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Role of Serum Creatinine Levels in Prognostic Risk Stratification of Prostate Cancer Patients

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Background: Studies on the relationship between serum creatinine and the prognosis of prostate cancer have been very limited. The aim of this study was to investigate the role of serum creatinine in the prognostic risk stratification of patients with prostate cancer.

Material/Methods: We identified 1134 eligible patients from the "Prostate Cancer Data Set" in the National Clinical Medical Science Data Center. Patients with prostate cancer were divided high- and low-risk prognostic groups according to prostate-specific antigen levels and Gleason scores and were divided into 5 groups according to serum creatinine quintile: *Q*1 (<70.1 umol/L), *Q*2 (70.1-76.8 umol/L), *Q*3 (76.8-83.4 umol/L), *Q*4 (83.4-92.1 umol/L), and *Q*5 (>92.1 umol/L). Multivariate logistic regression and a multiple restricted cubic spline method were used to evaluate the relationship between serum creatinine level and the level of prostate cancer prognostic risk.

Results: Of the 1134 patients with prostate cancer, 134 (11.8%) had a high-risk prognosis. Compared with the *Q*2 group (the reference group), the lowest serum creatinine levels in the *Q*1 group and the highest serum creatinine levels in groups *Q*5, *Q*3, and *Q*4 were associated with a high-risk prognosis, and this association remained significant after adjusting for confounders. The multiple restricted cubic spline regression model showed the relationship between serum creatinine level and high-risk prognosis was U-shaped.

Conclusions: Serum creatinine level was an independent predictor of high-risk prognosis. Controlling serum creatinine levels between 70.1 and 76.8 umol/L in patients with prostatic cancer may benefit the prognosis of patients with prostatic cancer.

Keywords: Creatinine • Prostatic Neoplasms • Prognosis • Risk Factors

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Background

Prostate cancer is a common genitourinary malignancy in men, and it is the second most common cancer worldwide and the fifth leading cause of cancer-related death in this sex [1]. According to the Centers for Disease Control, African Americans have the highest incidence of prostate cancer, followed by Europeans, and Asian ethnic groups have the lowest [2]. The incidence of prostate cancer in China has been increasing significantly in recent years. In 2015, the incidence of prostate cancer in China ranked sixth among male malignant tumors, and the death rate among male malignant tumors ranked tenth [3,4].

Early prostate cancer may not show associated symptoms, as its incubation period is imperceptible in development [5]. Most patients with prostate cancer are in the middle and advanced stages at the time of diagnosis, resulting in the overall prognosis of patients with prostate cancer in China being much lower than that in Western Europe and the United States [6]. Treatment modalities also vary widely among patients with different types of prostate cancer [7]. Patients with early, low-risk prostate cancer can achieve good therapeutic effects by radical surgery or radical radiotherapy and can even be cured [8]. However, patients with advanced, high-risk prostate cancer generally chose palliative treatment based on androgen deprivation therapy to prolong their survival [9]. The 2020 European Urological Association Prostate Cancer Diagnosis and Treatment Guidelines and the National Comprehensive Cancer Network Prostate Cancer Clinical Practice Guidelines point out that patients with different types of prostate cancer have different treatment modalities and also have different prognoses [10,11].

Serum creatinine is a metabolite of human muscle, which is closely related to the total amount of muscle in the body. The determination of serum creatinine concentration is an effective indicator for evaluating the glomerular filtration rate (GFR), which is important for clinical diagnosis and treatment [12]. In recent years, studies have shown that serum creatinine levels are correlated with serum-free prostate-specific antigen (PSA) levels, and changes in renal function can affect PSA [13]. Moreover, serum creatinine has been identified to be of clinical value in the diagnosis or prognosis of various neoplastic diseases, such as pancreatic cancer, vulvar cancer, and epithelial ovarian cancer [14-17].

At present, accurately distinguishing high-risk from low-risk patients in the clinical work of prostate cancer is one of the intractable problems facing clinicians and has an important impact on the treatment and prognostic measures of patients. However, studies on the prognostic role of serum creatinine in patients with prostate cancer are relatively scarce. Therefore, the primary aim of this study was to investigate the role of serum creatinine levels in the prognostic risk stratification of patients with prostate cancer to provide direction for clinical decision-making.

Material and Methods

The data of this study were obtained from the "Prostate Cancer Data Set" in the National Population Health Data Center (https://www.ncmi.cn/), which is a scientific data warehouse established by a number of scientific research institutions, universities, and hospitals in China that has stored more than 15 000 datasets to date. The "Prostate Cancer Data Set" (https://www.ncmi.cn/phda/dataDetails.do?id=CSTR:A0006.11.A0005.201905.000531) includes the data of prostate cancer patients collected by the Chinese PLA General Hospital from January 1, 2010, to December 31, 2019. The original data were retrieved from the Chinese PLA General Hospital electronic medical record system and cleaned by the 301 Hospital's data engineers. This dataset is freely available and includes data on 3000 patients (1406 with benign prostatic hyperplasia and 1134 with prostate cancer) hospitalized in the Chinese PLA General Hospital. We signed a data use agreement and obtained approval from the National Clinical Medical Science Data Center (the Chinese PLA General Hospital).

The criteria for exclusion were (1) patients with benign prostatic hyperplasia (n=1406); (2) patients with a missing Gleason score (n=524); (3) patients with a total missing PSA (n=226). Finally, a total of 1134 patients with prostate cancer met the analysis requirements of this study (**Figure 1** shows the flowchart of patients' inclusion and exclusion).

The prognostic risk of patients was classified according to the D'Amico risk classification of the EAU guidelines [18]. According to the Gleason score and total PSA, patients with a Gleason score ≥8 and total PSA >20 ng/mL were included in the high-risk prostate cancer group, while the remaining patients were included in the low-risk prostate cancer group4[19]. After grouping, there were 134 patients in the high-risk group and 1000 patients in the low-risk group. According to the serum creatinine level quintiles, the patients were divided into the following 5 groups: *Q*1 (<70.1 umol/L), *Q*2 (70.1-76.8 umol/L), *Q*3 (76.8-83.4 umol/L), *Q*4 (83.4-92.1 umol/L), and *Q*5 (>92.1 umol/L). Blood specimens of patients were collected and tested by a single laboratory within 15 days before a 12-core transperineal ultrasound-guided prostate biopsy was performed. Serum creatinine and other biochemical indexes were obtained from the results of blood tests.

Statistical Analysis

Continuous variables were expressed as mean±standard deviation, and the independent sample *t* test was used for

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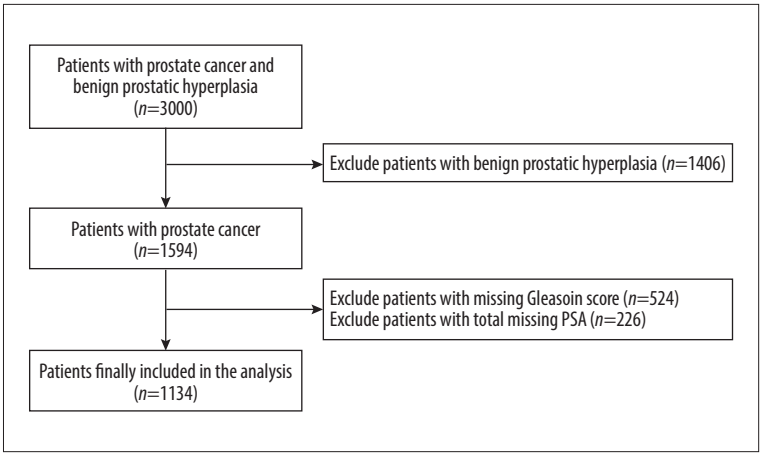

Figure 1. Patient flowchart.

comparison. Categorical variables were expressed as frequencies (%) and compared using the chi-square test. Logistic regression was used to assess the relationship between serum creatinine levels and the level of prognostic risk and to adjust for other potential confounders. First, a univariate logistic regression analysis was performed to determine factors associated with a high-risk prognosis. Then, to determine the independent association between serum creatinine and a high-risk prognosis, we developed 3 multiple logistic regression models (with *Q*2 as the reference group): model 1 (unadjusted), model 2 (adjusted for age and body mass index [BMI]), and model 3 (further adjusted for univariate analysis of statistically different variables on the basis of model 2, including age, BMI, serum albumin, alkaline phosphatase, creatine kinase isoenzyme, calcium, inorganic phosphorus, lactate dehydrogenase, low-density lipoprotein cholesterol, and apolipoprotein A1. In the curve fitting, we used restricted cubic splines to assess the curve relationship between serum creatinine levels and high-risk prognosis in prostate cancer patients. In view of the potential confounders associated with high-risk prostate cancer, we performed stratified analyses according to age (≥67 years, <67 years) and BMI (≥24 kg/m^2, <24 kg/m^2), respectively, and adjusted for confounders in model 3 (except stratification factors) to assess whether there was heterogeneity in the relationship between serum creatinine and the prevalence of a high-risk prognosis. R language (version 4.03) was used for plotting and statistical analysis. $P<0.05$ was considered statistically significant for all analyses.

Ethics

This study was based on publicly available data from the "Prostate Cancer Data Set" in the National Population Health Data Center and did not involve interaction with human participants or the use of personally identifiable information. The study did not require informed consent, and the authors obtained a data use agreement from the National Clinical Medical Science Data Center.

Results

Among the 1134 patients with prostate cancer, 134 (11.8%) had a high-risk prognosis. Their mean age was 66.9 years, with a standard deviation of 8.0 years; and the mean BMI was 24.9 kg/m^2, with a standard deviation of 3.0 kg/m^2. The results showed that the levels of alkaline phosphatase, creatine kinase isoenzyme, calcium, lactate dehydrogenase, and creatinine in the high-risk group were significantly higher than those in the low-risk group, while the levels of serum albumin, inorganic phosphorus, low-density lipoprotein cholesterol, and apolipoprotein A1 were higher in the low-risk group. The specific results are shown in **Table 1**.

In the unadjusted logistic regression model (**Table 2**), with serum creatinine group *Q*2 (70.1-76.8 umol/L) as the reference group, the rate of high-risk prostate cancer prognosis in *Q*1 (<70.1 umol/L), *Q*3 (76.8-83.4 umol/L), *Q*4 (83.4-92.1 umol/L), and *Q*5 (>92.1 umol/L) groups were statistically significant. After adjusting for age and BMI, the odds ratio (OR; 95% CI) of the rate of high-risk prostate cancer prognosis was 3.66 (1.75-7.67) and 3.76 (1.80-7.87) in the *Q*1 and *Q*5 groups, respectively, compared with the *Q*2 group. After adjusting for age, BMI, serum albumin, alkaline phosphatase, creatine kinase isoenzyme, calcium, inorganic phosphorus, lactate dehydrogenase, low-density lipoprotein cholesterol, and apolipoprotein A1 in model 3, the OR (95% CI) for the rate of high-risk prostate cancer prognosis was 5.46 (2.16-13.80) in the *Q*5 group, compared with the *Q*2 group, $P<0.001$. The curve fitting results showed that there was a U-shaped curve relationship between serum creatinine and a high-risk prognosis, and too low or too high serum creatinine levels increased the occurrence of a high-risk prognosis (**Figure 2**).

The results of the subgroup analysis showed that there was no significant heterogeneity between serum creatinine level and a high-risk prognosis (P-interaction >0.05) (**Table 3**).

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Table 1. Characteristics of patients with prostate cancer.

Characteristics	All patients (n=1134)	Low-risk patients (n=1000)	High-risk patients (n=134)	*P* value
Age, years	66.9 (8.0)	66.8 (8.1)	68.1 (7.5)	0.083
BMI (kg/m^2)	24.9 (3.0)	24.9 (3.0)	24.4 (2.8)	0.078
Serum albumin (g/L)	41.3 (3.1)	41.4 (3.0)	40.7 (3.5)	0.007
Alkaline phosphatase (U/L)	85.2 (156.6)	78.7 (142.2)	134.2 (233.4)	0.003
Creatine kinase isoenzyme (U/L)	15.4 (10.1)	15.2 (9.4)	17.5 (13.9)	0.032
Serum sodium (mmol/L)	142.5 (2.3)	142.6 (2.3)	142.4 (2.6)	0.407
Serum calcium(mmml/L)	2.3 (0.1)	2.3 (0.1)	22.2 (0.1)	0.012
Serum chlorine (mmol/L)	104.4 (3.1)	104.4 (3.0)	104.3 (3.5)	0.913
Serum phosphorus (mmol/L)	1.1 (0.2)	1.2 (0.2)	1.1 (0.2)	0.017
Lactic dehydrogenase (U/L)	155.9 (36.3)	154.4 (32.3)	167.2 (57)	0.001
Creatine kinase (U/L)	93.8 (52.5)	94.6 (52.4)	87.7 (53.4)	0.163
Serum creatinine (μmol/L)	83.2 (33.1)	81.8 (15.5)	93.9 (86)	0.007
Serum uric acid (μmol/L)	334.2 (80.4)	333.8 (79.0)	337.2 (91)	0.643
Triglyceride (mmol/L)	1.4 (0.9)	1.4 (0.9)	1.4 (1.2)	0.560
High-density lipoprotein cholesterol (mmol/L)	1.2 (0.3)	1.2 (0.3)	1.1 (0.3)	0.052
Low-density lipoprotein cholesterol (mmol/L)	2.8 (0.8)	2.9 (0.8)	2.7 (0.9)	0.016
Apolipoprotein A1(g/L)	1.3 (0.3)	1.3 (0.3)	1.2 (0.3)	0.004
Apolipoprotein B (g/L)	0.9 (0.2)	0.9 (0.2)	0.9 (0.2)	0.164

Table 2. Odds ratio and 95% confidence interval of 1134 patients with prostate cancer according to the quintiles of serum creatinine.

Model	Serum creatinine (umol/L)				
	Q1: <70.1	Q2: 70.1-76.8	Q3: 76.8-83.4	Q4: 83.4-92.1	Q5: ≥92.1
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
	P	*P*	*P*	*P*	*P*
Number of patients	222	225	227	229	228
Model1	3.62 (1.73, 7.56)	Ref	3.02 (1.43, 6.39)	3.24 (1.54, 6.80)	3.77 (1.81, 7.83)
	<0.001	Ref	0.004	0.001	<0.001
Model2	3.66 (1.75, 7.67)	Ref	3.00 (1.42, 6.34)	3.27 (1.55, 6.87)	3.76 (1.80, 7.87)
	<0.001	Ref	0.004	0.002	<0.001
Model3	4.87 (1.91, 12.38)	Ref	4.62 (1.81, 11.78)	4.25 (1.69, 10.71)	5.46 (2.16, 13.80)
	0.001	Ref	0.001	0.002	<0.001

Model 1: crude. **Model 2:** adjusted for age and BMI. **Model 3:** adjusted for age, BMI, serum albumin, alkaline phosphatase, creatine kinase isoenzyme, serum calcium, serum phosphorus, lactic dehydrogenase, low-density lipoprotein cholesterol, and apolipoproteinA1.

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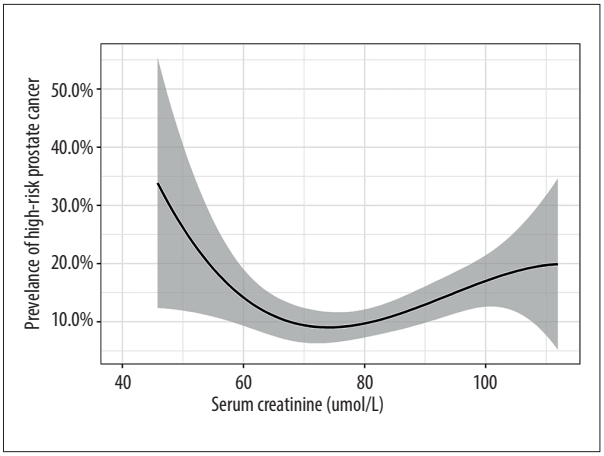

Figure 2. U-shaped relationship between serum creatinine level and high-risk prostate cancer prognosis.

Discussion

Based on data from 1134 patients with prostate cancer, the main finding of this study was that serum creatinine was an independent risk factor for a high-risk prostate cancer prognosis, and the relationship showed a U-shaped curve. Patients with decreased and increased serum creatinine levels have a significantly higher prognostic risk of prostate cancer. The prognostic risk of prostate cancer was lowest when serum creatinine levels were in the range of 70.1-76.8 umol/L. In the different adjusted models, the groups were consistent with the associations obtained before adjustment.

At present, there are very few studies on the relationship between serum creatinine and the prognosis of prostate cancer. A relevant domestic study has shown that the combined detection of sarcosine levels and matrix metallopeptidase 9 has diagnostic value for prostate cancer, and sarcosine is involved in the cancerous process of the prostate [20]. Moreover, in another study involving 262 patients with prostatic diseases, it was shown that sarcosine showed an increase during prostate cancer; however, it could also reflect the degree of invasion of prostate cancer [21]. The results of a case-control study in Nigeria showed that the increase in serum urea and creatinine concentrations and the decrease in cystatin C levels can increase the risk of renal dysfunction in patients with prostate cancer [22]. These studies suggest a possible implication of serum creatinine in the prognostic risk stratification in prostate cancer. After 1134 patients with prostate cancer in the present study were adjusted for age, BMI, serum albumin, alkaline phosphatase, calcium, and other risk factors, lower or higher serum creatinine levels were significantly associated with a high-risk prostate cancer prognosis. Our findings suggest an independent predictive role of serum creatinine in prostate cancer prognosis and suggest that controlling serum creatinine concentrations in patients with prostate cancer at 70.1 to 76.8 umol/L may have positive significance for patient prognosis.

Additional studies have been on the role of creatine and sarcosine in the development of prostate cancer and the role of serum creatinine in the diagnosis of prostate cancer [23,24]. However, there are very few studies on the relationship between serum creatinine and the prognostic risk of prostate cancer, and the exact mechanism is still unclear. Therefore, based on previous studies, we proposed the following hypothesis about the mechanism of the relationship between serum creatinine and high-risk prostate cancer prognosis: Serum creatinine levels can reflect the nutritional, metabolic, and renal status of patients to some extent [25]. Clinically, a decrease in serum creatinine indicates that the patient's total muscle mass

Table 3. Odds ratio and 95% confidence interval of high risk of prostatic cancer according to quintiles of creatinine: subgroup analyses.

Subgroups	Serum creatinine (umol/L)					P-interaction
	Q1	Q2	Q3	Q4	Q5	
Age, years						0.824
<67 (medium)	3.60 (0.94-1.39)	Ref	4.18 (1.05-1.66)	2.60 (0.63-1.08)	5.73 (1.44-2.28)	
≥67	5.81 (1.55-21.72)	Ref	5.45 (1.47-20.19)	6.39 (1.80-22.68)	6.07 (1.68-21.94)	
BMI, kg/m^2						0.129
<24	6.16 (1.29-29.37)	Ref	7.34 (1.57-34.20)	5.13 (1.04-25.36)	3.30 (0.59-18.59)	
≥24	4.31 (1.30-14.25)	Ref	3.00 (0.87-10.34)	4.16 (1.32-13.13)	6.64 (2.15-20.49)	

Except for stratified variables, all variables are adjusted according to Model 3 in Table 2.

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is reduced and malnourished, while an increase indicates impaired renal function [26]. Serum creatinine is mainly derived from the nonenzymatic conversion of creatine and phosphocreatine [27]. Most of the creatine and phosphocreatine are produced by muscle, and creatinine is excreted in the urine almost exclusively after renal filtration [28]. Some studies have shown that a too-low level of serum creatinine in malignant tumors affects the prognosis of patients [29]. They concluded that the decrease in serum creatinine in patients with malignant tumors is due to the presence of varying degrees of cachexia, resulting in thin muscles, hypoproteinemia, and severe malnutrition, which may lead to reduced survival time and poor prognosis [30]. Moreover, there are large differences in the metabolism between tumor cells and normal human cells [31]. In view of the rapid growth characteristics of tumor cells, more nutrients and adenosine triphosphate (ATP) conversion processes are often required to maintain their high metabolism and rapid growth characteristics [32]. Sarcosine plays an important role in the process of ATP metabolism [33]. Many studies have shown that cancer cells have increased sarcosine concentrations at high metabolic levels [34].

Sarcosine is the main amino acid for the synthesis of creatine and creatinine. A high concentration of sarcosine will lead to increased serum creatinine production, which also confirms the role of serum creatinine in cancer. Finally, studies have shown that blood lipids and lipoproteins are positively correlated with the high risk of prostate cancer [35]. Blood lipids are important factors affecting serum creatinine and therefore low levels of serum creatinine are mainly due to the low nutritional status of patients with prostate cancer, which affects patient prognosis [36]. High levels of serum creatinine can be involved in the conversion of nutrients and ATP in the growth of prostate tumor cells and the role of blood lipids and lipoproteins in the development of prostate cancer, resulting in an increased prevalence of prostate cancer and poor prognosis of prostate cancer patients.

Our study had limitations. First, the data of this study were obtained from a single center of the National Center for Clinical Medical Sciences (the Chinese PLA General Hospital), and the results were not as representative as those of a multicenter study. Second, we did not directly participate in the collection of study data and therefore there may be some limiting factors in the study. Third, there were some missing data on PSA and Gleason scores in the study. These patients were excluded from the data cleansing phase, which may have led to selection bias. Fourth, creatinine also reflects renal function to a degree, so preoperative renal function is an important parameter that may directly effect the prognosis of prostate cancer. In addition, prostate cancer patients with high Gleason scores can have urinary tract metastasis, which may also have had some influence on the results. Unfortunately, the dataset we requested does not have information on these 2 factors. Fifth, although confounding factors such as age and BMI were adjusted for in the multivariate model, it cannot be ruled out that other unmeasured or inadequately measured factors may have confounded the true association. Sixth, through data analysis, we concluded that the serum creatinine level has an effect on the prognostic risk of prostate cancer, but this study is a retrospective clinical observational study, and its results do not explain the causal relationship between the 2, as in longitudinal studies. Therefore, more studies are needed to provide strong evidence for the association between these 2 variables.

Conclusions

Serum creatinine levels are independently associated with a high-risk prognosis in column adenocarcinoma. The mechanism of the relationship between serum creatinine and prognosis in prostate cancer patients is still lacking strong evidence. However, our study showed that there is a U-shaped curve relationship between serum creatinine levels and the level of prostate cancer prognosis. Low or high serum creatinine levels increase the prognostic risk of prostate cancer. Controlling the serum creatinine level at 70.1 to 76.8 umol/L in patients with prostate cancer may be beneficial for their prognosis.

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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