5)	43 (18.5)	0.0688
Chronic lung disease	49 (33.1)	102 (43.8)	0.0380
Chronic kidney disease	27 (18.2)	91 (39.1)	<0.0001
<i>Acute risk factors (<48 h of ICU admission) [n (%)]</i>			
Hypotension	2 (1.4)	34 (14.6)	<0.0001
Mechanical ventilation	46 (31.1)	118 (50.6)	0.0002
Proteinuria	5 (3.4)	31 (13.3)	0.0013
Severe infection/sepsis	28 (18.9)	78 (33.5)	0.0020
Nephrotoxin exposure	3 (2.0)	23 (9.9)	0.0031
High-risk surgery	27 (18.2)	68 (29.2)	0.0161
<i>Laboratory test</i>			
Serum albumin (g/dL)	3.7 ± 2.1	3.3 ± 0.7	0.0141
Scr at ICU admission [mean (SD)] (mg/dL)	1.2 ± 1.3	2.2 ± 2.0	<0.0001
<i>Score</i>			
SOFA	3.7 ±	6.9 ± 4.3	<0.0001
<i>Outcomes</i>			
The length of MV	1.2 ± 2.2	4.5 ± 6.0	<0.0001
ICU mortality [n (%)]	2 (1.4)	21 (9.0)	0.0023
ICU stay [mean (SD)] (days)	1.5 ± 1.8	4.8 ± 6.4	<0.0001
Hospital mortality [n (%)]	3 (2.0)	34 (14.6)	<0.0001
Hospital stay [mean (SD)] (days)	6.2 ± 7.1	14.1 ± 6.2	<0.0001

AKI acute kidney injury, BMI body mass index, RRT renal replacement therapy, Scr serum creatinine

Table 3 Logistic regression for independent risk factors for AKI

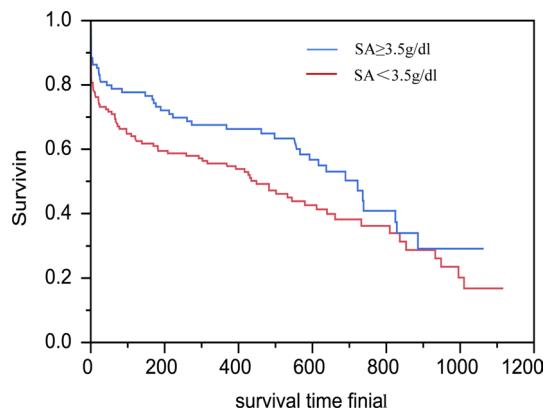
Variable	Odds ratio (95% CI)	<i>p</i> value
Age (≥65)	1.423 (0.856–2.371)	0.1733
Male	0.409 (0.241–0.686)	0.0006
Nephrotoxin exposure	7.642 (2.091–38.210)	0.0013
Mechanical ventilation	1.919 (1.148–3.234)	0.0128
High-risk surgery	2.177 (1.184–4.105)	0.0120
Serum albumin <3.5 g/dL	1.810 (1.102–2.992)	0.0191
Hypotension	12.455 (3.453–80.145)	<0.0001
Serum Scr (>1.3 mg/dL)	5.964 (3.491–10.513)	<0.0001
Chronic liver disease	1.133 (0.419–3.059)	0.8053

(OR 12.455, 95% CI 3.453–80.145), and serum creatinine (>1.3 mg/dL) on admission (OR 5.964, 95% CI 3.491–10.513) were significantly associated with AKI. However, chronic liver disease was not significant (OR 1.133, 95% CI 0.419–3.059). Table 4 shows risk factors for CKD₄. Hypoalbuminemia (OR 2.494, 95% CI 1.231–5.295), nephrotoxin exposure (OR 4.974, 95% CI 1.816–14.064), and serum creatinine (OR 5.608, 95% CI 2.637–12.955) were significantly associated with CKD₄, while age and gender were not.

After 4 years of follow-up, Kaplan–Meier survival analysis showed that patients with hypoalbuminemia died earlier than those with normal SA (Fig. 2) (*p* = 0.0393). In

Table 4 Logistic regression for independent risk factors for AKI progressing to CKD₄

Variable	Odds ratio (95% CI)	<i>p</i> value
Age (≥ 65)	1.901 (0.935–4.008)	0.0764
Male	0.692 (0.341–1.376)	0.2954
Nephrotoxin exposure	4.974 (1.816–14.064)	0.0019
Serum albumin < 3.5 g/dL	2.494 (1.231–5.295)	0.0107
Serum Scr (> 1.3 mg/dL)	5.608 (2.637–12.955)	< 0.0001

**Fig. 2** Kaplan–Meier analysis for the cumulative percentage of surviving patients at 4 years according to serum albumin levels (log-rank test, $p = 0.0393$)**Table 5** Multivariate Cox regression analysis of possible predictors for mortality in AKI patients

Variable	HR	95% CI	<i>p</i> value
Age (≥ 65)	2.657	1.822–3.927	< 0.0001
Male	0.809	0.560–1.160	0.2493
Chronic lung disease	1.509	1.056–2.152	0.0241
Serum albumin < 3.5 g/dL	1.500	1.042–2.183	0.0291
Serum Scr (> 1.3 mg/dL)	1.944	1.300–2.929	0.0014

the Cox proportional hazard model, chronic lung disease [hazard ratio (HR) 1.509, 95% CI 1.056–2.152], hypoalbuminemia (HR 1.5, 95% CI 1.402–2.183), and serum creatinine (HR 1.944, 95% CI 1.3–2.929) were strong independent predictors of long-term mortality (Table 5).

Discussion

AKI is a major health hazard affecting 10–20% of hospitalized patients. Certain patient groups are at particular risk, especially patients in the ICU, those with preexisting CKD, and patients receiving nephrotoxic agents. Any novel factor

for accurately predicting AKI would be highly advantageous. This study demonstrated that patients with hypoalbuminemia in the ICU have increased risk not only of developing AKI, but also of further progression to CKD₄. Duration of MV, length of ICU, and hospital stay, and hospital mortality are all higher in patients with low SA than in normal SA. After 4 years of follow-up, patients with hypoalbuminemia have higher mortality than those with normal SA. A Cox regression model showed that hypoalbuminemia has a significant association with AKI. Our results therefore suggest hypoalbuminemia is an independent prognostic factor for AKI and CKD₄ in the ICU.

It is well known that normal serum albumin in healthy adults is approximately 35–50 g/L. Hypoalbuminemia (SA < 3.5 g/dL) is a common phenomenon in critically ill patients as they often have comorbidities that reduce serum albumin levels. Factors that contribute to reduced serum albumin include systemic inflammation, peritoneal and urinary losses of protein, and liver synthesis dysfunction. A meta-analysis showed that hypoalbuminemia was an independent risk factor both for developing AKI and for AKI-related mortality [16]. These results are consistent with our findings. However, few studies have shown the relation between hypoalbuminemia and CKD₄ and long-term follow-up of patients with AKI.

Our study found that nearly two-thirds of patients in the ICU are at high risk of developing AKI, proving that AKI is an important health hazard in the ICU and that emphasis should be placed on identifying risk factors for its occurrence. Over the past decade, many studies have focused on the independent risk factors for AKI in specific clinical settings, such as in critically ill children, and after cardiac surgery, contrast exposure, and high-risk surgery [17–20]. Few studies have focused on occurrence of AKI in the general ICU. In addition to the high incidence of AKI, we found that patients with hypoalbuminemia had longer duration of MV, and of ICU and hospital stays. Albumin is critical for physiological function of macromolecules and carriers in vivo, and decrease of albumin in blood may cause multiple organ dysfunctions. Therefore, patients with hypoalbuminemia have more comorbidities and complications.

There are several possible mechanisms by which serum albumin protects kidney function: (a) Specific ligand-binding properties of albumin may mediate renoprotection [21]. (b) Albumin mitigates the nephrotoxicity of interleukin-2 (IL-2). Serum albumin concentration increased by approximately 1% could benefit survival of cultured renal tubular cells independently of either bound lipid or colloid osmotic pressure [22]. (c) The renoprotective action of albumin is mediated by its capabilities of scavenging reactive oxygen species, preventing oxidative damage, and binding and delivering lysophosphatidic protective acid [23]. (d) Albumin can prolong potent renal vasodilatation by reacting

with oxides of nitrogen or by binding of platelet-activating factor, which resulted in improved renal perfusion [24]. (e) Albumin can also stimulate renal tubular cell DNA synthesis via signaling pathways involving Ca^{2+} , protein kinase C, epidermal growth factor receptor, mitogen-activated protein kinases, and nuclear factor-KB [25, 26].

There is strong evidence that hypoalbuminemia is associated with poor outcomes in a variety of diseases including ESRD, surgical illness, and acute stroke [27]. Therefore, serum albumin level has been included as one of the component parameters in the Acute Physiology and Chronic Health Evaluation III score because of its importance as an outcome predictor [28].

Although our study identified hypoalbuminemia is an independent prognostic factor for AKI and AKI progressing to CKD_4 in the ICU, a study about albumin replacement showed that correction of hypoalbuminemia did not improve patient outcomes [29]. At the heart of the controversy is causality—whether hypoalbuminemia directly contributes to poor outcomes, in which case albumin replacement therapy might be beneficial, or merely serves as a marker for other “upstream” pathologic processes such as malnutrition or inflammation, in which case exogenous albumin might be ineffective in altering the clinical course.

Conclusion

Hypoalbuminemia in the general ICU is independently associated with an increased risk of development of AKI and of AKI progressing to CKD_4 .

Authors' contributions MS participated in the design and drafted the paper. SYW contributed equally with MS to the paper. PKP participated in critical review of the manuscript. MS played a principal role in the design, analysis, and preparation of the manuscript.

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Compliance with ethical standards

Conflict of interest There are no conflicts in our manuscript file.

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