RESEARCH ARTICLE

U-shape association of serum albumin level and acute kidney injury risk in hospitalized patients

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Abstract

Background

While an association between hypoalbuminemia and increased risk of acute kidney injury (AKI) is well-established, the risk of AKI development and its severity among patients with elevated serum albumin is unclear. The aim of this study was to evaluate the risk of AKI in hospitalized patients stratified by various admission serum albumin levels.

Methods

This single-center retrospective study was conducted at a tertiary referral hospital. All adult hospitalized patients who had admission albumin levels available between January 2009 and December 2013 were enrolled. Admission albumin was categorized based on its distribution into six groups ($\leq$2.4, 2.5–2.9, 3.0–3.4, 3.5–3.9, 4.0–4.4, and $\geq$4.5 mg/dL). The primary outcome was the incidence of hospital-acquired AKI (HAKI). Logistic regression analysis was performed to obtain the odds ratio of AKI for various admission albumin strata using the albumin 3.5 to 3.9 mg/dL (lowest incidence of AKI) as the reference group.

Results

Of the total 9,552 studied patients, HAKI occurred in 1,556 (16.3%) patients. The incidence of HAKI among patients with admission albumin $\leq$2.4, 2.5–2.9, 3.0–3.4, 3.5–3.9, 4.0–4.4, and $\geq$4.5 mg/dL was 18.3%, 14.3%, 15.5%, 14.2%, 16.7%, and 26.0%, respectively. After adjusting for potential confounders, admission serum albumin levels $\leq$2.4 and $\geq$4.5 mg/dL were associated with an increased risk of HAKI with odds ratios of 1.52 (95% CI 1.18–1.94) and 2.16 (95% CI 1.74–2.69), respectively. While stage 1 HAKI was significantly more frequent among patients with admission albumin $\geq$4.5 mg/dL (23.0% vs. 11.6%, P<0.001), incidence of stage 3 HAKI was higher in those with albumin $\leq$2.4 mg/dL (2.8% vs 0.3%, P<0.001).

Conclusion

Admission serum albumin levels ≤2.4 and ≥4.5 mg/dL were associated with an increased risk for HAKI. Patients with admission albumin ≥4.5 mg/dL had HAKI with a lower intensity when compared with those who had admission albumin levels ≤2.4 mg/dL.

Introduction

Acute kidney injury (AKI) is a substantial healthcare burden worldwide affecting almost 13.3 million patients per year [1, 2], associated with high morbidity and mortality, progression to chronic kidney disease (CKD), and significant healthcare costs [1–4]. AKI-related mortality has been reported to be as high as 23% or greater than 1.7 million deaths per year [1–3]. Previous studies have attempted to identify novel biomarkers of AKI, effective pharmacological interventions, and treatments to improve survival, lessen injury, or promote recovery [2, 4–10]. Most treatment strategies have been unfortunately unsuccessful [2, 7, 11]. Therefore, early identification and prevention of AKI among patients at-risk of AKI are critical.

Albumin is an important protein synthesized by the liver with multiple vital functions including osmotic pressure regulation, a carrier of poorly water-soluble molecules, antioxidant and anti-inflammatory effects [12–14]. Hypoalbuminemia is prevalent among hospitalized patients, with an incidence ranging from 16% up to 82% [12, 14–19]. Studies have shown associations of hypoalbuminemia with AKI and mortality in various clinical settings including general hospitalized patients, intensive care unit (ICU), coronary bypass surgery, emergency department, and liver transplantation [14, 15, 20–25]. Conversely, there are no studies that reported data on the incidence and effects of elevated serum albumin among patients admitted to the hospital. Thus, the objective of this study was to evaluate the risk of AKI in hospitalized patients stratified by various admission serum albumin levels.

Materials and methods

Study population

This is a single-center retrospective cohort study conducted at a tertiary referral hospital. All adult (≥18 years old) hospitalized patients who had admission albumin available between January 2009 and December 2013 at Mayo Clinic, Rochester, MN, USA were enrolled in this study. Exclusion criteria were patients who did not provide research authorization, those without serum albumin measurement within 24 hours of admission, individuals with end-stage renal disease (ESRD) and patients who had AKI at hospital admission. For patients with multiple admissions during this period, only the first hospitalization was analyzed. ESRD and the need for initiation of renal replacement therapy following acute kidney injury were identified based on ICD-9 (International Classification of Diseases, 9th) code assignment (S1 Table). This study was reviewed and approved by the Mayo Clinic Institutional Review Board. Informed consent was waived due to its minimal risk nature.

Data collection

The data collection was previously described in detail in a prior study [26]. Clinical characteristics, demographic information, and laboratory data were collected using automated retrieval from the institutional electronic medical record system. The admission serum albumin level was defined as the first serum albumin level within 24 hours of hospital admission. eGFR was

derived using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [27]. CKD was defined as a calculated eGFR < 60 mL/min/1.73m². The Charlson Comorbidity score [28] was computed for comorbidities at the time of admission. Principal diagnoses were grouped based on ICD-9 codes at admission (S2 Table).

Clinical outcomes

The primary outcome was hospital-acquired AKI (HAKI), based on the KDIGO serum creatinine criterion [29]. HAKI was defined as an increase in serum creatinine of ≥ 0.3 mg/dL within 48 hours after admission date or ≥ 1.5 times baseline within 7 days after admission date. If outpatient baseline serum creatinine was not available, the Modification of Diet in Renal Disease equation [30] was used to estimate baseline serum creatinine level, assuming normal baseline GFR of 75 mL/min/1.73m², in accordance with this guideline [29].

Statistical analysis

Continuous variables are reported as mean ± SD. All categorical variables are described as counts with percentages. Baseline demographics and clinical characteristics were compared among admission serum albumin groups, using ANOVA for continuous variables and the Chi-square test for categorical variables. We categorized admission serum albumin levels, based on its distribution at 10th, 25th, 50th, 75th and 90th percentiles, into six groups ($\leq$2.4, 2.5–2.9, 3.0–3.4, 3.5–3.9, 4.0–4.4, and $\geq$4.5 mg/dL). Serum albumin level 3.5 to 3.9 mg/dL, given the lowest incidence of AKI, was selected as the reference group (Table 1). We performed univariate analysis and then multivariable logistic regression analysis to assess the independent association between various admission albumin levels and HAKI. Odds ratio (OR) with 95% confidence interval (CI) are reported. OR was adjusted for a priori defined variables. The adjusting variables were age, sex, race, baseline eGFR, principal diagnosis, Charlson comorbidity score, comorbidities, medications, the need for vasopressor and mechanical ventilator at hospital admission, and alcohol use. Comorbidities were coronary artery disease (CAD), hypertension (HTN), diabetes mellitus (DM), congestive heart failure (CHF), peripheral vascular disease (PVD), stroke, and cirrhosis. Medications were angiotensin-converting-enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), nonsteroidal anti-inflammatory Drugs (NSAIDs) and diuretics. A two-tailed P value of <0.05 was considered statistically significant. All analyses were performed using JMP statistical software (version 10.0, SAS Institute, Cary, NC).

Results

A total of 14,075 patients with available serum albumin measurement within 24 hours were identified. Among all screened patients, 968 individuals with ESRD, 3,551 patients with AKI at admission, and 4 patients without serum creatinine measurement during hospitalization were excluded. Finally, 9,552 unique patients were enrolled in the analysis (S1 Fig).

Baseline characteristics

The baseline characteristics of the 9,552 patients with various serum albumin levels are summarized in Table 1. The distribution of serum albumin levels was as follows: $\leq$2.4 mg/dL, 672 patients (7.0%); 2.5–2.9 mg/dL, 1,231 patients (12.9%); 3.0–3.4 mg/dL, 2,147 patients (22.5%); 3.5–3.9 mg/dL, 2,654 patients (27.8%); 4.0–4.4 mg/dL, 2,086 patients (21.8%); and $\geq$4.5 mg/dL, 762 patients (8.0%%). Of the 9,552 patients, 8,613 (90%) patients were whites and 5,028 (53%) were male. Mean (±SD) age was 60±18 years. Patient comorbidities included HTN

Table 1. Baseline clinical characteristics.

Variables	All	Serum albumin level at hospital admission (mg/dl)						
		≤2.4	2.5–2.9	3.0–3.4	3.5–3.9	4.0–4.4	≥4.5	p
N	9552	672	1231	2147	2654	2086	762	
Age (year)	60±18	59±16	61±17	63±18	62±18	57±18	49±17	<0.001
Male	5028 (53)	351 (52)	652 (53)	1148 (53)	1400 (53)	1080 (52)	397 (52)	0.92
White	8613 (90)	597 (89)	1106 (90)	1943 (90)	2393 (90)	1891 (91)	683 (90)	0.77
Charlson Comorbidity Score	2.1±2.6	2.0±2.5	2.6±3.0	2.5±2.8	2.2±2.7	1.8±2.4	1.1±1.8	<0.001
GFR (ml/min/1.73m2)	87±25	93±25	90±16	86±25	85±25	86±24	92±22	<0.001
Comorbidities								
- Coronary artery disease	1576 (16)	78 (12)	192 (16)	377 (18)	519 (20)	351 (17)	59 (8)	<0.001
- Hypertension	4154 (43)	261 (39)	507 (41)	1017 (47)	1284 (48)	885 (42)	200 (26)	<0.001
- Diabetes mellitus	1752 (18)	110 (16)	253 (21)	415 (19)	552 (21)	357 (17)	65 (9)	<0.001
- Congestive heart failure	677 (7)	28 (4)	86 (7)	155 (7)	225 (8)	151 (7)	32 (4)	<0.001
- Peripheral vascular disease	238 (2)	11 (2)	46 (4)	61 (3)	65 (2)	45 (2)	10 (1)	<0.001
- Stroke	651 (7)	24 (4)	87 (7)	143 (7)	238 (9)	132 (6)	27 (4)	<0.001
- Cirrhosis	624 (7)	95 (14)	155 (13)	175 (8)	122 (5)	61 (3)	16 (2)	<0.001
Principal diagnosis								<0.001
- Cardiovascular	1579 (17)	32 (5)	133 (11)	286 (13)	560 (21)	447 (21)	121 (16)	
- Hematology/Oncology	1708 (18)	108 (16)	203 (16)	403 (19)	447 (17)	399 (19)	148 (19)	
- Infectious disease	442 (5)	85 (13)	104 (8)	124 (6)	93 (4)	28 (1)	8 (1)	
- Endocrine/Metabolic	445 (5)	28 (4)	65 (5)	105 (5)	124 (5)	102 (5)	21 (3)	
- Respiratory	561 (6)	40 (6)	92 (7)	164 (8)	154 (6)	93 (4)	18 (2)	
- Gastrointestinal/Hepatology	1699 (18)	203 (30)	313 (25)	436 (20)	436 (16)	233 (11)	78 (10)	
- Injury/Poisoning	1569 (16)	84 (13)	149 (12)	312 (15)	360 (14)	419 (20)	245 (32)	
- Other	1549 (16)	92 (14)	172 (14)	317 (15)	480 (18)	365 (17)	123 (16)_	
Urgency of admission								<0.001
- Emergent	4267 (45)	286 (43)	551 (45)	1074 (50)	1326 (50)	823 (40)	207 (27)	
- Urgent	2468 (26)	241 (36)	373 (30)	567 (26)	678 (26)	466 (22)	143 (19)	
- Elective	2817 (29)	145 (20)	307 (25)	506 (24)	650 (24)	797 (38)	412 (54)	
Surgical procedures requiring general anesthesia	3397 (36)	240 (36)	404 (33)	702 (33)	791 (30)	833 (40)	427 (56)	<0.001
Medication								
- ACEI/ARB	2878 (30)	148 (22)	305 (25)	664 (31)	896 (34)	676 (32)	189 (25)	<0.001
- Diuretics	3443 (36)	287 (43)	510 (41)	812 (38)	958 (36)	701 (34)	175 (23)	<0.001
- NSAID	1633 (17)	99 (15)	169 (14)	352 (16)	448 (17)	395 (19)	170 (22)	<0.001
Received contrast media	2970 (31)	306 (46)	490 (40)	775 (36)	821 (31)	456 (22)	122 (16)	<0.001
Received IV Fluid Bolus	1000 (10)	165 (25)	167 (14)	236 (11)	214 (8)	159 (8)	59 (8)	<0.001
Vasopressor use	459 (5)	58 (9)	72 (6)	108 (5)	97 (4)	76 (4)	49 (6)	<0.001
Mechanical ventilator	945 (10)	110 (16)	142 (12)	235 (11)	202 (8)	180 (9)	76 (10)	<0.001
Alcohol use	926 (10)	103 (15)	118 (10)	209 (10)	249 (9)	197 (9)	50 (7)	<0.001
Urine Protein (mg/dL), Median (IQR)	213 (106–463)	321 (157–668)	303 (148–617)	243 (131–509)	180-93-364)	139 (78–355)	127 (72–236)	<0.001

Continuous data are presented as mean ± SD; categorical data are presented as count (percentage)

(43%), DM (18%), CAD (16%), and CHF (7%). Prior to admission, 36% of the patients were taking diuretics, 30% were on ACEIs or ARBs, and 17% were receiving NSAIDs.

Analysis of the principle admission diagnosis showed that patients with a diagnosis of gastrointestinal tract/liver-related problems presented with low admission serum albumin levels,
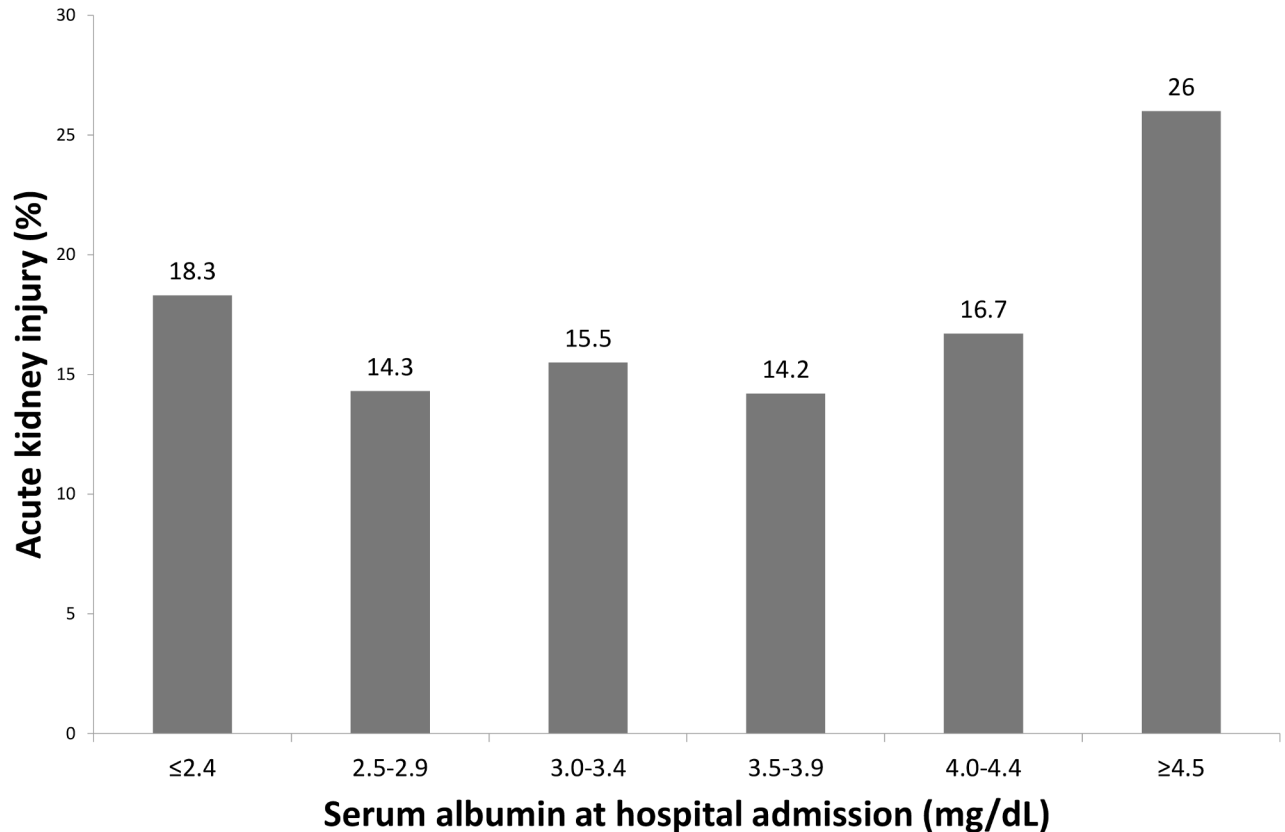
Fig 1. Hospital acquired acute kidney injury (HAKI) incidence with various admission serum albumin levels.

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while patients with trauma/injury and poisoning diagnoses presented with high admission serum albumin levels (Table 1).

Admission serum albumin levels and risk of acute kidney injury

The incidence of HAKI was 18.3%, 14.3%, 15.5%, 14.2%, 16.7%, and 26.0% in patients with admission albumin ≤2.4, 2.5–2.9, 3.0–3.4, 3.5–3.9, 4.0–4.4, and ≥4.5 mg/dL, respectively (Fig 1, Table 2). Severity and HAKI staging and the incidence of renal replacement therapy initiation after HAKI among patients with various admission serum albumin levels are

Table 2. Hospital acquired acute kidney injury (HAKI) and mortality among patients with various admission serum albumin levels.

Outcome	All (N = 9552)	Serum albumin level at hospital admission (mg/dl)						
		≤2.4 (N = 672)	2.5–2.9 (N = 1231)	3.0–3.4 (N = 2147)	3.5–3.9 (N = 2654)	4.0–4.4 (N = 2086)	≥4.5 (N = 762)	P
HAKI	1556 (16.3)	123 (18.3)	176 (14.3)	333 (15.5)	378 (14.2)	348 (16.7)	198 (26.0)	<0.001
HAKI stage								<0.001
- Stage 1	1275 (13.3)	78 (11.6)	136 (11.0)	261 (12.2)	319 (12)	306 (14.7)	175 (23.0)	
- Stage 2	188 (2.0)	26 (3.9)	18 (1.5)	44 (2.0)	45 (1.7)	34 (1.6)	21 (2.8)	
- Stage 3	93 (1.0)	19 (2.8)	22 (1.8)	28 (1.3)	14 (0.5)	8 (0.4)	2 (0.3)	
Need for renal replacement therapy	119 (1.3)	23 (3.4)	24 (2.0)	27 (1.3)	30 (1.1)	10 (0.5)	5 (0.7)	<0.001
In-hospital mortality	247 (2.6)	52 (7.7)	43 (3.5)	66 (3.1)	63 (2.4)	17 (0.8)	6 (0.8)	<0.001

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shown in Table 2. While the incidence of stage 1 HAKI among admission albumin ≥4.5 mg/dL group was significantly higher than the incidence among admission serum albumin ≤2.4 mg/dL group (23.0% vs. 11.6%, P<0.001), the incidence of stage 3 HAKI in admission serum albumin ≤2.4 mg/dL group was significantly higher than the incidence in admission serum albumin ≥4.5 mg/dL group (2.8% vs. 0.3%, P<0.001). This, in turn, translated to higher need for renal replacement therapy rate among patients with serum albumin ≤2.4 mg/dL when compared with patients with admission serum albumin of ≥4.5 mg/dL (3.4% vs. 0.7%, P<0.001).

Among 9,552 patients, 247 (2.6%) died in the hospital. The lowest in-hospital mortality (0.8%) was observed in patients with admission serum albumin of ≥4.0 mg/dL (Table 2). The in-hospital mortality progressively increased with lower levels of admission serum albumin. The highest crude in-hospital mortality was observed in patients with admission serum albumin ≤2.4 mg/dL.

To assess whether admission serum albumin levels were independently associated with HAKI development, logistic regression models were built, using 3.5–3.9 mg/dL (lowest incidence of HAKI) as a reference range. In unadjusted analysis, an admission albumin ≤2.4 mg/dL, 4.0–4.4 mg/dL, and ≥4.5 mg/dL were associated with an increased risk of HAKI with odds ratios of 1.35 (95% CI 1.07–1.68), 1.21 (95%CI 1.03–1.41), and 2.11 (95%CI 1.74–2.57), respectively. When adjusted for potential confounders, admission albumin ≤2.4 mg/dL and ≥4.5 mg/dL were associated with an increased risk of HAKI with odds ratios of 1.52 (95% CI 1.18–1.94) and 2.16 (95%CI 1.74–2.69), respectively (Table 3). Admission serum albumin levels between 2.5 and 4.4 mg/dL were not predictive for the development of HAKI during hospitalization.

Subgroup analysis based on cirrhosis and chronic kidney disease

Of the 9,552 patients, 624 patients had cirrhosis. After adjusting for potential confounders, admission serum albumin ≤2.4 mg/dL were associated with an increased risk of HAKI in patients with cirrhosis with adjusted OR of 2.60 (95% CI 1.32–5.21) (Table 4). In analyses of 8,928 non-cirrhotic patients, admission serum albumin ≤2.4 and ≥ 4.5 mg/dL were associated with an increased risk of HAKI with adjusted odds ratios of 1.34 (95% CI 1.01–1.76) and 2.19 (95%CI 1.75–2.74), respectively (Table 4).

Within the main cohort, 959 patients had chronic kidney disease. In this subgroup, there was no significant association between admission serum albumin and HAKI (Table 5).

Table 3. Odds ratios for the association between admission serum albumin levels and hospital acquired acute kidney injury (HAKI) occurrence.

Serum albumin level at hospital admission (mg/dl)	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	Adjusted OR (95% CI)	p
≤2.4	1.35 (1.07–1.68)	0.01	1.52 (1.18–1.94)	0.001
2.5–2.9	1.004 (0.83–1.22)	0.96	1.05 (0.85–1.29)	0.65
3.0–3.4	1.11 (0.94–1.30)	0.21	1.10 (0.93–1.31)	0.27
3.5–3.9	1 (ref)		1 (ref)	
4.0–4.4	1.21 (1.03–1.41)	0.02	1.18 (0.99–1.39)	0.06
≥4.5	2.11 (1.74–2.57)	<0.001	2.16 (1.74–2.69)	<0.001

Adjusted for age, sex, race, Charlson Comorbidity score, baseline GFR, history of coronary artery disease, hypertension, diabetes mellitus, congestive heart failure, peripheral vascular disease, stroke, cirrhosis, principal diagnosis, use of ACEI/ARB, NSAID, diuretics, the need for vasopressor and mechanical ventilator at hospital admission, alcohol use

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Table 4. Odds ratios for the association between admission serum albumin levels and hospital acquired acute kidney injury (HAKI) occurrence in subgroups of patients with and without cirrhosis.

Serum albumin level at hospital admission (mg/dl)	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	Adjusted OR (95% CI)	p
Cirrhosis (n = 624)				
≤2.4	1.87 (1.04–3.37)	0.03	2.60 (1.32–5.21)	0.006
2.5–2.9	0.83 (0.47–1.46)	0.52	1.07 (0.56–2.02)	0.84
3.0–3.4	1.16 (0.69–1.98)	0.58	1.07 (0.59–1.97)	0.82
3.5–3.9	1 (ref)		1 (ref)	
4.0–4.4	0.60 (0.26–1.29)	0.20	0.79 (0.32–1.87)	0.60
≥4.5	0.44 (0.07–1.69)	0.25	0.53 (0.07–2.32)	0.42
Without cirrhosis (n = 8928)				
≤2.4	1.11 (0.86–1.43)	0.41	1.34 (1.01–1.76)	0.04
2.5–2.9	0.96 (0.78–1.18)	0.72	1.05 (0.83–1.31)	0.68
3.0–3.4	1.06 (0.90–1.26)	0.50	1.09 (0.91–1.31)	0.34
3.5–3.9	1 (ref)		1 (ref)	
4.0–4.4	1.26 (1.07–1.48)	0.006	1.19 (0.99–1.41)	0.06
≥4.5	2.24 (1.83–2.73)	<0.001	2.19 (1.75–2.74)	<0.001

Adjusted for age, sex, race, Charlson Comorbidity score, baseline GFR, history of coronary artery disease, hypertension, diabetes mellitus, congestive heart failure, peripheral vascular disease, stroke, principal diagnosis, use of ACEI/ARB, NSAID, diuretics, the need for vasopressor and mechanical ventilator at hospital admission, alcohol use

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Discussion

In this large retrospective cohort study, we demonstrated that admission serum albumin levels ≤2.4 and ≥4.5 mg/dL were associated with an increased risk for HAKI. Admission serum albumin levels ≥4.5 mg/dL were associated with the highest risk (2.16-fold) of HAKI. However, compared with serum albumin levels ≤2.4 mg/dL, the severity of HAKI among patients with serum albumin ≥4.5 mg/dL was significantly lower. Among patients with cirrhosis, only admission serum albumin level ≤2.4 mg/dL was associated with risk of HAKI (2.60-fold).

Several factors can influence hypoalbuminemia including inflammation and/or infections, malnutrition and/or protein-losing disorders, oxidative stress, cancer cachexia, and liver

Table 5. Odds ratios for the association between admission serum albumin levels and hospital acquired acute kidney injury (HAKI) occurrence in subgroups of patients with chronic kidney disease (n = 959).

Serum albumin level at hospital admission (mg/dl)	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	Adjusted OR (95% CI)	p
≤2.4	2.06 (0.97–4.23)	0.06	2.17 (0.93–4.88)	0.07
2.5–2.9	1.00 (0.57–1.71)	0.99	1.08 (0.59–1.93)	0.79
3.0–3.4	1.23 (0.84–1.81)	0.29	1.21 (0.80–1.83)	0.37
3.5–3.9	1 (ref)		1 (ref)	
4.0–4.4	1.06 (0.70–1.59)	0.78	1.12 (0.72–1.74)	0.61
≥4.5	0.77 (0.32–1.66)	0.52	0.84 (0.33–1.92)	0.69

Adjusted for age, sex, race, Charlson Comorbidity score, baseline GFR, history of coronary artery disease, hypertension, diabetes mellitus, congestive heart failure, peripheral vascular disease, stroke, cirrhosis, principal diagnosis, use of ACEI/ARB, NSAID, diuretics, the need for vasopressor and mechanical ventilator at hospital admission, alcohol use

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dysfunction [31–37]. Thus, hypoalbuminemia may indicate the severity of an underlying disease and/or a marker of malnutrition [13, 38]. In addition, studies have also consistently demonstrated that hypoalbuminemia is independently associated with increased risks of AKI development and mortality in critically ill, among various surgical and other settings [14, 15, 20–25]. In addition to the albumin role in maintenance of plasma volume by preserving colloid osmotic pressure, it also provides many physiological effects, including coupling and carrying various endogenous and exogenous toxic substances, scavenging free radicals, maintaining capillary membrane permeability, providing a physiological reservoir of nitric oxide, imparting an anti-inflammatory effect, and finally inhibition of apoptosis [15, 38, 39]. Several studies have suggested that serum albumin can preserve the kidneys from toxic agents and maintain optimal oncotic pressure and kidney perfusion [40–45]. In multivariate analysis adjusted for potential confounders, we confirmed an association between admission hypoalbuminemia and an increased risk of AKI among general hospitalized patients.

Our study is the first to demonstrate an association between elevated admission serum albumin ≥4.5 mg/dL and an increased risk of HAKI. Elevated serum albumin levels have been described in patients with dehydration and high protein diet consumption [46–48]. Although high-protein diets can increase albumin synthesis [49], albumin only increases by small increments, and high serum albumin levels ≥4.5 mg/dL are mostly caused by volume depletion [46–48]. Thus, intravascular volume depletion likely explains the association between elevated admission serum albumin and an increased risk of HAKI in our study. This likely explains why the HAKI severity in the setting of elevated serum albumin ≥4.5 mg/dL is lower, compared with HAKI occurring in patients with serum albumin levels ≤2.4 mg/dL who may have more severe underlying illness. The findings from our study demonstrated that hospital mortality did not reflect the U-shaped association as seen with AKI incidence. On the contrary, death was lowest for those with serum albumin levels ≥4 mg/dL. Additionally, these findings support our assumption that increased rates of lower stages of AKI among patients with serum albumin levels ≥4.5 mg/dL are mostly due to volume depletion and of minor clinical relevance.

Although there is potential evidence that use of intravenous albumin may reduce the risk of AKI in particular patient population, such as off-pump coronary artery bypass surgery (CABG) patients [50], it is unclear if normalization of admission serum albumin can reduce the risk of in-hospital AKI among general hospitalized patients. In a meta-analysis of 17 randomized controlled trials assessing the effect of albumin as a resuscitation fluid for patients with sepsis [51], the use of albumin-containing solutions was associated with lower mortality compared with other fluid resuscitation regimens. Lee et al. [50] recently conducted a trial assessing effect of exogenous albumin on the incidence of postoperative AKI in patients undergoing off-pump CABG with a preoperative albumin level <4.0 g/dL and demonstrated that 20% exogenous albumin administration immediately before the operation increased urine output during surgery and decreased the risk of postoperative AKI [50]. A recent retrospective cohort study by Yu et al. suggested that replacement of albumin after the development of AKI may also promote renal recovery [14]. In a meta-analysis of eleven randomized clinical trials evaluating the effect of hyperoncotic colloids on AKI in a wide variety of clinical scenarios including ascites, surgery, sepsis and spontaneous bacterial peritonitis, Wiedermann et al. demonstrated that administration of hyperoncotic albumin solutions could decrease the odds of AKI by 76% [52]. Thus, future prospective trials assessing the potentially beneficial effect of intravenous albumin administration on the risk of AKI among general hospitalized patients are warranted.

There are some limitations that bear mentioning. First, this is a single-center, historical cohort study. The patient population in our cohort is comparatively homogeneous consisting

of predominantly whites. Future studies with a more diversified population and more comprehensive clinical information are needed to better assess the effects of admission serum albumin levels on HAKI. Second, the number of patients with the diagnosis of cirrhosis was small (N = 624). The failure to observe any association between elevated admission serum albumin levels ≥4.5 mg/dL and HAKI in patients with cirrhosis could be due to small sample size (Type II error). Lastly, based on the retrospective nature of this design a causal relationship could not be inferred.

In summary, this study demonstrates that admission serum albumin levels ≤2.4 and ≥4.5 mg/dL are associated with an increased risk for in-hospital AKI. However, AKI in patients with admission serum albumin ≥4.5 mg/dL is less severe and has a lower association with higher mortality rates, compared to those with serum albumin levels ≤2.4 mg/dL.

Supporting information

S1 Table. ICD-9 for end-stage renal disease.
(DOCX)

S2 Table. ICD-9 for principal diagnosis.
(DOCX)

S1 Fig. Study flow.
(DOCX)

S1 Dataset. Dataset.
(JMP)

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