Relationship Between the BUN-to-Creatinine Ratio and All-Cause Mortality in Patients with Chronic Kidney Disease

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Abstract

Objective: We explored the relationship between all-cause mortality and the ratio of blood urea nitrogen (BUN) to creatinine in patients with chronic kidney disease.

Methods: Data were collected from patients with chronic kidney disease who had undergone radionuclide renal dynamic imaging between January 1, 2009 and July 31, 2016 at the Third Affiliated Hospital of Sun Yat-sen University. A total of 1276 patients with chronic kidney disease were ultimately selected, and the relationship between the BUN-to-creatinine ratio and all-cause mortality was evaluated with the Cox proportional hazard model.

Results: In contrast to results from previous studies, the single-variable Cox proportional hazard model indicated that BUN/creatinine ratio correlates with all-cause mortality of chronic kidney disease (p = 0.015). However, after adjustment for factors such as the measured glomerular filtration rate, renal function-related indicators, nutritional indicators, proteinuria levels, cardiovascular disease, and diabetes, the BUN-to-creatinine ratio was not significantly correlated with all-cause mortality (p = 0.543, 0.990, 0.887, 0.459, and 0.801, respectively).

Conclusion: There is no significant correlation between the BUN-to-creatinine ratio and all-cause mortality in patients with chronic kidney disease

Introduction:

Creatinine and blood urea nitrogen (BUN) reflect the degree of impairment in glomerular filtration function. BUN is also affected by extra-renal factors such as high-protein diets, gastrointestinal bleeding, dehydration, and high catabolism, which can increase BUN. When exogenous creatinine intake is stable, and the body's creatinine production is constant, creatinine levels are mainly determined by the glomerular filtration ability and thus are a more accurate indicator of glomerular filtration than urea nitrogen. Therefore, the ratio of BUN to creatinine has clinical value. Most patients with chronic kidney disease (CKD) have low-protein dietary requirements and are prone to malnutrition, especially in patients on maintenance dialysis. Malnutrition is also associated with poor prognosis.[1 2 3] In addition, patients with CKD often experience cardiovascular events, and previous studies have shown that the BUN-to-creatinine ratio is correlated with cardiovascular event prognosis.[4 5 6 7]

However, few studies have examined the relationship between the BUN-to-creatinine ratio and all-cause mortality, although some studies have shown that the BUN-to-creatinine ratio is related to patient mortality.[8 9 10] The BUN-to-creatinine ratio indeed reflects the body's metabolic burden, and is assumed to be independent predictor of prognosis in patients with CKD. Therefore, this study explored the relationship between the BUN-to-creatinine ratio and all-cause mortality in patients with CKD.

Methods:

Data source and research population: This study examined patients with CKD who had undergone radionuclide renal dynamic imaging between January 1, 2009 and July 31, 2016. Renal ECT's measurement of glomerular filtration rate refers to the ability of the kidney to remove a substance from plasma in a unit of time. (Kidney ECT examination is a single-photon computed tomography scanner. It is a method of performing physical examinations using radioactive elements, mainly to check renal function and determine the degree of renal function damage.) The glomerular filtration rate is usually determined by the clearance rate, and the number of millilitres of plasma that the kidney can remove from the substance per minute is extrapolated and corrected by body surface area. Generally, the serum creatinine concentration is measured when the body is in a steady state, and the value of GFR (eGFR) is estimated by a specific

formula. These formulas based on blood creatinine are affected by muscle content, intake of cooked red meat, and abnormalities in the secretion of creatinine by the renal tubules caused by drugs (such as trimethoprim). It is recommended to use the concentration of Cystatin C (CysC) to estimate the GFR value. Although the GFR estimation formula based on CysC has nothing to do with muscle content and diet, it will be affected by inflammation, obesity, thyroid disease, diabetes and hormone consumption. In some specific cases, measuring GFR (mGFR) is more meaningful than eGFR, such as stratifying long-trm risks for potential living donors who are planning to undergo nephrectomy. The mGFR measured by plasma clearance technology, using iohexol or radionuclide-labeled phenolphthalein salt and other contrast agents, can effectively avoid these deficiencies.

The exclusion criteria were as follows: 1) under 18 years of age; 2) refusal to participate in the study; 3) incomplete data for relevant research indicators; and 4) ongoing kidney replacement therapy. Ultimately, 1276 patients were enrolled, and their CKD stage was classified according to K/DOQI guidelines (CKD 1, GFR > 90 ml/min/1.73 m2, CKD 2, GFR 60–89 ml/min/1.73 m2, CKD 3a, GFR 45–59 ml/min/1.73 m2, CKD 3b, GFR 30–44 ml/min/1.73 m2,CKD 4, GFR 15–29 ml/min/1.73 m2, CKD 5, GFR < 15 ml/min/1.73 m2).

The experiment was approved by the Ethics Committee at the Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China. Patients enrolled after July 25, 2011 provided written informed consent. Patients (or their family members) enrolled before that time were contacted by telephone or mail to provide informed consent, and the Ethics Committee approved these exemptions. After removal of missing cases, 1276 cases remained.

Baseline characteristics and study variables: The baseline variables included demographic characteristics (age, sex, and body-mass index) and comorbidities (diabetes, defined as fasting blood glucose ≥ 7.0 mmol/l and/or OGTT 2-hour blood glucose ≥ 11.1 mmol/l, or a clear diagnosis of diabetes; hypertension, defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg or a clear prior hypertension diagnosis; heart failure; myocardial infarction; cerebral infarction; and cerebral hemorrhage, as obtained from the previous medical history). The laboratory nutrition indicators included serum albumin, hemoglobin, and other laboratory data—serum potassium, serum calcium, serum phosphorus, serum uric acid, and qualitative urine protein. Whether death occurred and the time of death were determined. The glomerular filtration rate was measured in the emission computed tomography examination room at the Third Affiliated Hospital of Sun Yat-sen University, and laboratory examination data were measured in the clinical laboratory at the hospital. The study variables were the values of urea nitrogen and creatinine during the initial visit of the patients with CKD.

Primary endpoint: All-cause mortality (death due to any cause during follow-up).

Statistical analysis: Continuous variables are expressed as the mean ± standard deviation. Baseline BUN-to-creatinine ratios were grouped into quartiles. Overlapping BUN-to-creatinine ratios were divided into groups according to a random allocation principle. Summary statistics based on these quartiles are expressed as a percentage of categorical data. Chi-squared tests were used for categorical variables. Continuous variables with approximate normal distributions were subjected to analysis of variance, and skewed continuous variables were subjected to Kruskal–Wallis tests. The Cox proportional hazard model was used to assess the relationship between the BUN-to-creatinine ratio quartile and the incidence of all-cause mortality. In addition, to exclude other related factors, we divided the data into seven groups on the basis of the measured GFR (mGFR), proteinuria, renal function indicators (blood potassium, blood phosphorus, calcium, and uric acid), comorbidities, nutritional indicators, and other variables. These groups were also analyzed with the Cox model.

Results:

Characteristic description: There were a total of 1276 cases. The average age of the cohort was 56.39 ± 15.01 years, and 58.31% were male, 59.1% had diabetes, and 65.91% had cardiovascular or cerebrovascular diseases. The average mGFR was 57.24 ± 28.38 ml/min/1.73 m^2. Follow-up time: (42.61 ± 20.21) months.

As the BUN-to-creatinine ratio increased, the proportion of patients with diabetes, and the levels of mGFR and blood calcium, also increased (p = 0.000, 0.000, and 0.000, respectively); the levels of uric acid, proteinuria, and blood phosphorus decreased (p = 0.000, 0.000, and 0.000, respectively) (Table 1)

Table 1
Baseline characteristics

	Q1: 76.51–17.07	Q2: 101.94–76.59	Q3: 135.73-101.97	Q4: 391.24-135.94	Total	p
Quantity	319	319	319	319	1276	
Age	51.08 ± 15.10	57.58 ± 15.15	58.08 ± 14.27	58.83 ± 13.25	56.39 ± 15.01	0.000
Sex (male)	71.5%	66.5%	58.31%	37%	58.31%	0.171
BMI	23.41 ± 3.62	24.38 ± 3.93	24.47 ± 3.75	24.09 ± 3.72	24.09 ± 3.77	0.001
diabetes	31.3%	54.9%	70.85%	79%	59.1%	0.000
Cardiovascular disease	71.2%	69.3%	63.95%	59.25%	65.91%	0.604
Serum potassium(mmol/l)	4.16 ± 0.59	4.05 ± 0.48	4.05 ± 0.47	4.05 ± 0.44	4.08 ± 0.50	0.014
Serum calcium(mmol/l)	2.21 ± 0.21	2.29 ± 0.17	2.30 ± 0.16	2.31 ± 0.15	2.28 ± 0.18	0.000
Serum phosphorus(mmol/l)	1.34 ± 0.41	1.20 ± 0.26	1.21 ± 0.28	1.26 ± 0.26	1.25 ± 0.31	0.000
Serum uric acid(mmol/l)	465.59 ± 137.05	428.69 ± 145.20	408.45 ± 139.52	371.72 ± 135.56	418.61 ± 143.30	0.000
Hemoglobin(g/l)	106.45 ± 29.23	122.72 ± 23.41	124.18 ± 23.17	124.11 ± 20.58	119.37 ± 25.40	0.000
Proteinuria level	2+: 176(55.17%) +-TO+: 69(21.63%) 0: 74(23.20)	2+: 90(28.21%) +-TO+: 61(19.12%) 0: 168(52.66%)	2+: 57(17.87%) +-TO+: 50(15.67%) 0: 212(66.46%)	2+: 52(16.30%) +-TO+: 44(13.79%) 0: 223(69.91%)	2+: 375(29.39%) +-TO+: 224(17.55%) 0: 677(53.06%)	0.000
Serum albumin(g/l)	36.67 ± 5.33	38.45 ± 4.96	39.58 ± 5.16	39.26 ± 5.53	38.49 ± 5.36	0.000
mGFR(ml/min/1.73 m^2)	36.59 ± 25.56	55.55 ± 25.57	64.27 ± 24.86	72.54 ± 24.26	57.24 ± 28.38	0.000
BMI: Body Mass Index						

The univariate Cox model indicated that the urea-nitrogen-creatinine ratio was associated with all-cause death in patients with CKD (P = 0.015). However, demographics and mGFR were corrected separately and analyzed according to: demographics, mGFR, and renal function-related indicators; demographics, mGFR, and comorbidities; demographics,

mGFR, and nutrition-related indicators; demographics, mGFR, and urinary protein. There was no significant correlation between the urea-nitrogen-creatinine ratio and death in patients with CKD (P = 0.803, 0.990, 0.801, 0.887, 0.459, and 0.989) (Table 2).2

Table 2
Relationship between BUN-to-creatinine ratio and all-cause mortality in patients with CKD

	B	SE	Wald	df	Sig	Exp(B)	Exp(B) 95.0% CI	
							Lower limit	Cap
Model 1	− .005	.002	5.910	1	.015	.995	.991	.999
Model 2	.001	.002	.062	1	.803	1.001	.996	1.005
Model 3	.000	.003	.000	1	.990	1.000	.995	1.005
Model 4	.001	.002	.064	1	.801	1.001	.996	1.005
Model 5	.002	.002	.548	1	.459	1.002	.997	1.007
Model 6	.000	.002	.020	1	.887	1.000	.996	1.005
Model 7	.000	.002	.000	1	.989	1.000	.995	1.005
Model 1: The relationship between urea-nitrogen creatinine ratio and all-cause mortality in patients with CKD, unadjusted, P = 0.015; the results are statistically significant.								
Model 2: Relationship between urea nitrogen-creatinine ratio and all-cause mortality in patients with CKD. Baseline characteristics: age, sex, mGFR, P = 0.803; the results were not statistically significant.								
Model 3: Relationship between urea nitrogen creatinine ratio and all-cause mortality in patients with CKD, baseline characteristics: sex, age, mGFR, renal function related indicators (blood potassium, blood calcium, blood phosphorus, and uric acid), P = 0.990; the results were not statistically significant.								
Model 4: Relationship between urea nitrogen creatinine ratio and all-cause mortality in patients with CKD, baseline characteristics: sex, age, mGFR, comorbidities (cardio-cerebral vascular disease, and diabetes), P = 0.801; the results were not statistically significant.								
Model 5: Relationship between urea nitrogen creatinine ratio and all-cause mortality in patients with CKD, baseline characteristics: sex, age, mGFR, proteinuria level, P = 0.459; the results were not statistically significant.								
Model 6: Relationship between urea nitrogen creatinine ratio and all-cause mortality in patients with CKD, baseline characteristics: sex, age, mGFR, nutritional indicators (BMI, albumin, and hemoglobin), P = 0.887; the results were not statistically significant.								
Model 7: The relationship between urea-nitrogen creatinine ratio and all-cause mortality in patients with CKD. Baseline characteristics: all factors, P = 0.989; the results were not statistically significant.								

Urea nitrogen and creatinine ratio of normal value 20–100.The patients were evenly divided into two groups according to the BUN-to-creatinine ratio: a low-level group (< 100) ,a high-level group (≥ 100). Cox model analysis was performed according to the categorical variables. Analysis of the six subgroups indicated that when the BUN-to-creatinine ratio was abnormally high or low, the ratio was not associated with all-cause death in patients with CKD (p = 0.919, 0.733, 0.919, 0.912, 0.995, and 0.842, respectively; details in Table 3).

Table 3
Cox analysis results of each model between the high-level group and low-level group

	Quantity	HR(95%CI)							
Group	1276	Model 1	P	Model 2	P	Model 3	P	Model 4	P
Low level group	613	1(reference)		1(reference)		1(reference)		1(reference)	
High level group	663	1.427	0.049	1.021	0.919	1.073	0.733	1.021	0.919
Group	1276	Model 5	P	Model 6	P	Model 7	P		
Low level group	613	1(reference)		1(reference)		1(reference)			
High level group	663	0.912	0.662	0.995	0.980	1.043	0.842		
Model 1: The relationship between the urea-nitrogen-creatinine ratio and all-cause mortality in patients with CKD was not adjusted. The high-level group had a P value of 0.049. The results were statistically significant.									
Model 2: The relationship between urea nitrogen-creatinine ratio and all-cause mortality in patients with CKD. Baseline characteristics: age, sex, mGFR. The high-level group had a P value of 0.919. The results were not statistically significant.									
Model 3: Relationship between urea nitrogen creatinine ratio and all-cause mortality in patients with CKD. Baseline characteristics: sex, age, mGFR, renal function related indicators (blood potassium, blood calcium, blood phosphorus, and uric acid). The high-level group had a P value of 0.733. The results were not statistically significant.									
Model 4: The relationship between urea nitrogen creatinine ratio and all-cause mortality in patients with CKD. Baseline characteristics: sex, age, mGFR, comorbidities (cardio-cerebral vascular disease, and diabetes). The high-level group had a P value of 0.919, and the results were statistically significant.									
Model 5: The relationship between urea nitrogen creatinine ratio and all-cause mortality in patients with CKD. Baseline characteristics: sex, age, mGFR, proteinuria level. The high-level group had a P value of 0.662. The results were not statistically significant.									
Model 6: The relationship between urea nitrogen creatinine ratio and all-cause mortality in patients with CKD. Baseline characteristics: sex, age, mGFR, nutritional indicators (BMI, albumin, and hemoglobin). The high-level group P was 0.980. The results were not statistically significant.									
Model 7: The relationship between urea-nitrogen creatinine ratio and all-cause mortality in patients with CKD. Baseline characteristics: all factors. The high-level group had a P value of 0.842. The results were not statistically significant.									

Discussion:

In contrast to results from previous studies, we found only one model (Model 1) in which an abnormally high or low BUN-to-creatinine ratio was associated with increased mortality in patients with CKD. In the other models, after adjustment for the mGFR, comorbidities, proteinuria, renal function indicators, nutrition-related indicators, and other factors, we confirmed that the BUN-to-creatinine ratio was not significantly associated with all-cause mortality. In Model 2, for example, after correcting for the mGFR, we found that the BUN-to-creatinine ratio was not significantly associated with mortality, possibly because CKD is associated with varying degrees of impaired renal function, and creatinine is

primarily excreted by the kidneys. Thus, the effect of the BUN-to-creatinine ratio on mortality may be mediated by the mGFR. Indeed, for patients with CKD, treatment aims to delay the decline in the GFR and to reduce all-cause mortality.

Similarly, in Model 4, after correcting for cardiovascular and cerebrovascular diseases, as well as other factors, we found that the BUN-to-creatinine ratio was not significantly associated with mortality. Indeed, cardiovascular events are the leading cause of death in patients with CKD.[11 12] Moreover, Model 3 indicated that the BUN-to-creatinine ratio is not significantly correlated with mortality. Because abnormal calcium and phosphorus metabolism can increase the risk of cardiovascular and cerebrovascular diseases, an increase in phosphorus is closely associated with mortality.[13 14 15 16 17 18 19] Consequently, these models indicate no significant, direct correlation between the BUN-to-creatinine ratio and mortality.

Although we adopted the gold standard GFR, which accurately reflects changes in all-cause mortality, this study has several limitations. Urea nitrogen is affected by many factors, and we did not exclude patients with gastrointestinal bleeding during data collection. Such patients were likely to have abnormal BUN levels and prerenal failure. In addition, we studied a retrospective cohort, the sample size was small, and we excluded patients who had received kidney replacement therapy. Thus, our results do not fully reflect all patients with CKD. In future research, we will conduct a large-scale randomized controlled trial for more comprehensive evaluation of the relationship between the BUN-to-creatinine ratio and mortality in patients with CKD.

Conclusion

There is no significant correlation between the BUN-to-creatinine ratio and all-cause mortality in patients with chronic kidney disease.

Abbreviations

BUN blood urea nitrogen

CysC Cystatin C

ANOVA Analysis of variance

BMI Body mass index

CKD chronic kidney disease

mGFR measuring glomerular filtration rate

GFR glomerular filtration rate

WHO World Health Organization

Declarations

Consent and Ethical Approval

The protocol used here was approved by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University. The details of the ethical approval have been reported in previously published studies.

Publication Consent

Yes.

Data and Material Availability

The datasets utilized and analyzed herein can be accessed by contacting the corresponding author.

Competing interests

Authors have no conflicting interests.

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Contributions of the authors

Research concept and the design of the study: Liu X; acquisition of data: Li MJ, Fu SX; data analysis/interpretation: Li R，Li MJ; statistical analysis: Li R; supervision or mentorship: Liu X, Liu HY and Zhang YQ. Each author contributed crucial intellectual knowledge in drafting of the manuscript, in the revisions, and takes responsibility for all the research work by ascertaining that queries regarding the authenticity or credibility of each part of this study is accurately examined and worked through. Li R accepts accountability that we have reported this study and the findings with honest, accuracy, and transparency; i.e., no crucial details of this study have been excluded; moreover, any variations from the study as planned have been described. The final manuscript was read and approved by all authors.

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