

Causal relationship between hypoalbuminemia and acute kidney injury

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Abstract

Our meta-analysis published in 2010 provided evidence that low levels of serum albumin (hypoalbuminemia) are a significant independent predictor of acute kidney injury (AKI) and death following AKI. Since then, a large volume of additional data from observational clinical studies has been published further evaluating the relationship between serum albumin and AKI occurrence. This is an updated review of the literature to re-evaluate the hypothesis that hypoalbuminemia is independently associated with increased AKI risk. Eligible studies published from September 2009 to December 2016 were sought in PubMed (MEDLINE) and forty-three were retained, the great majority being retrospective observational cohort studies. These included a total of about 68000 subjects across a diverse range of settings, predominantly cardiac surgery and acute coronary interventions, infectious diseases, transplant surgery, and cancer. Appraisal of this latest data set served to conclusively corroborate and confirm our earlier hypothesis that lower serum albumin is an independent predictor both of AKI and death after AKI, across a range of clinical scenarios. The body of evidence indicates that hypoalbuminemia may causally contribute to development of AKI. Furthermore, administration of human albumin solution has the potential to prevent AKI; a randomized, controlled study provides evidence that correcting hypoalbuminemia may be renal-protective. Therefore, measurement of serum albumin to diagnose hypoalbuminemia may help identify high-risk patients who may benefit from treatment with exogenous human albumin. Multi-center, prospective, randomized, interventional studies are warranted, along with basic research to define the mechanisms through

which albumin affords nephroprotection.

Key words: Acute kidney injury; Acute renal failure; Hypoalbuminemia; Mortality; Prevention

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Core tip: The relationship between hypoalbuminemia and acute kidney injury (AKI)-related morbidity/mortality is now confirmed. This association is consistently evident in a wealth of observational studies conducted across a wide range of clinical settings, and suggests a causal link. Prospective studies adequately powered to assess severe AKI, mortality and causality are needed, as is evaluation of the trigger and appropriate target serum levels and albumin dose necessary to confer renal protection. Basic research is also warranted to define the mechanisms through which albumin affords nephroprotection. Serum albumin should be measured to identify patients with increased AKI risk who may benefit from treatment correcting underlying hypoalbuminemia.

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INTRODUCTION

Acute kidney injury (AKI), formerly referred to as acute renal failure (ARF), is a syndrome in which kidney function deteriorates rapidly over a period of hours or days. It is characterized by increased serum creatinine level (of ≥ 0.3 mg/dL in 48 h and/or 1.5-fold within 7 d) and decreased urine output. The staging system for AKI has evolved from the risk, injury, failure, loss of kidney function, and end-stage kidney disease (RIFLE) criteria, to the acute kidney injury network (AKIN) scheme, and most recently to the Kidney Disease Improving Global Outcomes (KDIGO) score (for a review of AKI diagnosis, see^[1]).

AKI is an acute systemic disease with major consequences for other organs besides the kidney, and is associated with significant short-term effects (e.g., fluid, electrolyte, and acid-base abnormalities, uremic toxin accumulation, cytokine elevation, systemic inflammation) and long-term adverse outcomes (e.g., myocardial infarction, chronic kidney disease, end-stage renal disease, mortality)^[2,3]. Need for dialysis and transplantation are increased, as is length of hospital stay^[4,5].

AKI is recognized as a major global health problem, with increasing incidence in both high- and low-income nations, and high associated healthcare costs^[6,7]. It is a common disorder encountered in multiple settings,

occurring in 21% of hospital admissions worldwide and in more than 13 million people each year^[5], especially critically ill patients^[1], where incidence rates well above 50% were reported in the recent prospective AKI-EPI study^[8]. The International Society of Nephrology's Oby25 initiative sets out a framework to eradicate preventable death from AKI by 2025 based on the 5 Rs: Risk, Recognition, Response, Renal Support, and Rehabilitation^[5].

The etiology of AKI includes community-acquired causes (common in developing countries), such as infections (malaria, dengue, gastroenteritis, pneumonia), acute glomerular disease, underlying chronic disease (kidney, cardiac, diabetes), and trauma, as well as hospital-acquired causes (especially in industrialized nations), such as surgery, hemorrhage, infection, septic shock, drug toxicity, and underlying chronic disease (reviewed in^[7]). The pathogenesis of AKI is multifactorial and several risk factors have been identified, both modifiable (e.g., dehydration, intravascular volume depletion, hypotension, anemia, hypoxia, body mass index) and non-modifiable (e.g., age, sex, prior invasive procedures, high-risk surgery, and comorbid disorders such as cancer and lung, liver or gastrointestinal disease)^[5,9].

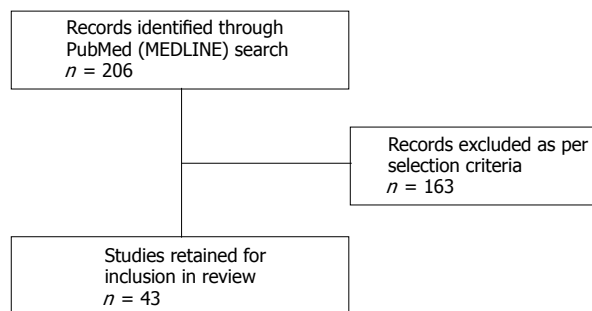
Hypoalbuminemia, or low levels of serum albumin (often defined as < 3.5 - 4.0 g/dL or ≤ 3.5 mmol/L), is a well-established risk factor for increased morbidity and mortality^[10] and has also been associated with an increased risk of AKI occurrence; it is modifiable by infusion of human albumin solution. Our systematic review and meta-analysis published in 2010 found evidence, from observational studies in surgical and ICU patients, that low serum albumin is a significant independent predictor of AKI [pooled odds ratio (OR) = 2.34, 95%CI: 1.74-3.14] and of death following AKI (pooled OR = 2.47, 95%CI: 1.51-4.05)^[9].

Since then, a large volume of additional clinical data has been published on hypoalbuminemia and AKI, across an expanded range of settings. Therefore, we performed an updated review of the literature to define the role of hypoalbuminemia and albumin administration in the development and prevention of AKI. Detailed discussion of the potential nephroprotective mechanisms of albumin is beyond the scope of the present review but was the subject of a separate review^[11].

RESEARCH

Literature was sourced by conducting a systematic search of the PubMed (MEDLINE) database using phrases and synonyms for "kidney injury", "albumin", "hypoalbuminemia" and "mortality" (Table 1). The search was limited to articles published from September 2009 to December 2016 (inclusive), *i.e.*, since the end of the search period used in our 2010 systematic review^[9].

Only studies meeting the following selection criteria



	Cardiac	Infection	Transplant	Cancer	Other	Total
No. of studies	8	8	6	6	15	43
PRO, INT	1	-	-	-	-	1
PRO, OBS	2	1	1	1	-	5
RET, OBS	5	7	5	5	15	37
Total studies	4344	5623	5032	7028	46235	68262

Figure 1 Flow diagram summarizing the literature screening and the designs and settings of the included studies. The numbers presented for the sizes of the data sets include control populations and do not represent only patients with acute kidney injury/acute renal failure and/or hypoalbuminemia. OBS: Observational; INT: Interventional; PRO: Prospective; RET: Retrospective.

Table 1 PubMed (MEDLINE) search strategy

- 1 Search: "acute kidney injury" OR AKI OR "acute renal failure" OR ARF
- 2 Search: mortality OR survival OR death
- 3 Search: "serum albumin" OR hypoalbuminemia* OR hypoalbuminaemia*
- 4 Filter: Publication date from 2009/09/01 to 2016/12/31
- 5 Search: #1 AND #2 AND #3 AND #4

The search was conducted without applying restrictions to language or publication type.

were retained for inclusion in the present review: Reported original data on associations between serum albumin levels (absolute levels, variously defined by authors as < 3.5 or < 3.0 or < 2.5 g/dL, or percentage prevalence of hypoalbuminemia) and the development of AKI (during the different observation periods, depending on the indication), or on mortality in patients with both AKI and hypoalbuminemia.

From included studies, data were extracted on clinical setting/population, study design and size, assessment of albumin levels/hypoalbuminemia, AKI occurrence/risk, and mortality (Tables 2-5).

INCLUDED STUDIES

Our search retrieved a total of 206 entries on PubMed (MEDLINE). The titles and abstracts of all hits were screened and research articles that did not report relevant data as stated in the selection criteria were discarded, along with any review/opinion articles. A total of 43 research articles were retained for inclusion in the present review (Figure 1). The great majority of these were retrospective in nature (37 of 43 studies), except

for a single interventional randomized controlled trial (RCT), conducted in off-pump coronary artery bypass (OPCAB) surgery, and five prospective observational studies: Two in cardiac settings, one in HIV-infected patients, one in liver transplant recipients, and one in patients with hepatocellular carcinoma (HCC) with ascites. In total, the data set comprises approximately 68000 patients across a range of clinical settings, as described and discussed below.

CARDIAC SURGERY AND ACUTE CORONARY INTERVENTIONS

AKI is a common complication following cardiac surgery, and is associated with significant morbidity, mortality, and hospital costs (reviewed in^[12]). We identified eight studies, involving more than 4000 subjects, which explored the role of albumin in AKI occurring after cardiac surgery or coronary intervention (Table 2).

In the only interventional drug study among the 43 retained articles, Lee *et al.*^[13] recently performed a single-center, randomized, parallel-arm, double-blind trial which evaluated the effects of exogenous 20% human albumin solution vs saline on the incidence of postoperative AKI in adult patients with hypoalbuminemia (< 4.0 g/dL) undergoing off-pump coronary artery bypass (OPCAB) surgery. Dose was 100, 200, or 300 mL immediately before surgery, stratified according to preoperative serum albumin level of 3.5-3.9, 3.0-3.4, or < 3.0 g/dL, respectively. In the saline group, rate of postoperative AKI (KDIGO-criteria patients) appeared to increase as postoperative serum albumin level decreased (29.5%, 31.1%, 41.7% for 3.5-3.9, 3.0-3.4, < 3.0 g/dL, respectively). The incidence of postoperative AKI (KDIGO criteria) was

Table 2 Included studies on cardiac surgery and acute coronary interventions

Ref.	Population/ setting	Study design	Overall study size	Albumin measurement	Hypoalbuminemia-related outcomes	
					AKI/ARF	Mortality
Lee <i>et al</i> ^[13]	OPCAB surgery	Prospective RCT	220	Postoperative albumin 3.5-3.9 vs < 3.0 g/dL	Increased rate: 29.5% vs 41.7%. AKI rate lower with albumin vs control (13.7% vs 25.7%; <i>P</i> = 0.048)	ND
Grodin <i>et al</i> ^[20]	Acute heart failure	Prospective, observational	456	Admission albumin level (continuous and stratified by median \geq 3.5 g/dL)	NS	NS
Moguel-González <i>et al</i> ^[16]	Cardiac surgery	Prospective, observational, longitudinal	164	Preoperative albumin < 4.0 g/dL	Increased risk: OR = 3.852 (95%CI: 1.101-13.473; <i>P</i> = 0.063)	ND
Lee <i>et al</i> ^[14]	OPCAB surgery	Retrospective, observational, propensity score matching	1182 (incl. 323 matched pairs)	Preoperative albumin < 4.0 g/dL	Increased risk: OR = 1.83 (95%CI: 1.27-2.64); <i>P</i> = 0.001; propensity analysis: OR = 1.62 (95%CI: 1.12-2.35); <i>P</i> = 0.011	ND
Murat <i>et al</i> ^[21]	ACS and PCI	Retrospective, observational	890	Albumin level at hospitalization	Low albumin (3.52 g/dL vs 3.94 g/dL) predictive of CI-AKI: OR = 0.177 (95%CI: 0.080-0.392; <i>P</i> < 0.001)	ND
Kim <i>et al</i> ^[17]	Thoracic aorta repair with CPB	Retrospective, observational, propensity score matching	702 (incl. 183 matched pairs)	Preoperative albumin < 4.0 g/dL	Increased risk: OR = 2.50 (95%CI: 1.39-4.50; <i>P</i> = 0.002)	ND
Findik <i>et al</i> ^[15]	CAB surgery	Retrospective, observational	530	Preoperative albumin < 3.5 g/dL	Increased rate: OR = 1.661 (95%CI: 1.037-2.661); <i>P</i> = 0.035	ND
Go <i>et al</i> ^[19]	LVAD implantation	Retrospective, observational	200	< 2.5 g/dL (low) vs 2.5-3.5 g/dL (mid-range) vs > 3.5 g/dL (normal)	Increased ARF: 42.9% vs 16.5% vs 17.3%; <i>P</i> = 0.05	NS

ACS: Acute coronary syndromes; AKI: Acute kidney injury; ARF: Acute renal failure; CI-AKI: Contrast-induced acute kidney injury; CPB: Cardiopulmonary bypass; LVAD: Left ventricular assist device; ND: Not disclosed; NS: Not significant; OPCAB: Off-pump coronary artery bypass; OR: Odds ratio; PCS: Percutaneous coronary intervention; RCT: Randomized, controlled trial.

Table 3 Included studies on infectious diseases

Ref.	Population/ setting	Study design	Overall study size	Albumin measurement	Hypoalbuminemia-related outcomes	
					AKI/ARF	Mortality
Prakash <i>et al</i> ^[22]	HIV	Prospective, observational	3540	Albumin level at hospitalization	ND	2.14 g/dL in patients who died vs 3.2 g/dL in survivors; <i>P</i> < 0.001
Vannaphan <i>et al</i> ^[34]	Severe falciparum malaria	Retrospective, observational	915	Albumin < 3.5 g/dL	Associated with ARF (<i>P</i> < 0.001)	ND
Lee <i>et al</i> ^[39]	Acute viral hepatitis A	Retrospective, observational	391	Albumin < 3.0 g/dL	OR = 8.24 (95%CI: 2.53-26.86; <i>P</i> < 0.0001)	ND
Lee <i>et al</i> ^[35]	Scrub typhus	Retrospective, observational	246	Admission albumin < 3.0 g/dL vs \geq 3.0 g/dL	Increased rate of non-oliguric ARF (40.4% vs 11.1%; <i>P</i> < 0.001)	ND
Mehra <i>et al</i> ^[40]	Dengue fever	Retrospective, observational	223	Admission Albumin level	Lower albumin (2.65 g/dL) in patients with vs without AKI (3.09 g/dL; <i>P</i> < 0.001)	ND
Vikrant <i>et al</i> ^[36]	Scrub typhus	Retrospective, observational	174	Admission albumin level	ND	2.4 g/dL in patients who died vs 2.9 g/dL in survivors; <i>P</i> < 0.001
Ceylan <i>et al</i> ^[41]	Antibiotic therapy	Retrospective, observational	112	Albumin level at start of colistin therapy	Lower albumin (2.4 g/dL vs 2.7 g/dL) predicts colistin-induced AKI: OR = 0.643 (95%CI: 0.415-0.994; <i>P</i> = 0.047)	ND
Trimarchi <i>et al</i> ^[37]	H1N1 pneumonia	Retrospective, observational	22	Albumin level at study inclusion	NS	ARF in 10 of 12 deaths: 1.82 g/dL in patients who died vs 2.61 g/dL in survivors; <i>P</i> < 0.01

AKI: Acute kidney injury; ARF: Acute renal failure; ND: Not disclosed; OR: Odds ratio; NS: Not significant.

lower in the albumin group compared with the saline group (17.6% vs 31.7%; *P* = 0.031). Multivariate

Table 4 Included studies on transplant surgery

Ref.	Population/setting	Study design	Overall study size	Albumin measurement	Hypoalbuminemia-related outcomes	
					AKI/ARF	Mortality
Tinti <i>et al</i> ^[45]	Liver transplantation	Prospective, observational	24	Preoperative albumin level	Lower albumin (3.1 g/dL vs 3.7 g/dL) predictive of ARF (<i>P</i> = 0.02)	ND
Moore <i>et al</i> ^[48]	Renal transplantation	Retrospective, observational	2763	Albumin < 4.0 g/dL	Predictive of transplant failure: HR = 1.71 (95%CI: 1.18-2.49; <i>P</i> < 0.001)	ND
Sang <i>et al</i> ^[46]	LDLT	Retrospective, observational, propensity score matching	998 (incl. 249 matched pairs)	Albumin < 3.0 g/dL vs ≥ 3.0 g/dL before surgery	Albumin < 3.0 g/dL associated with increased AKI: OR = 0.42 (95%CI: 0.28-0.64; <i>P</i> < 0.001)	Survival rate lower with postoperative albumin < 3.0 g/dL (<i>P</i> = 0.02)
Park <i>et al</i> ^[47]	LDLT	Retrospective, observational	538	Preoperative albumin level	Albumin < 3.5 g/dL: OR = 1.76 (95%CI: 1.05-2.94; <i>P</i> = 0.032)	ND
Yang <i>et al</i> ^[49]	Renal transplantation	Retrospective, observational	375	Preoperative albumin < 3.5 g/dL vs 3.5-3.9 g/dL vs 4.0-4.4 g/dL vs ≥ 4.5 g/dL	Lowest risk of graft failure with ≥ 4.5 g/dL: HR = 0.536 (<i>P</i> = 0.029) vs < 3.5 g/dL	ND
Chen <i>et al</i> ^[44]	Liver transplantation	Retrospective, observational, matching	334 (incl. 118 matched pairs)	Preoperative albumin ≤ 3.5 g/dL	OR = 2.785 (95%CI: 1.427-5.434; <i>P</i> = 0.003); risk factor for posttransplantation AKI or ARF	ND

AKI: Acute kidney injury; ARF: Acute renal failure; HR: Hazard ratio; LDLT: Living donor liver transplantation; ND: Not disclosed; OR: Odds ratio.

Table 5 Included studies on cancer

Ref.	Population/setting	Study design	Overall study size	Albumin measurement	Hypoalbuminemia-related outcomes	
					AKI/ARF	Mortality
Hsu <i>et al</i> ^[51]	HCC with ascites	Prospective, observational	591	Albumin < 3.3 g/dL	Independently associated with ARF: OR = 7.3 (95%CI: 1.47-35.7; <i>P</i> = 0.009)	ND
Kim <i>et al</i> ^[50]	Gastric cancer surgery	Retrospective, observational	4718	Preoperative albumin < 4.0 g/dL	Independent predictor of AKI: OR = 1.40 (95%CI: 1.11-1.77; <i>P</i> = 0.005)	ND
Mizuno <i>et al</i> ^[55]	Chemotherapy-induced hypotension	Retrospective, observational	972	Hypoalbuminemia defined as ≤ 3.5 g/dL	Associated with low BP: OR = 1.497 (95%CI: 1.070-2.095; <i>P</i> = 0.019). Low BP associated with AKI	ND
Lahoti <i>et al</i> ^[56]	AML or HR-MDS	Retrospective, observational	537	Albumin level at baseline (median 3.3 g/dL)	Hypoalbuminemia predictive of AKI: OR = 0.7 (95%CI: 0.5-0.99; <i>P</i> = 0.049)	ND
Haynes <i>et al</i> ^[57]	Multiple myeloma	Retrospective, observational	107	Albumin ≥ 3.5 g/dL vs < 3.5 g/dL	ND	Higher albumin predictive of survival: HR = 0.56 (95%CI: 0.35-0.91; <i>P</i> = 0.02)
Fischler <i>et al</i> ^[59]	Cancer	Retrospective, observational	103	Albumin level at start of CVVHDF	ND	Low albumin (median 2.5 g/dL vs 3.05 g/dL) associated with mortality: OR = 3.341 (95%CI: 1.229-9.077); <i>P</i> = 0.02

AKI: Acute kidney injury; AML: Acute myelogenous leukemia; ARF: Acute renal failure; BP: Blood pressure; CVVHDF: Continuous venovenous hemodiafiltration; HCC: Hepatocellular carcinoma; HR: Hazard ratio; HR-MDS: High-risk myelodysplastic syndrome; ND: Not disclosed; OR: Odds ratio.

logistic regression revealed a renal-protective effect of albumin therapy (OR = 0.42, 95%CI: 0.21-0.83; *P* = 0.012). Administration of albumin increased urine output during surgery (median 550 mL vs 370 mL; *P* = 0.006). No differences were observed between the two groups in the incidence of severe AKI, need for renal replacement therapy (RRT), or mortality.

These findings are interesting for a number of reasons. First, the inverse relationship apparent between serum albumin level and postoperative AKI rate, in the setting of a randomized double-blind trial, provides the highest-quality and most compelling evidence yet that

serum albumin level is an independent driver of AKI risk. This corroborates an earlier retrospective analysis in 1182 consecutive adult patients undergoing OPCAB, conducted by the same group^[14]. Moreover, the data from Lee *et al*^[13] further underline the importance of the relationship between albumin level and renal health, as correction of hypoalbuminemia by exogenous albumin supplementation resulted in smaller increases in serum creatinine and conferred a degree of protection against AKI occurrence. That no significant treatment effect on severe AKI was observed (≥ KDIGO stage 2) might reflect an underpowered analysis due to the relatively

low sample size/event rate. Alternatively, either albumin supplementation is beneficial only in milder AKI, or the dosing regimen was insufficient.

Lee *et al.*^[13] did not investigate the mechanism(s) underlying the renal-protective effect they observed with albumin administration but speculated whether this might be attributable to augmentation of intravascular volume over correction of hypoalbuminemia. Indeed, both hemodynamic and pharmacodynamic mechanisms may contribute to the beneficial renal effects of albumin, supporting a possible causal link. Pharmacodynamic properties of human albumin with renal-protective potential include mitigation of nephrotoxicity of medications, restoration of balanced net fluid balance, protection against loss of glycocalyx, and maintenance of glomerular filtration (reviewed in^[11]). Further studies are needed to ascertain in which clinical indications such properties might be beneficial. In addition, data from large-scale RCTs are needed to define trigger and target levels and dosing for pre-emptive albumin therapy as a strategy for protecting against postoperative renal morbidity and mortality.

Whereas in the RCT performed by Lee *et al.*^[13] no differences were evident between the albumin and saline treatment groups with respect to subsequent need for RRT or mortality, precedent does exist for the impact of albumin level on both of these outcomes. Findik *et al.*^[15] recently performed a retrospective review of data collected prospectively from 530 adults with normal renal function who underwent isolated CAB surgery. Their analysis divided the patient population based on preoperative serum albumin level and found that RRT ($P = 0.018$) and death within 30 d (6.8% vs 2.4%; $P = 0.037$) after surgery were more frequent in the group with albumin < 3.5 g/dL. Mean duration of ventilatory support (7.9 h vs 11.4 h; $P = 0.001$), ICU stay (66.0 h vs 59.0 h; $P = 0.026$), and hospital stay (7.7 d vs 7.1 d; $P = 0.022$) were also greater in the lower albumin group.

Beyond CAB surgery, a prospective, observational, longitudinal study of 164 adult patients undergoing any type of elective cardiac surgery used univariate logistic regression analysis to identify low serum albumin (< 4 g/dL), among other variables [high preoperative blood urea nitrogen (BUN), creatinine, and uric acid], as a major risk factor for postoperative development of AKI^[16]. Similarly, Kim *et al.*^[17] also identified preoperative albumin level < 4.0 g/dL as an independent risk factor for AKI in 183 patients who underwent surgery on the thoracic aorta with cardiopulmonary bypass (CPB) and subsequently developed AKI, matched by propensity score with controls without AKI. The authors suggested that correction of preoperative hypoalbuminemia might protect against AKI in the studied population. However, when patients converted to CPB were included in the randomized analysis performed by Lee *et al.*^[13], the effect of albumin treatment was unclear. Further research is needed to evaluate the effects of exogenous albumin treatment in patients undergoing

cardiac surgery with CPB, though such studies will be complicated by the fact that CPB itself is associated with AKI and contributes to its pathogenesis (reviewed in^[18]).

In a single-center, retrospective review, Go *et al.*^[19] aimed to establish the impact of different serum albumin strata (< 2.5 g/dL, low; 2.5-3.5 g/dL, mid-range; > 3.5 g/dL, normal) on outcomes after left ventricular assist device (LVAD) implantation in 200 patients. Consistent with findings in cardiac surgery patients, lower albumin was associated with significantly increased rates of postoperative ARF (Table 2) and prolonged hospitalization (median 28.5 d vs 16 d vs 15.5 d; $P = 0.008$). Survival at 6 mo, 1 year, and 5 years appeared to reflect albumin levels (79%, 79%, 49% with low; 84%, 78%, 51% with mid-range; 94%, 88%, 60% with normal), though this trend was not statistically significant ($P = 0.22$). The authors concluded that hypoalbuminemia (in this case defined as < 2.5 g/dL) should not be considered a contraindication to LVAD candidacy, and called for more data on the utility of albumin levels for predicting morbidity and mortality after LVAD implantation.

Two studies reported data on albumin levels in patients undergoing acute coronary interventions. In a prospective, observational study of 456 acute heart failure patients undergoing decongestive therapy, no significant associations were found between serum albumin levels at admission and clinical outcomes, either short-term (worsening renal function, worsening heart failure, clinical decongestion by 72 h) or longer-term (60-d mortality, re-hospitalization, unscheduled emergency room visits)^[20]. The authors concluded that serum albumin levels might not be relevant in guiding decongestion strategies. They also acknowledged that their post-hoc analysis used a carefully selected cohort drawn from the DOSE-AHF and ROSE-AHF trials that were inadequately powered to detect clinical end points according to baseline albumin, and that their findings may not be generalizable. A separate study, by Murat *et al.*^[21], retrospectively looked at the impact of serum albumin levels on AKI occurrence in a cohort of 890 patients with acute coronary syndromes (ACS) treated with percutaneous coronary intervention (PCI). Serum albumin was inversely associated with AKI risk and, along with a number of other variables [age, female gender, creatinine kinase-myocardial band, and glomerular filtration rate (GFR)], was independently predictive of AKI occurrence. This was the first such report in ACS patients receiving PCI and requires confirmation by prospective, randomized trial. Nonetheless, these preliminary findings suggest that measurement of serum albumin, widely available and relatively inexpensive, should be included in the risk stratification of ACS patients before undergoing PCI.

INFECTIOUS DISEASES

Our review identified eight studies conducted across a total of more than 5500 subjects with infections and

data on albumin levels and renal injury (Table 3). The only prospective study was an observational analysis of AKI in HIV-seropositive adults^[22]. AKI was noted in 138/3540 (3.9%) patients and in most cases was AKIN stage II (42.1%) or III (48.5%). Mean serum albumin at baseline was 2.92 g/dL. Low serum albumin was one of few variables found to be significantly associated with death of HIV-infected patients following AKI. Prerenal factors (*e.g.*, clinical/laboratory evidence of volume depletion or reduced renal blood flow), ischemic acute tubular necrosis (ATN), and sepsis were among the most frequent causes of AKI in this population. These observations are consistent with clinical trials suggesting efficacy and mortality benefit of albumin therapy for volume resuscitation in sepsis patients^[23-30], as well as mechanistic data indicating a role for albumin in preservation of renal tubular cells^[31-33].

The largest study on AKI occurrence in an infectious disease setting to be published during the review period was a 10-year retrospective analysis of AKI occurrence in 915 severe falciparum malaria patients^[34]. AKI is a major contributor to morbidity and mortality in severe malaria infection, and hypoalbuminemia (< 3.5 g/dL) was significantly more prevalent in patients with AKI (135/195; 69%) vs those without AKI (308/720; 43%). The authors concluded that although causality could not be deduced, correction of ARF risk factors such as hypoalbuminemia should be incorporated into the management of patients with severe malaria.

Two retrospective studies reported associations between serum albumin level and AKI outcomes in scrub typhus infection. Lee *et al.*^[35] divided a population of 246 adults with scrub typhus into two groups based on serum albumin level. Their analysis revealed that serum albumin < 3.0 g/dL was closely related to AKI occurrence as well as various other complications (*e.g.*, confusion, pulmonary edema, pleural effusion, arrhythmia), leading to longer mean hospital stay (additional 5.5 d) and higher direct hospital costs (additional United States \$1222). Whereas this study found no difference in mortality with lower vs higher albumin (overall deaths 9/246; 3.7%), a subsequent study by Vikrant *et al.*^[36] did detect a difference. This later study was smaller overall than that conducted by Lee *et al.*^[35] but provided a larger cohort of scrub typhus patients with AKI and substantially more deaths occurred (28/174; 16.1%), providing greater power to assess mortality. Mean serum albumin was 2.8 g/dL and hypoalbuminemia, again defined as < 3.0 g/dL, was present in 56.9% of study subjects. Serum albumin was significantly higher in survivors vs non-survivors (mean 2.9 g/dL vs 2.4 g/dL; $P = 0.001$).

An association between lower serum albumin and mortality has also been observed in critically compromised patients with H1N1 pneumonia. In a 2-mo, retrospective, ICU study, both hypoalbuminemia and AKI were significantly associated with death ($P < 0.01$), and serum albumin appeared to be lower in those with vs without AKI (1.95 g/dL vs 2.59 g/dL), though this

difference did not reach statistical significance in this small cohort ($n = 22$)^[37]. Larger, multivariate analysis is required to confirm these results. The authors suggested that rhabdomyolysis (life-threatening muscle disintegration) is likely to be the main pathophysiologic mechanism of renal dysfunction in this setting, and a separate study subsequently linked hypoalbuminemia with AKI in patients with severe rhabdomyolysis^[38].

Other reports on low serum albumin as a predictive factor for AKI include a chart review and multivariate analysis of data from 391 patients with acute viral hepatitis A^[39]. AKI was present in 45 (11.5%) patients, and the AKI group had significantly decreased albumin levels compared with the non-AKI group at presentation (mean 3.3 g/dL vs 3.8 g/dL; $P < 0.0001$) and at peak during illness (mean 2.7 g/dL vs 3.4 g/dL; $P < 0.0001$). Among 223 patients with dengue fever, AKI developed in 24 (10.8%) and was associated with lower serum albumin (2.65 g/dL vs 3.09 g/dL; $P < 0.001$)^[40]. Low serum albumin (median 2.4 g/dL vs 2.7 g/dL) has also been shown to be independently predictive of acute renal injury in patients receiving antibiotic therapy with colistin ($n = 112$)^[41], consistent with previous observations^[42,43].

TRANSPLANT SURGERY

Hypoalbuminemia is common before and after liver transplantation, especially in patients with cirrhosis^[44], and there is a growing body of research exploring the implications of this. Our searches retrieved six relevant studies (including > 5000 subjects) published since September 2009 that reported albumin levels in relation to AKI occurrence after transplantation (Table 4). Four of these were in the setting of liver transplantation (approximately 2000 subjects), while 2 studies focused on renal transplant recipients. All six studies were non-interventional and all except one were conducted retrospectively.

In the only prospective study, data on 24 patients were collected from health records before, during and after deceased donor orthotopic liver transplantation (OLT)^[45]. Reduced pre-OLT serum albumin level was found to be associated with ARF (RIFLE classification), whereas no other pre-OLT parameters (*e.g.*, creatinine, GFR, serum sodium, serum bilirubin) were. Interestingly though, higher Model for End-Stage Liver Disease (MELD) score (mean 22 vs 18; $P = 0.02$) was also associated with AKI, leading the authors to speculate that the significance of hypoalbuminemia and higher MELD score as risk factors in this population might reflect the close relationship between renal and hepatic function in cirrhosis.

The largest of the three retrospective, observational studies assessing hypoalbuminemia in liver transplantation was a propensity score analysis of 998 consecutive living donor liver transplantation (LDLT) patients in a single center^[46]. This analysis aimed to ascertain the influence of early postoperative serum

albumin level on subsequent development of AKI. Serum albumin < 3.0 g/dL within 48 h postoperatively was identified by multivariate analysis as an independent risk factor for AKI (AKIN or RIFLE classification; Table 4), the first such report in the setting of LDLT. Furthermore, ICU ($P = 0.006$) and hospital ($P < 0.001$) stays were prolonged in the low albumin group and overall mortality was also higher ($P = 0.02$), making this one of the few studies retained from our literature review to report data associating serum albumin level with mortality. The findings of Sang *et al.*^[46] are consistent with an earlier, smaller retrospective study by Chen *et al.*^[44] in which multivariable analysis of 118 matched pairs of liver transplantation patients with/without postoperative renal injury demonstrated that preoperative hypoalbuminemia (≤ 3.5 g/dL) was strongly predictive of AKI within the first week after surgery. Similarly, Park *et al.*^[47] also identified by multivariate analysis that preoperative serum albumin < 3.5 g/dL was an independent, modifiable risk factor for AKI (RIFLE classification) in patients ($n = 538$) undergoing LDLT. Interestingly, the authors also identified MELD score > 20 as a significant risk factor for post-LDLT AKI (OR = 2.01, 95%CI: 1.17-3.44; $P = 0.011$), as in the study by Tinti *et al.*^[45], providing further evidence of renal-hepatic interactions in patients undergoing liver transplantation.

Notwithstanding the inherent limitations of retrospective, observational analysis, Sang *et al.*^[46] postulated that, when considering their results together with evidence accruing from other studies, hypoalbuminemia may be one of the major contributors to AKI development. Park *et al.*^[47] noted the reported nephroprotective capacity of albumin, through enhanced renal perfusion and reduced apoptosis/increased proliferation of renal tubular cells^[31-33]. However, they questioned whether exogenous augmentation of serum albumin could modify renal dysfunction within a short timeframe and reduce the risk of postoperative AKI. Sufficiently powered, prospective, interventional, randomized trials will be required to answer this question. Additional research will also be needed to further elucidate the mechanism(s) by which albumin can positively influence renal function, in LDLT surgery and other settings.

Fewer studies provide evidence on albumin levels in renal transplantation; however, these studies enrolled more subjects than those discussed above in the setting of liver transplantation. One large retrospective study, by Moore *et al.*^[48], analyzed data from 2763 adult kidney transplant recipients who were enrolled into the Long Term Efficacy and Safety Surveillance study and survived for ≥ 12 mo post transplantation. Multiple regression analysis revealed that hypoalbuminemia in the preceding 6 mo was independently associated with renal transplant failure, both in the death-censored analysis [< 3.5 g/dL, hazard ratio (HR) = 2.19, 95%CI: 1.58-3.05; $P < 0.001$] and overall (Table 4). Yang *et al.*^[49] also found a relationship between serum albumin level and likelihood of renal graft failure. In their single-

center study of 375 renal transplant recipients, the relative risk of graft failure was lowest in the group with highest serum albumin (≥ 4.5 g/dL) before transplantation. Chronic rejection (36.2%) and delayed graft function (12.8%) were most frequent in patients with albumin < 3.5 g/dL, though these results were not statistically significant. The authors concluded that hypoalbuminemia before kidney transplantation is associated with more serious complications and worse short- and long-term graft outcomes.

CANCER

An association between hypoalbuminemia and AKI morbidity/mortality has also been noted in cancer studies. We identified six relevant studies published during the search period, involving a total of more than 7000 patients, the majority of whom had gastric cancer^[50] (Table 5).

One of these studies was prospective ($n = 591$) and included data on incidence and risk factors of AKI in a subset of 87 patients with HCC with ascites undergoing transarterial chemoembolization (TACE) at a single center^[51]. Lower serum albumin was more common in HCC patients with vs without ascites (mean 3.2 g/dL vs 3.8 g/dL; $P < 0.001$). Furthermore, hypoalbuminemia (< 3.3 g/dL) occurred in 82% vs 38% of ascitic HCC patients who did ($n = 11$) vs did not ($n = 76$) develop AKI after TACE ($P = 0.009$). Logistic regression analysis among HCC patients with ascites found that hypoalbuminemia was the only risk factor independently predictive of post-TACE AKI. Based on earlier reports, the authors speculated whether nephroprotection by albumin might result from increased renal blood flow and GFR^[52], decreased changes in electrolyte and serum creatinine levels^[52], or plasma expansion^[53,54].

The largest retained study in cancer patients was a retrospective analysis of AKI occurrence after partial or total gastrectomy for gastric cancer ($n = 4718$)^[50]. Multivariate analysis identified hypoalbuminemia (< 4 g/dL), along with male gender, hypertension, chronic obstructive pulmonary disease, use of diuretics, vasopressors, or contrast agents, and packed red blood cell transfusions, as an independent predictor of postoperative AKI (Table 5). Prevalence of hypoalbuminemia tended to increase with severity of AKI (KDIGO staging). The authors acknowledged that the mechanisms through which hypoalbuminemia causes AKI are not fully understood, but noted that albumin plays a critical role in maintaining the integrity and function of renal tubular cells^[32,33].

Smaller retrospective studies also found significant associations between serum albumin level and AKI development in cancer settings. Mizuno *et al.*^[55] demonstrated significantly lower serum albumin in patients receiving cisplatin as first-line chemotherapy who had low ($n = 229$) vs normal ($n = 743$) blood pressure (mean 3.73 g/dL vs 3.87 g/dL; $P = 0.001$), suggesting that hypoalbuminemia associates with low blood pressure,

leading to renal hypoperfusion and thereby promoting ischemic AKI. Hypoalbuminemia was similarly associated with AKI in patients with acute myelogenous leukemia or high-risk myelodysplastic syndrome undergoing induction chemotherapy ($n = 537$; 187 with AKI)^[56]. In a 20-year, single-center, retrospective study of patients with multiple myeloma and acute severe renal failure ($n = 107$), serum albumin ≥ 3.5 g/dL was one of three factors (along with use of chemotherapy, and dialysis independence) found to be independently associated with survival^[57], though serum albumin is already incorporated into the International Staging System for multiple myeloma^[58]. A recent multivariate analysis of 103 consecutive ICU patients with cancer (any type) and AKI revealed low albumin level to be statistically associated with in-hospital mortality, leading to the conclusion that hypoalbuminemia (and presumably correction thereof) must be considered before initiating RRT in cancer patients^[59].

OTHER INDICATIONS

The majority of the recent studies generating data on hypoalbuminemia and AKI occurrence were conducted in the settings of cardiac/coronary interventions, infectious diseases, transplantation, or cancer, as described above. However, a further fifteen studies, all retrospective and observational in nature and involving a total of more than 46000 patients, also reported data on albumin levels and kidney outcomes, across numerous other patient populations.

By far the largest albumin data set among all of the literature retained for this review was a retrospective analysis of 37143 patients in the American College of Surgeons National Surgical Quality Improvement Program who underwent primary total knee arthroplasty (TKA) and had serum albumin data available^[60]. Mortality was higher in patients with albumin < 3.5 g/dL vs ≥ 3.5 g/dL (0.64% vs 0.15%; OR = 3.17, 95%CI: 1.58-6.35; $P = 0.001$), as were AKI (0.32% vs 0.06%, OR = 5.19, 95%CI: 1.96-13.73; $P = 0.001$) and a range of other major perioperative complications. The authors drew encouragement from these findings since hypoalbuminemia may be more easily modifiable than other risk factors (*e.g.*, morbid obesity). Results from two subsequent studies also involving thousands of patients undergoing TKA (primary^[61] or revision^[62]) were consistent with these findings.

In a recent analysis of 408 patients with amyloidosis, serum albumin < 2.5 g/dL at admission was highly associated with requirement for RRT within 30 d of autologous stem cell transplantation ($P < 0.001$)^[63]. A smaller study in amyloidosis patients receiving high-dose melphalan with stem cell transplantation yielded similar results^[64]. Recent evidence in other clinical scenarios comes from isolated studies involving a total of more than 2500 patients. Hypoalbuminemia has been associated with AKI-related morbidity/mortality in patients with severe rhabdomyolysis^[38], pyogenic liver

abscess^[65], contrast-induced nephropathy^[66], hospital-acquired AKI^[67,68], and in critically ill patients requiring continuous RRT^[69], geriatric patients^[70-72], and those undergoing open ventral hernia repair^[73].

Taken together, the recent evidence discussed herein clearly demonstrates that hypoalbuminemia is an important consideration for AKI risk in a broad range of patients. However, each clinical scenario is multifactorial and presents its own complexities, and comorbidities that might also impact the development of AKI and thus be confounders in assessing the relative importance/contribution of serum albumin level in AKI. In diverse clinical settings there is a need for controlled, interventional studies to evaluate exogenous albumin therapy aimed at correcting hypoalbuminemia and reducing the risk of subsequent AKI, mortality, and other adverse outcomes. Also required will be mechanistic studies to define the pathways involved in nephroprotection by albumin.

LIMITATIONS

Limitations of this review include the fact that most of the included studies were observational with patient populations in the various clinical settings that are still quite heterogeneous. In addition definitions of AKI were often creatinine-dependent and based on different classification systems for AKI including RIFLE, AKIN, and KDIGO. As the systematic search of the literature was restricted to PubMed (MEDLINE), additional studies may be missing.

CONCLUSION

The association between hypoalbuminemia and development of AKI and subsequent morbidity/mortality can be regarded as confirmed. This robust association is consistently evident in a wealth of observational studies conducted across a wide range of clinical settings and involving tens of thousands of patients, and may be interpreted as an indication of a causal link.

Furthermore, a prospective RCT conducted in cardiac surgery patients, demonstrated for the first time that correction of low albumin level is associated with lower increase in creatinine, suggesting improved renal function with human albumin therapy and also supporting a causal link. These observations justify further interventional studies with albumin therapy, in cardiac surgery (including CPB) and other settings, such as transplantation other than liver or renal. Multi-center, prospective studies adequately powered to assess severe AKI, mortality and causality would be valuable, as would evaluation of the appropriate trigger and target serum levels and albumin dose necessary to confer renal protection. Basic research is also warranted to define the mechanisms through which albumin affords protection from renal injury. Moreover, because the development of AKI in high-risk patients is multifactorial, modification of a single risk factor might

not be sufficient for prevention. Therefore, further research is needed to advance our understanding of the combinatorial nature of AKI pathogenesis.

In the meantime, the large volume of data already available underscores the need to be alert to risk factors for AKI. Serum albumin level should be monitored to aid early identification of patients who may be at increased risk and who may stand to benefit from treatment to correct hypoalbuminemia.

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