

Can Serum Nutritional Related Biomarkers Predict Mortality Of Critically Ill Older Patients With Acute Kidney Injury?

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Background: Critically ill older patients with acute kidney injury (AKI), also referred to as acute renal failure, are associated with high in-hospital mortalities. Preexisting malnutrition is highly prevalent among AKI patients and increases in-hospital mortality rate. This study is to evaluate the predictive power of some serum nutritional related biomarkers predicting the 90 days in-hospital mortality of critically ill older patients with AKI.

Methods: A prospective, observational study was conducted in a university teaching hospital. One hundred and five critically ill older patients with AKI aged 60–95 were enrolled and were divided into survival group (n=44) and non-survival group (n=61) in the light of their final outcomes. Receiver operating characteristic analyses (ROC) were performed to calculate the area under ROC curve (AUC). Sensitivity and specificity of in-hospital mortality prediction were calculated.

Results: Significant differences were found between the survival group and non-survival group of critically ill older patients with AKI. AUC of low density lipoprotein (LDL) and albumin were 0.686 and 0.595, respectively. The asymptotic 95% confidence intervals of LDL and albumin were 0.524–0.820 and 0.488–0.696, respectively. Sensitivity of the 90 days in-hospital mortality prediction of LDL and albumin were 68.71% and 69.09%, respectively. Specificity of 90 days in-hospital mortality prediction of LDL and albumin were 69.23% and 50.0%, respectively.

Conclusion: LDL and albumin did not have sufficient power to predict the 90 days in-hospital mortality of critically ill older patients with AKI. Further research on the association between malnutrition and poor prognosis of critically ill older patients with AKI is needed in the future.

Trial registration: ClinicalTrials.gov identifier: NCT00953992.

Keywords: critically ill older patients, acute kidney injury, mortality, nutritional related biomarker

Plain Language Summary

Critically ill older patients with acute kidney injury (AKI), also as acute renal failure, are associated with high in-hospital mortality. In-hospital mortality prediction is of great importance in guiding treatment and predicting prognosis. This study is to evaluate predictive power of some serum nutritional related biomarkers predicting the 90 days in-hospital mortality of critically ill older patients with AKI. A prospective, observational study was conducted in a university teaching hospital. One hundred and five critically ill older patients with AKI aged 60 to 95 were enrolled and were divided into survival group and non-survival group in the light of their final outcomes. Receiver operating characteristic analyses (ROC) were performed to calculate the area under ROC curve (AUC). Significant differences were found between the survival group and non-survival group of critically ill older patients with

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AKI. AUC of low density lipoprotein (LDL) and albumin was 0.686 and 0.595, respectively. In this study, it was found LDL and albumin did not have sufficient power to predict the 90 days in-hospital mortality of critically ill older patients with AKI. Further researches on the association between malnutrition and poor prognosis of critically ill older patients with AKI are needed in the future.

Introduction

Acute kidney injury (AKI), previously referred to as acute renal failure (ARF), is a serious clinical state that affects more than 50% of critically ill patients worldwide and is independently related to longer hospital stay.¹ AKI represents a frequent complication in older patients with increased mortality.² Critically ill older patients with AKI are associated with high in-hospital mortalities. In clinical practice, in-hospital mortality prediction is of great importance in guiding treatment and predicting prognosis. Over the past years, several novel serum molecules have been found as biomarkers of early diagnosis of AKI and biomarkers of AKI progression,^{3–5} but they have not considered the malnutrition state of patients with AKI. Malnutrition is highly prevalent among patients with AKI and increases the in-hospital mortality rate.⁶ Serum nutritional related biomarkers such as pre-albumin, albumin, and cholesterol are recommended to assess the nutritional status of patients with AKI in accordance with the expert panel convened by the International Society of Renal Nutrition and Metabolism and the American Society of Nephrology.⁷ Xie et al.⁸ reported that a higher ratio of C-reactive protein/pre-albumin was associated with mortality of AKI patients and was a valuable predictor for the prognosis. However, there are no studies which have reported the association between malnutrition and poor prognosis of critically ill older patients with AKI. The prognostic relevance of preexisting malnutrition in critically ill older patients with AKI is still unknown. This study is to evaluate the predictive power of some serum nutritional related biomarkers predicting the 90 days in-hospital mortality of critically ill older patients with AKI.

Materials And Methods

A prospective, observational study was conducted in a university teaching hospital. In this study, 189 critically ill patients with AKI of all age groups (from 18 years old to 95 years old) were investigated. Among them, 105 critically ill older patients with AKI aged 60–95 were enrolled into this study according to the newly defined age stratification of older people of the World

Health Organization. The critically ill older patients with AKI were divided into a survival group ($n=44$, mean age= 74.0 ± 7.94 years old) and a non-survival group ($n=61$, mean age= 75.98 ± 8.68 years old) in the light of their final outcomes. In the survival group, 31 were men and 13 were women. In the non-survival group, 45 were men and 16 were women. AKI was diagnosed on the basis of the Risk, Injury, Failure, Loss, or End-stage kidney disease criteria (RIFLE),^{9,10} which standardized the diagnosis of AKI. Patients with AKI caused by glomerulonephritis, post-renal obstruction, and kidney transplantation were excluded. The demographic and outcome characteristics and laboratory features including serum nutritional related biomarkers such as albumin, pre-albumin, total protein, triglyceride, serum total cholesterol (Cho), low density lipoprotein (LDL), and high density lipoprotein (HDL) of all critically ill older patients with AKI were recorded within 24 hours of the patients' admission of hospital. Three kinds of severity scoring systems, including Sepsis-related Organ Failure Assessment (SOFA), version II of Acute physiology and chronic health evaluation II (APACHE II), and Simplified acute physiology score (SAPS II) counts were also assessed within the first 24 hours following admission. We compared the clinical characteristics, scores of three kinds of severity scoring systems, and laboratory test results including serum nutritional related biomarkers of the survivor group and the non-survivor group of critically ill older patients with AKI. Please see [Table 1](#).

Analyses were performed using IBM SPSS Statistics, Version 20.0 (IBM Inc., Chicago, IL, USA). Continuous variables were analyzed by Student's *t*-test and expressed as the mean \pm standard deviation or median and interquartile range. Categorical variables were analyzed by chi-square test or Fisher's exact test. *p*-value<0.05 was considered statistically significant. Receiver operating characteristic (ROC) curves analysis was applied, and ROC curves were drawn up to assess the effectiveness of serum nutritional related biomarkers for the prediction of in-hospital mortality of critically ill older patients with AKI. Then, the area under the ROC curve (AUC) was calculated and analyzed.

All patients provided written informed consent, and this study was conducted in accordance with the Declaration of Helsinki.

Table 1 Clinical Characteristics And Laboratory Test Results Including Serum Nutritional Related Biomarkers Of The Survivor Group And Non-survivor Group Of Critically Ill Older Patients With Acute Kidney Injury

Variables	Survival Group (n=44)	Non-Survival Group (n=61)	p-value
Mean ages (years) (\pm SD)	74.0 \pm 7.94	75.98 \pm 8.68	0.234
Gender (male/female)	31/13	45/16	0.708
Presence of sepsis	0.57 \pm 0.50	0.34 \pm 0.48	0.022
Outcomes	39/2	1/53	0.000
Complications	36/4	32/22	0.001
Use of dopamine	23/21	51/10	0.001
Use of RRT	36/8	56/5	0.125
Complicated with MODS	16/28	48/13	0.000
Assisted breathing with ventilator	23/21	56/5	0.000
WBC ($\times 10^3/\mu$ L)	13.53 \pm 6.14	11.98 \pm 9.91	0.374
Neutrophils (%)	85.01 \pm 6.03	73.08 \pm 17.37	0.000
Total protein (g/L)	47.36 \pm 139.25	80.33 \pm 82.67	0.148
LDH (IU/L)	561.69 \pm 287.92	31.316 \pm 6.08	0.678
Albumin (g/L)	31.36 \pm 6.08	33.21 \pm 6.31	0.328
pre-albumin (mg/L)	151.03 \pm 82.84	168.04 \pm 74.66	0.328
SCr at the time of the diagnosis of AKI (μ mol/L)	240.95 \pm 176.50	187.38 \pm 114.72	0.064
BUN at the time of the diagnosis of AKI (mmol/L)	21.19 \pm 11.32	15.98 \pm 8.11	0.011
CRP (μ g/L)	68.29 \pm 72.69	20.49 \pm 27.20	0.175
Cho (mmol/L)	3.50 \pm 1.37	3.77 \pm 1.06	0.435
HDL (mmol/L)	0.88 \pm 0.45	0.88 \pm 0.32	0.982
LDL (mmol/L)	1.80 \pm 0.96	2.43 \pm 0.83	0.028
BMI (kg/m ²)	22.36 \pm 3.58	22.19 \pm 2.98	0.831
RIFLE (Rc/lc/Fc)	12/14/16	10/18/33	0.204
Scores of SOFA	4.66 \pm 3.05	10.24 \pm 4.29	0.000
Scores of APACHEII	14.33 \pm 4.61	24.79 \pm 8.07	0.000
Scores of SAPSII	37.97 \pm 12.13	60.53 \pm 16.57	0.000

Abbreviations: RRT, renal replacement therapy; MODS, complicated with multiple organ dysfunction syndrome; WBC, total blood count of white blood cell; SCr, serum creatinine; BUN, serum urea nitrogen; CRP, C-reactive protein; Cho, serum total cholesterol; BMI, body mass index; RIFLE, risk, injury, failure, loss, or end-stage kidney disease criteria.

Results

There were 105 critically ill older patients with AKI aged 60–95 who were analyzed (76 were male and 29 were female). Significant differences were found between the survival group and the non-survival group in the presence of sepsis, use of dopamine, outcomes, complications, complicated with multiple organ dysfunction syndrome (MODS), assisted breathing with ventilator, LDL, and Scores of SOFA, APACHEII, SAPS II. There were no significant differences found between the survival group and the non-survival group in baseline SCr, length of stay in hospital, length of stay in Intensive Care Unit (ICU), operation history, use of renal replacement therapy (RRT), C-reactive protein, Apolipoprotein-A1, Apolipoprotein-B, Body Mass Index (BMI), RIFLE stage, etc. Analysis of clinical characteristics and laboratory test results including serum nutritional related biomarkers of the survivor

group and the non-survivor group of critically ill older patients with AKI is shown in [Table 1](#).

In this study, comparison of the differences of serum nutritional related biomarkers including pre-albumin, albumin, total protein, triglyceride, serum total cholesterol, HDL, LDL between the survivor group and the non-survivor group of critically ill older patients with AKI was conducted. As a result, significant differences ($p < 0.05$) were found in LDL ($p = 0.025$) and albumin ($p = 0.029$) between the survival group and the non-survival group. Comparison of differences of serum nutritional related biomarkers between the survivor group and the non-survivor group of critically ill older patients with AKI is shown in [Table 2](#).

Receiver operating characteristic (ROC) curves analysis was conducted in this study. ROC curves of LDL and albumin were drawn up to assess their effectiveness of predicting the 90 days in-hospital mortality of critically

Table 2 Comparison Of Differences Of Serum Nutritional Related Biomarkers Between The Survivor Group And Non-Survivor Group Of Critically Ill Older Patients With Acute Kidney Injury

	Non-Survivor Group		Survivor Group		t	Sig.
	Mean	SD	Mean	SD		
pre-albumin	148.24	74.36	164.66	69.74	-1.303	0.195
Total protein	41.48	113.23	17.24	27.70	1.711	0.092
Triglyceride	2.41	2.28	2.26	2.22	0.254	0.8
Cho	3.69	1.41	4.07	1.60	-0.97	0.335
HDL	0.79	0.43	0.83	0.36	-0.371	0.712
LDL	1.89	0.97	2.57	1.14	-2.292	0.025
albumin	30.77	6.38	33.04	6.84	-2.202	0.029

Abbreviations: Cho, serum total cholesterol; HDL, high density lipoprotein; LDL, low density lipoprotein.

ill older patients with AKI. Please see [Figure 1](#). Area under the ROC curve (AUC) of LDL and albumin was calculated, which was 0.686 and 0.595, respectively. The asymptotic 95% Confidence Interval of LDL and albumin was 0.524–0.820 and 0.488–0.696, respectively. In this study, the sensitivity of the 90 days in-hospital mortality prediction of LDL and albumin was 68.71% and 69.09%, respectively. The specificity of the 90 days in-hospital mortality prediction of LDL and albumin was 69.23% and 50.0%, respectively. These results indicated that LDL and albumin did not have sufficient power to predict the 90 days in-hospital mortality of critically ill older patients with AKI. The comparison of effectiveness of LDL and albumin in predicting the 90 days in-hospital

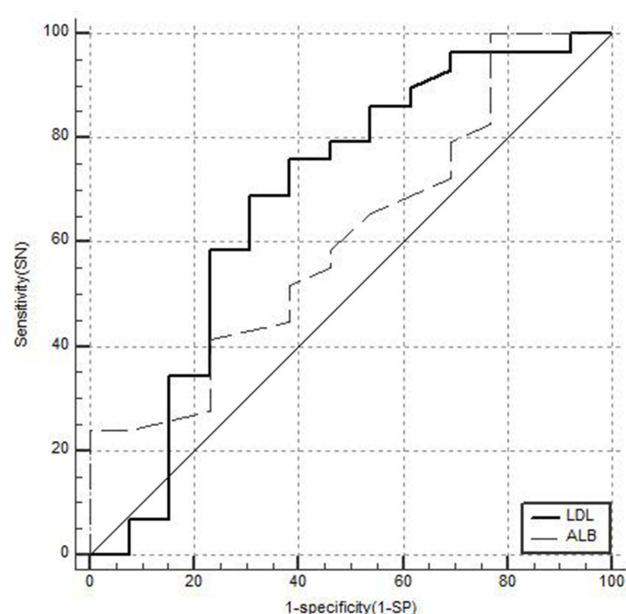


Figure 1 Receiver operating characteristic curves of low density lipoprotein and albumin to assess the effectiveness of predictive abilities of the 90 days in-hospital mortality on critically ill older patients with acute kidney injury.

mortality of critically ill older patients with AKI is shown in [Table 3](#).

Discussion

AKI is associated with high mortality, particularly in critical ill older patients who are prone to develop AKI. AKI is one of the main causes leading to multiple organ dysfunction syndrome (MODS) and the in-hospital death of critically ill older patients. Critically ill older patients with AKI are usually associated with severe malnutrition and rapid changes in the condition. Accurate in-hospital mortality prediction is of great value in clinical practice. Since evidence-based medical evidence is lacking, the results of some clinical studies of geriatric AKI are not uniform. The assessment of nutrition status is a useful tool for the clinical monitoring of critically ill older patients with AKI. But the underlying diseases, primary disease, complications, accompanied diseases, and renal replacement therapy may interfere in the status of malnutrition of these patients.

Status of malnutrition is associated with higher in-hospital mortality and more complications. Some serum nutritional related biomarkers such as albumin, cholesterol, and pre-albumin have been proved to be useful to predict poor outcomes and higher mortality in AKI patients.¹¹ Recent studies have focused on the relationship between malnutrition and AKI. In the study of Chertow et al.¹² it was found that hypoalbuminemia was one of the predictors of death of critically ill patients with AKI due to acute tubular necrosis. Hypoalbuminemia was considered as one of the serum biomarkers of malnutrition of critically ill older patients with AKI. In the study of Li et al.¹³ it was found that hypoalbuminemia was one of the risk factors of the poor outcomes of renal function in older patients with AKI (≥ 75 years old) and other risk

Table 3 Effectiveness Of Low Density Lipoprotein And Albumin In Predicting The 90 Days In-Hospital Mortality Of Critically Ill Older Patients With Acute Kidney Injury

	Area	Std. Error	Asymptotic 95% Confidence Interval	The Threshold Value	Youden Index	Sensitivity	Specificity
LDL	0.686	0.0998	0.524–0.820	>1.98	0.3820	68.71%	69.23%
ALB	0.595	0.0599	0.488–0.696	>29	0.1909	69.09%	50.0%

Abbreviations: LDL, low density lipoprotein; ALB, albumin.

factors were low pre-albumin level, Body Mass Index (BMI), and more severe AKI stage. In the study of Liu et al.,¹⁴ hypoalbuminemia was found to be the major risk coefficient that affected the prognosis of older patients with AKI (80–100 years old) undergoing continuous renal replacement therapy (CRRT), and was related to the turnover of these patients. These results showed that malnutrition is one of the main causes of death and albumin is a predictor for the mortality of critically ill older patients with AKI. In the study of Nie et al.¹⁵ it was found that albumin, BMI, total blood count of white blood cell, and total blood count of platelets were the predictors of mortality of AKI patients. Albumin belongs to the biomarkers of malnutrition and total blood count of white blood cell is a biomarker of inflammation. Malnutrition and inflammation may lead to death of critically ill older patients with AKI. The results of the study of Nie et al indicated that albumin can be a predictor of mortality of AKI patients. These results were different from that of our study, which found albumin was associated with in-hospital mortality of critically ill older patients with AKI, but couldn't effectively predict the 90 days in-hospital mortality. This was because the AKI patients in the study of Nie et al were patients with AKI of all age groups and the AKI patients in our study were critically ill older patients with acute kidney injury aged 60–95. The difference of patient's age of two studies will inevitably lead to the difference of nutritional status of patients. The factors leading to malnutrition in older patients are more complex than they are in the general population. This is why in this study we found that albumin was associated with the in-hospital mortality of critically ill older patients with AKI but can't effectively predict the 90 days in-hospital mortality.

Findik et al¹⁶ reported that low levels of preoperative serum albumin increase the mortality of patients with severe AKI after isolated coronary artery bypass graft surgery (CABG), which revealed that serum albumin level is an important predictor of the mortality of AKI patients undergoing cardiac surgery. But the target

population of our study was critically ill older patients with AKI who have more underlying disease, complications, or accompanied disease which may interfere in the status of malnutrition of patients. At the same time, since these patients were critically ill older patients with AKI, most of them needed renal replacement therapy which could lead to loss of serum albumin of these patients.

In addition, other scholars have studied the clinical value of albumin in predicting mortality in different types of AKI patients, including critically ill patients with septic AKI and critically ill patients requiring CRRT. In the study of Shum et al.¹⁷ it was demonstrated that albumin, potassium, and pH value independently predicted 90-day mortality of critically ill patients with septic AKI. Kritmetapak et al.¹⁸ found that, in critically ill patients requiring CRRT, serum albumin is a good prognosticator of renal outcome, and dietary protein intake is a good predictor of survival.

In the patients undergoing surgical operation, some serum nutritional index can predict the patients' mortalities. In the study of Kim et al.¹⁹ it was found that a preoperative serum albumin level of <3.8g/dL was independently associated with AKI and mortality in patients undergoing brain tumor surgery. Kim et al.²⁰ found that the serum albumin level <3.0g/dL (within 2 postoperative days) was an independent risk factor for AKI of patients who undergo total knee arthroplasty. The results of these two studies make clear that the low serum albumin level before and after surgical operation is a predictor of the mortality of patients with AKI.

LDL is another serum index of malnutrition which induces dysfunction of the endothelium and causes vascular wall inflammation. In the study of Liu et al.²¹ it was found that the plasma LDL cholesterol level of patients undergoing percutaneous coronary intervention (PCI) may be helpful to identify the mortality of patients with contrast-induced-AKI (CI-AKI). CI-AKI is a special kind AKI which is induced by contrast medium and is a serious iatrogenic complication that accounts for a significant number of causes of hospital-acquired renal failure, with

adverse effects on prognosis. The results showed that LDL was associated with mortality of patients with CI-AKI and a predictor for the mortality.

In the study of Shao et al.²² it was found that hypoalbuminemia in critically ill patients is independently associated with an increased risk of AKI progressing to stage 4 chronic kidney diseases (CKD4). The results suggested that albumin is independently associated with the progression of critically ill patients with AKI. This result is similar to that of our study. It has been proved that pre-existing and/or hospital-acquired malnutrition was identified as an important factor contributing to the persistent high mortality in acutely ill patients with AKI.²³ Appropriate dietary management of patients with AKI is essential to improve their long-term prognosis.²⁴ Nutrition management has more important clinical value in critically ill older patients with AKI. Reasonable nutritional therapy is fundamental to reduce the mortality of AKI patients. However, due to the strict control of transfusion volume of patients with AKI, many nutrients can't be effectively replenished. New techniques of renal replacement therapy, including continuous renal replacement therapy (CRRT), offer the opportunity to adapt nutrition to each individual patient's need, and there is no reason to reduce nutrition because of fluid restriction, as is often necessary in intermittent hemodialysis.²⁵

There is high heterogeneity in the critically ill older patients with AKI. The cause is not very clear and the mechanism is not found. Critically ill older patients with AKI are associated with high in-hospital mortality rates. Although there is a certain relationship between the malnutrition and poor prognosis, it was found that LDL and albumin can't predict the 90 days in-hospital mortality of critically ill older patients with AKI in this study.

Conclusion

LDL and albumin did not have sufficient power to predict the 90 days in-hospital mortality of critically ill older patients with AKI. Further research with more patients and centers on the association between malnutrition and poor prognosis of critically ill older patients with AKI is needed in the future.

Abbreviations

AKI, acute kidney injury; ROC, receiver operating characteristic analyses; AUC, area under receiver operating characteristic analyses curve; LDL, low density lipoprotein; RIFLE, risk, injury, failure, loss, or end-stage kidney

disease criteria; Cho, serum total cholesterol; HDL, high density lipoprotein; BMI, body mass index; RRT, renal replacement therapy; SOFA, sepsis-related organ failure assessment; APACHE II, version II of Acute physiology and chronic health evaluation II; SAPS II, Simplified acute physiology score; MODS, multiple organ dysfunction syndrome; ICU, intensive care unit.

Ethics Approval And Informed Consent

The protocol for this research project has been approved by the Ethics Committee of Huashan Hospital, Fudan University, and the reference number is 2009-206.

Data Availability

All data generated or analysed during this study are included in this published article.

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Author Contributions

Yu Gong, Feng Ding, and Yong Gu contributed substantially to the conception and design, acquisition of data, or analysis and interpretation of data; drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Disclosure

The authors report no conflicts of interest in this work.

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