

Clinical research

Serum albumin level as a predictor of contrast-induced acute kidney injury following coronary angiography

Jayakumar Sreenivasan¹, Muhammad S. Khan², Qiyu Wang², Sagar Ranka³, Tauseef Akhtar², Jishanth Mattumpuram², Rohit Agrawal², Min Zhuo⁴, Wilbert S. Aronow¹, Neha Yadav²

¹Department of Cardiology, Westchester Medical Center, Valhalla, USA

²Department of Medicine, John H. Stroger Jr. Hospital of Cook County, Chicago, USA

³Department of Cardiology, Kansas University Medical Center, KC, USA

⁴Department of Nephrology, Beth Israel Deaconess Medical Center, Boston, MA

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Corresponding author:

Jayakumar Sreenivasan
Department of Cardiology
Westchester Medical Center
United States
E-mail: jayakumars101@gmail.com

Abstract

Introduction: The association between serum albumin level and the risk of contrast-induced acute kidney injury (CI-AKI) after coronary angiography has not been well established.

Material and methods: A retrospective chart review was performed for all patients who underwent coronary angiography with or without percutaneous coronary intervention (PCI) at a tertiary care medical center over a period of 5 years. CI-AKI was defined as an absolute increase in creatinine of 0.3 mg/dl from baseline within 48 h of contrast exposure. Mean pre-procedural albumin level was compared between patients who developed CI-AKI and those who did not. The optimal cut-off point was obtained from the receiver operating characteristic (ROC) curve and univariate multiple logistic regression analysis was used to assess the associated risk of CI-AKI.

Results: Among 1319 patients (females = 32.3%, mean age: 58.2 ± 13.6 years) included in the study, 201 (15.2%) developed CI-AKI. Baseline serum albumin (3.5 vs. 3.8 gm/dl, $p < 0.001$) was significantly lower in patients who developed CI-AKI. ROC curve analysis revealed an optimal cutoff value for serum albumin of 3.85 gm/dl to predict CI-AKI with 67.2% sensitivity and 52.2% specificity (area under the curve (AUC) = 0.62, $p < 0.001$). Serum albumin < 3.85 gm/dl is significantly associated with higher risk of developing CI-AKI (adjusted odds ratio (AOR) = 1.5, 95% CI: 1.1–2.1, $p = 0.02$).

Conclusions: Serum albumin < 3.85 gm/dl is an independent predictor of CI-AKI in patients undergoing coronary angiography.

Key words: contrast media, kidney diseases, percutaneous coronary intervention, hypoalbuminemia, coronary angiography.

Introduction

Percutaneous coronary intervention (PCI) is the preferred treatment modality for acute coronary syndromes and progressive symptomatic coronary artery disease refractory to medical management across all age groups [1–3]. Contrast-induced acute kidney injury (CI-AKI) is one of the common complications of PCI [4]. Pathophysiology of CI-AKI is poorly understood [5]. Animal models have shown a pattern of acute tubular necrosis among patients with CI-AKI; however, the mechanism of tubular damage is unclear [5, 6]. Contrast causing direct chemical damage to

the tubular cells, contrast-induced local inflammation and cellular damage, and contrast-induced vasoconstriction causing renal tissue hypoxia are a few of the suggested mechanisms of CI-AKI [5, 6]. There are emerging data to suggest that CI-AKI may be of less clinical significance in patients undergoing contrast computed tomography (CT) studies [7]. However, CI-AKI remains a significant cause of morbidity and mortality in patients undergoing coronary angiography with or without coronary intervention [8]. The development of severe acute kidney injury (AKI) after contrast exposure is associated with short-term complications including the requirement for urgent renal replacement therapy, which has a high in-hospital mortality as well as worse long-term renal outcomes [8, 9]. In 2004, Mehran *et al.* proposed a risk score for prediction of CI-AKI after PCI, which includes hypotension, intra-aortic balloon pump (IABP) use, congestive heart failure, age > 75, anemia, diabetes and baseline renal function [10, 11]. Most of these universal risk factors of CI-AKI are largely non-modifiable and irreversible. Therefore, it is important to recognize the association of some novel risk factors such as hypoalbuminemia with the development of CI-AKI, which can potentially be modified to reduce the incidence and sequelae of CI-AKI. Serum and urine albumin levels have been evaluated as potential markers of poor prognosis and predictors of various inflammatory diseases [12, 13].

In our study, we aimed to evaluate the association of serum albumin level with the incidence of CI-AKI in patients undergoing coronary angiography.

Material and methods

Data source

We conducted an extensive retrospective electronic chart review of all patients who underwent coronary angiography with or without percutaneous coronary intervention (PCI) at John H. Stroger Jr. Hospital of Cook County, Chicago, USA between January 2012 and December 2016. Patients with end stage renal disease (ESRD) at the time of the procedure and those who did not have a pre-procedural serum albumin level (defined as the serum albumin level within a month prior to the procedure) were excluded. A total of 1319 patients were included in the study. Clinical and laboratory characteristics were obtained by chart review. This study was approved by John H. Stroger Jr. Hospital of Cook County institutional research board (IRB) (Approval License Number – CCH IRB ID: 17-606). IRB waived the requirement for informed consent due to the retrospective chart review study design.

Definitions

The Acute Kidney Injury Network (AKIN) criteria for AKI, as defined as ≥ 0.3 mg/dl rise in creatinine from baseline within 48 h of exposure to a nephrotoxic agent was used as the definition for CI-AKI in our study [14]. It is acknowledged that there is no consistent definition of CI-AKI among epidemiological studies. There is also no universal definition of hypoalbuminemia, and in our study, we did not use any pre-defined serum albumin level as a classification criterion. Instead, the optimal cut-off value for serum albumin level was obtained from receiver operating characteristic (ROC) curve analysis.

Statistical analysis

Mean pre-procedural albumin level was compared between CI-AKI and non-CI-AKI groups by using the independent sample *t*-test. ROC curve analysis was performed to obtain the optimal cut-off point for maximal sensitivity and specificity. Area under the curve (AUC) was estimated to define the discriminatory power of the optimal cut-off value of the serum albumin level. AUC of 0.5 indicates no discriminatory power for the test under consideration and AUC closer to or more than 0.7 is considered as good discriminatory power for any test. Patients were then further classified into a low serum albumin group and a normal serum albumin group using this cut-off value for serum albumin level. Baseline demographic characteristics were compared using the independent sample *t*-test for continuous variables, and the Pearson χ^2 test for categorical variables. Univariate multiple logistic regression analysis was used to assess the risk of CI-AKI associated with age, previous diagnosis of heart failure, access type (radial vs. femoral), pre-procedural hemoglobin level, cardiogenic shock and baseline chronic kidney disease. All *p*-values are 2-sided and a *p*-value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS software (SPSS Inc., Chicago, IL).

Results

Among the 1319 patients (females = 32.3%, mean age: 58.2 ± 13.6 years) who were included in our study, 201 (15.2%) developed CI-AKI. Baseline serum albumin (3.5 vs. 3.8 gm/dl, $p < 0.001$) was significantly lower in the CI-AKI group. As shown in Table I, which includes all baseline characteristics and outcomes of the study population, patients with a serum albumin level < 3.85 gm/dl had a higher incidence of CI-AKI (20.2%) compared to the group with a normal serum albumin level (10.1%) ($p < 0.001$). There was a higher proportion of African Americans and congestive heart failure

Table I. Baseline characteristics and outcomes of study population

Baseline characteristics and outcomes	Subgroups	Total (n = 1319)	Hypoalbuminemia		P-value
			No (n = 668)	Yes (n = 651)	
Mean age [years]		58.2 ±13.6	58.1 ±15.7	58.3 ±11.1	0.76
Female		425 (32.2%)	191 (29.3%)	234 (35.0%)	0.02
Race/ethnicity:	African American	613 (46.5%)	268 (41.2%)	345 (51.6%)	< 0.001
	Caucasian	279 (21.2%)	164 (25.2%)	115 (17.2%)	
	Hispanic	229 (17.4%)	123 (18.9%)	106 (15.9%)	
	Asian	156 (11.8%)	73 (11.2%)	83 (12.4%)	
Current smoking		546 (41.4%)	281 (43.2%)	265 (39.7%)	0.11
Hypertension		983 (74.5%)	510 (78.3%)	473 (70.8%)	< 0.001
Diabetes mellitus		472 (35.8%)	222 (34.1%)	250 (37.4%)	0.11
Prior CAD, stroke or CABG		399 (30.3%)	211 (30.4%)	188 (28.1%)	0.14
Prior heart failure		294 (22.3%)	127 (19.5%)	167 (25.0%)	0.01
Mean LVEF (%)		48.7 ±17.1	50.7 ±16.2	46.8 ±17.8	< 0.001
Statin use		561 (42.5%)	276 (42.4%)	285 (42.7%)	0.48
Prior CKD:	No CKD	581 (44.0%)	289 (44.4%)	292 (43.7%)	< 0.001
	Stage 2 (GFR 61 to 90)	519 (39.3%)	276 (42.4%)	243 (36.4%)	
	Stage 3 (GFR 31 to 60)	166 (12.6%)	75 (11.5%)	91 (13.6%)	
	Stage 4 (GFR 15 to 30)	42 (3.2%)	7 (1.1%)	35 (5.2%)	
	Stage 5 (GFR less than 15)	11 (0.8%)	4 (0.6%)	7 (1.0%)	
Clinical presentation:	Stable angina	186 (14.1%)	109 (16.7%)	77 (11.5%)	< 0.001
	Unstable angina	332 (24.4%)	175 (26.9%)	147 (22.0%)	
	Non-STEMI	429 (32.5%)	216 (33.2%)	213 (31.9%)	
	STEMI	140 (10.6%)	57 (8.8%)	83 (12.4%)	
	Heart failure	219 (16.6%)	83 (12.7%)	136 (20.4%)	
Cardiogenic shock at presentation or within 24 h		40 (3.0%)	15 (2.3%)	25 (3.7%)	0.08
Intra-aortic balloon pump use		18 (1.4%)	3 (0.5%)	15 (2.2%)	< 0.001
No percutaneous coronary intervention		902 (68.4%)	433 (66.5%)	469 (70.2%)	0.46
No. of coronary stents:	1	309 (23.4%)	165 (25.3%)	144 (21.6%)	0.46
	2	90 (6.8%)	45 (6.9%)	45 (6.7%)	
	3	15 (1.1%)	6 (0.9%)	9 (1.3%)	
	4	3 (0.2%)	2 (0.3%)	1 (0.1%)	
Mean contrast volume [ml]		125.4 ±86.8	130.6 ±90.3	120.3 ±82.9	0.07
Contrast volume use [ml]	< 100	698 (52.9%)	327 (50.2%)	371 (55.5%)	0.30
	101–200	404 (30.6%)	210 (32.3%)	194 (29.0%)	
	201–300	169 (12.8%)	86 (13.2%)	83 (12.4%)	
	301–400	34 (2.6%)	19 (2.9%)	15 (2.2%)	
	> 400	14 (1.1%)	9 (1.4%)	5 (0.7%)	
Mean baseline Hb [gm/dl]		13.1 ±2.0	13.5 ±1.9	12.6 ±2.0	< 0.001

Table I. Cont.

Baseline characteristics and outcomes	Subgroups	Total (n = 1319)	Hypoalbuminemia		P-value
			No (n = 668)	Yes (n = 651)	
Mean GFR [ml/h]		86.5 ±31.6	87.7 ±27.8	85.2 ±35.0	0.14
Mean pre-procedural creatinine [mg/dl]		1.1 ±0.6	1.0 ±0.5	1.1 ±0.7	< 0.001
Acute kidney injury		201 (15.2%)	66 (10.1%)	135 (20.2)	< 0.001
Requirement for new hemodialysis		12 (0.9%)	1 (0.2%)	11 (1.6%)	0.03
Requirement for blood transfusion		24 (1.8%)	8 (1.2%)	16 (2.4%)	0.08
Length of hospital stay		5.2 ±5.1	4.6 ±4.4	5.7 ±5.6	< 0.001

CABG – coronary artery bypass grafting, CAD – coronary artery disease, CKD – chronic kidney disease, GFR – glomerular filtration rate, LVEF – left ventricular ejection fraction, STEMI – ST elevation myocardial infarction.

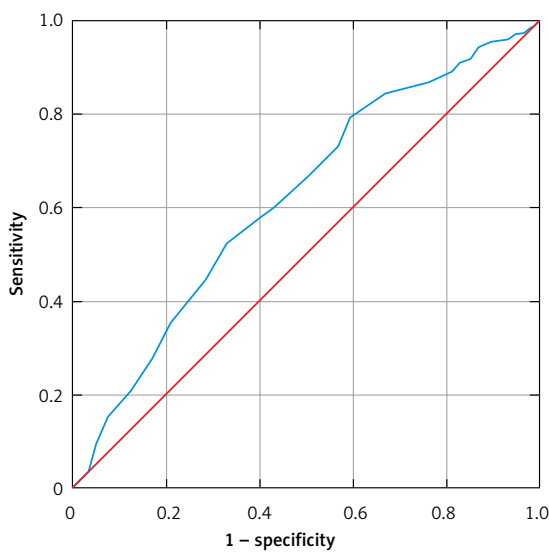


Figure 1. Receiver operating curve analysis. Receiver operating curve analysis of pre-procedural serum albumin for predicting contrast-induced acute kidney injury

Diagonal segments are produced by ties.

patients in the low serum albumin group. Mean baseline hemoglobin level was lower in the low serum albumin group, and this group had a higher composition of patients with at least stage 3 chronic kidney disease (CKD), defined as estimated glomerular filtration rate (eGFR) < 60 ml/min. Length of hospital stay was significantly longer in the low serum albumin group. The ROC curve analysis (Figure 1) revealed an optimal cut-off value for serum albumin as 3.85 gm/dl to predict CI-AKI with 67.2% sensitivity and 52.2% specificity (AUC = 0.62, 95% confidence interval (CI): 0.58–0.66, *p* < 0.001).

In addition, serum albumin level < 3.25 gm/dl offers a reasonably good specificity of 87.9% at the expense of poor sensitivity with a good positive predictive value in diagnosing CI-AKI. As shown in Table II, age, radial vs femoral access, prior heart failure, intra-aortic balloon pump (IABP) use, cardiogenic shock at presentation, pre-procedural hemoglobin level, pre-existing CKD and serum albumin < 3.85 gm/dl were identified as significant predictors of CI-AKI following coronary

Table II. Univariate multiple regression analysis of hypoalbuminemia as an independent predictor of CI-AKI adjusted for covariates

Variables	Odds ratio (95% CI)	P-value	Adjusted odds ratio (95% CI)	P-value
Age	1.2 (1.1–1.3)	0.02	1.0 (0.9–1.1)	0.32
Radial vs. femoral access	2.0 (1.4–2.8)	< 0.001	2.4 (0.6–5.7)	0.09
Prior heart failure	2.1 (1.5–2.8)	< 0.001	1.6 (1.2–2.3)	0.01
Cardiogenic shock	2.8 (1.4–5.5)	< 0.001	1.3 (0.6–3.0)	0.44
Intra-aortic balloon pump use	3.6 (1.4–9.4)	< 0.001	1.8 (0.6–5.7)	0.25
Pre-procedural hemoglobin	0.6 (0.5–0.7)	< 0.001	0.7 (0.6–0.8)	0.00
Glomerular filtration rate < 60 ml/min	3.3 (2.2–5.1)	< 0.001	1.7 (1.2–2.1)	0.02
Serum albumin < 3.85 gm/dl	2.2 (1.6–3.0)	< 0.001	1.5 (1.1–2.1)	0.02

CI – confidence interval, CI-AKI – contrast-induced acute kidney injury.

angiography. Serum albumin level < 3.85 gm/dl was independently associated with higher risk of developing CI-AKI following coronary angiography (adjusted odds ratio (AOR) = 1.5, 95% CI: 1.1–2.1, $p = 0.02$) adjusted for all other significant covariates (Table II).

Discussion

In our study, we found that hypoalbuminemia defined as serum albumin < 3.85 gm/dl is as an independent risk factor for development of CI-AKI in patients undergoing coronary angiography with or without PCI. To the best of our knowledge this is the first study in the United States to evaluate hypoalbuminemia as an important predictor of CI-AKI following contrast exposure. The result of our study supports the hypothesis that low albumin state serves as an independent risk factor for CI-AKI. It is also consistent with a previous Turkish study which identified an inverse association between serum albumin level and the development of contrast-induced AKI after urgent coronary angiography with PCI for patients with acute coronary syndrome [15].

Although the mechanism of CI-AKI is not completely understood, there are several mainstream hypotheses on how contrast agents cause renal injury: intense vasoconstriction induced by contrast media mediated by endothelin and other vasoactive substances, release of reactive oxygen species (ROS) caused by tissue ischemia, and a direct renal tubular toxic effect by contrast media leading to acute tubular cell necrosis [16]. The production of ROS has been the main pharmacologic target to prevent the development of CI-AKI in various scientific studies, although the protective effects remain inconsistent [17]. Albumin, traditionally viewed as a carrier protein, is in fact also a major natural free radical scavenger in the blood. The cysteine and methionine residues in the albumin structure play a key role in this function [18]. Therefore, low serum albumin level theoretically reflects a state of low free radical clearance capacity, predisposing the body to oxidative injuries.

Hypoalbuminemia has been shown as an independent risk factor for AKI and post-AKI mortality in various clinical scenarios irrespective of contrast utilization. In a meta-analysis performed in 2010 by Wiedermann *et al.*, lower serum albumin served as an independent predictor of AKI [19]. In addition, albumin being one of the negative acute phase reactants, hypoalbuminemia is a reflection of an underlying inflammatory state in the body which is characterized by increased free radical production [20]. Patients who are extremely sick with multiple co-morbidities and organ failure tend to have low albumin because of their profound inflammatory response state and poor nu-

trition. Our finding of a significant association between hypoalbuminemia and CI-AKI could also be because of reverse causation bias where the sickest patients are at the highest risk for CI-AKI and they have the lowest serum albumin levels because of the aforementioned reasons. Previous studies have suggested the role of inflammation in pathogenesis of contrast-induced nephropathy using C-reactive protein (CRP) as a marker. In the Athens study, pre-procedural high-sensitivity CRP was validated as one of the predictors of CI-AKI in patients with ACS who had urgent PCI [21]. Whether hypoalbuminemia is the primary driving factor in causing CI-AKI or it basically proxies other known risk factors of CI-AKI needs to be further investigated by randomized controlled studies adjusting for unknown confounders.

Scientific evidence is scarce on the use of parenteral albumin infusion for prevention of CI-AKI. A small retrospective study from South Korea found no difference in incidence of CI-AKI between the parenteral albumin group and the sodium bicarbonate group among patients with liver cirrhosis who underwent contrast CT study [22]. Pre-procedure albumin infusion in comparison to the current standard of care of intravenous saline hydration may be studied as a potentially superior preventive strategy in reducing the incidence of CI-AKI in high risk patients. But cost effectiveness and adverse risks of parenteral albumin infusion will be a significant concern.

Our study has several limitations. First of all, the retrospective nature of the study contributes to selection bias. Patients with no pre-procedural serum albumin level were excluded from this study. Serum albumin level is subject to fluctuations based on hydration status, and due to limited availability of data on retrospective chart review, peri-procedural volume status along with several other factors including urine output and administration of nephrotoxic medications could not be accurately assessed and hence was not incorporated into the regression analysis. Reverse causation bias is inevitable in our study as the sickest patients are at the highest risk for CI-AKI and they have a low albumin level to begin with. Further randomized controlled studies are required to adjust for unknown confounders to mitigate these biases. Lastly, we did not study the etiology of hypoalbuminemia in our study population and those etiologies might have directly contributed to development of CI-AKI.

In conclusion, serum albumin < 3.85 gm/dl is an independent predictor of CI-AKI in patients undergoing coronary angiography. Further prospective clinical studies are necessary to validate serum albumin level as a risk prediction tool for CI-AKI following coronary angiography.

Conflict of interest

The authors declare no conflict of interest.

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