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The Clinical Diagnostic Value of Serum Cystatin C in Patients with Prostate Cancer

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Abstract: Objective To investigate the value of serum cystatin C (Cys-C) in the clinical diagnosis of prostate cancer patients (PCa). Methods We utilized data from the 2001-2002 National Health and Nutrition Examination Survey (NHANES) cycle. Variables were downscaled by LASSO regression to screen for influencing factors, and parallel multifactorial cox regression analyses were performed to assess the association between Cys-C and prostate cancer, as well as restricted cubic spline (RCS) analyses. Subgroup analyses by age, education, race, body mass index, and smoking history were also performed. The correlation between age and Cys-C was analyzed using Spearman's correlation analysis. Results Mean ± standard deviation (SD) Cystatin C levels were higher than normal in prostate patients. The ratios (95% confidence intervals) of the univariate and multivariate models I, II and III were 1.6117 (0.0412,0.9144), 1.5841 (-0.0192,0.8819), and 1.3357 (-0.3876,0.8454), respectively. Restricted cubic spline regression analysis did not show a nonlinear correlation between cystatin C and PCa (nonlinear p=0.007). Spearman's correlation analysis showed that serum cystatin C levels were statistically significantly correlated with age (r=0.476,P<0.01). Kaplan-Meier survival curves showed that patients with high levels of Cystatin C had a faster downward trend in the survival curves. Elevated Cys-C was significantly associated with an increased risk of PCa, and prostate cancer patients with elevated Cys-C had a shorter time to survival and a lower survival rate. Conclusion Cys-C is positively correlated with the presence of PCa, serum Cys-C level has significant correlation with age, and Cys-C should be given clinically can be used as an auxiliary diagnostic index for regular monitoring of prostate cancer patients of different ages and normal people.

Keywords: Prostate Cancer; Cystatin-C; Tumor Suppressor.

1. Introduction

Prostate cancer is one of the common tumors in men. Prostate cancer (PCa) develops in unique glands of the male reproductive system and is harmful to men's health [1]. in 2015, PCa was ranked as the second most commonly diagnosed cancer in men worldwide and the fifth leading cause of cancer deaths worldwide [2]. The incidence of PCa varies widely around the world. PCa is least common in South and East Asia, most common, and moderately prevalent in Europe [3]. Despite extensive research, the exact mechanisms of prostate cancer have not been fully elucidated and further studies are needed [4]. The key to improving the survival rate of prostate cancer patients lies in early diagnosis, therefore, the study of early screening markers and therapeutic targets for prostate cancer with high specificity and sensitivity has become a hot topic in this field [5].

Cystatin C (Cys-C) is a non-glycosylated, low relative molecular mass (13×103) basic protein produced by nucleated cells [6, 7], and its secretion and excretion are not restricted by gender, age, diet, or muscle mass [8]. Related studies have shown that Cys-C is abnormally expressed in tumors, but the mechanism is not fully understood [9]. Cystatin C (Cys-C), encoded by the CST3 gene, belongs to the type 2 cystatin superfamily and has been extensively studied since it was first described in 1961 [10]. CST3 is located on the short arm of chromosome 20, spans 7.3 kb, contains four exons, encodes a 120 amino acid inhibitor of reactive cysteine proteases, and shares several features with housekeeping genes. Cys- C is ubiquitously expressed in nucleated cells of tissues such as testis, epididymis, seminal vesicles, and prostate, and is then secreted into a variety of human body fluids to inhibit the activity of cysteine proteases such as papain and histones B, H, K, and L. Cys-C is also known to inhibit the activity of cysteine proteases, such as papain and histones B, H, K, and L. In addition, Cys-C is thought to be a p53-induced tumor suppressor and apoptotic mediator that negatively regulates histone L activity during carcinogenesis. Thus, Cys-C is thought to play a key role in the tumor suppressor function of p53 as well as in extracellular protein homeostasis. An imbalance between Cys-C and cysteine proteases has been observed in the pathogenesis of several diseases, including cancer. However, the diagnostic role of Cys-C in cancers such as renal cell carcinoma and pancreatic tumors has been overlooked. Recent studies by Wegiel et al. and Jiborn et al. have shown that Cys-C is downregulated in PCa specimens. Cys-C was also found to regulate PCa cell invasion through the androgen receptor and MAPK/Erk2 pathways [11]. Abnormal expression of CysC has been associated with neuroendocrine differentiation of PCa. Another group of studies also showed that serum Cys-C levels differentiated PCa patients from BPH patients [12] and served as an indicator of metastatic PCa treatment with zoledronic acid in a small group of patients [13]. In summary, published studies have reported positive and negative effects of serum Cys-C levels in predicting malignancy [14]. Therefore, the feasibility of using serum Cys-C levels in cancer detection remains controversial. The present study focused on the relationship between serum Cys-C levels and prostate cancer to provide a new theoretical basis and research direction for prostate cancer screening and prevention.

2. Materials and Methods

2.1. Database Sources

NHANES is a cross-sectional, nationally representative survey designed to assess the health and nutritional status of noninstitutionalized civilians in the United States. The survey is unique in that it combines interviews and physical examinations. A stratified, multistage, probability survey sample was obtained based on the selection of counties, neighborhoods, households, and persons in households, with oversampling of low-income persons, adults aged 60 years or older, African Americans, and Mexican Americans. Demographic, socioeconomic, and health data were collected through household interviews by trained staff. In addition, multiple measurements, including anthropometric measurements, blood pressure, and laboratory tests, were performed on all or some of the study participants at mobile examination centers (MECs) managed by health professionals. NHANES has been an ongoing surveillance system since 1999. In the present analysis, we used the NHANES dataset from 2001-2002. Informed consent was obtained from all participants, and the Institutional Review Board of the National Center for Health Statistics of the U.S. Centers for Disease Control and Prevention (CDC) approved all protocols of the NHANES, a comprehensive description of which can be downloaded from the CDC website. (www.cdc.gov/nchs/nhanes/tutorials/default.asp)

2.2. Study Population and Exclusion Criteria

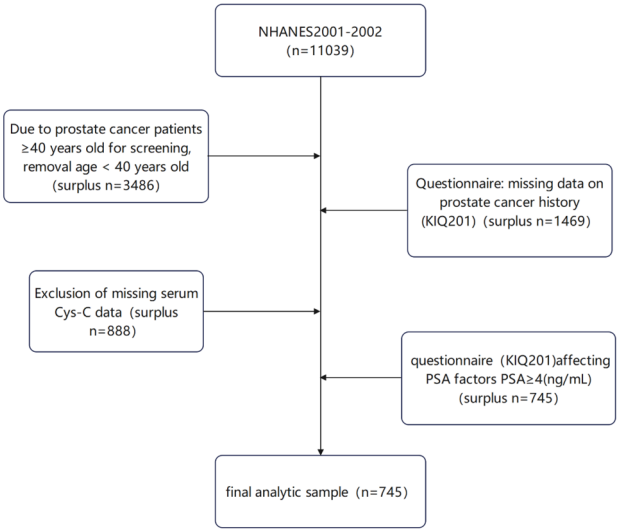

fig 1. Flowchart

Population: 11,039 NHANES participants in 2001-2002 were screened for baseline elimination, 1. Age <40 years was excluded because prostate cancer patients were screened at ≥40 years of age, 2. Based on the questionnaire, "Have you ever been told by a doctor or health professional that {you/he} has prostate cancer?" questionnaire, excluding those who refused to answer and those with missing data, 3. excluding those with missing serum Cys-C data, 4. because of the use of the "Ever been told by a doctor or health professional that {you/he} has prostate cancer?" questionnaire, in which among the participants who answered negatively, there were those who did not know whether they actually had prostate cancer or had prostate cancer without being told, and Prostate Specific Antigen (PSA) is commonly used for prostate cancer screening as a prostate cancer-specific antigen, which contains Prostate Specific Antigen (PSA) >=4 (ng/mL) can be recognized as high risk of having prostate cancer, so PSA<4 can be considered as non-prostate cancer patients, so exclude the answer of no and Prostate Specific Antigen (PSA)>=4 (ng/mL), and finally there were 745 eligible study subjects (the flowchart is presented comprehensively in Fig.1), of which there were 56 patients with prostate cancer, and 689 patients with non-prostate cancer. patients and 689 non-prostate cancer patie.

2.3. Variables

The independent variables were as follows: categorical variables included race, education, and smoking history, and continuous variables included age (years), Cystatin C (mg/L), Creatinine (mg/dL), Blood urea nitrogen (mg/dL), Cholesterol (mg/dL), Uric acid (mg/dL)

2.4. Statistical Analysis

The normal distribution of quantitative data in each group was assessed by the Kolmogorov-Smirnov test. Normally distributed data are expressed as mean ± standard deviation (SD), whereas data that did not follow a normal distribution are reported as median (range). Qualitative data were reported as numbers and percentages, and the Pearson χ test was used to compare differences between groups. Spearman correlation analysis was used for correlation between serum Cys-C levels and age. The correlation between serum Cys-C levels and age was analyzed using SPSS 16.0and DecisionLinnc Core Team (2023). DecisionLinnc. 1.0. November 2023. DecisionLinnc is a platform that integrates multiple programming language environments and enables data processing, data analysis, and machine learning through a visual interface. CHN. <https://www.statsape.com/> analyzes and processes data.

3. Results

3.1. Baseline Characteristics of Study Participants

Results From 2001-2002 a total of 11,039 NHANES participants of which 745 were included in the study, the study sample of 715 adult men, of which 56 patients had prostate cancer and 689 were non-prostate cancer patients with prostate cancer patients were over 60 years of age. Of the 715 adult men, nearly 61% were non-Hispanic whites, 66% had more than a high school education, 20% were current smokers, and 29% were obese (Table 1). It is noteworthy that prostate patients had Cys-C mean ± standard deviation (SD) of 1.22 ± 0.456 (mg/L), which is higher than the normal level of Cys-C (0.51-1.09 mg/L), and that no prostate cancer patients (No prostate cancer patients (No prostate cancer patients)) had a higher level of prostate cancer than the normal level of Cys-C (0.51-1.09 mg/L). There were significant differences in age, race, education level, and smoking behavior between the No prostate cancer and Has prostate cancer groups, with non-Hispanic whites being the main participants in our study.

3.2. Least Absolute Shrinkage and Selection Operator, LASSO-Cox

A total of 10 potentially influential factors were included in this study, Due to the possible correlation between the included study variables and the small number of prostate cancer cases, the 10 variables were downscaled by LASSO regression to screen the most representative factors influencing prostate outcomes. The optimal parameter (λ) in

the LASSO model was selected by minimum standard using 5-fold cross-validation with partial likelihood bias as the Y-axis and log(λ) as the X-axis, with the 1SE of the minimum λ value and the minimum λ value Dashed vertical lines were plotted at the optimal value, with the minimum λ value as the optimal value of the model, see Fig. 2. Coefficient profiles were generated based on the log(λ) series, and the LASSO coefficient profiles for the 10 variables are shown in Fig. 3. Counting the number of variables corresponding to the nonzero regression coefficients, the LASSO regression results showed that the age, BMI, ethnicity, Cystatin C (mg/L), Blood urea nitrogen (mg/dL), and Uric acid (mg/dL). 6 variables were the influencing factors of whether or not to develop prostate cancer. A multifactorial Cox proportional risk regression model was constructed with the presence of prostate cancer (prostate cancer = 1, non-prostate cancer = 0) as the dependent variable, and the six variables screened by the LASSO regression model as the independent variables, in which age, Cystatin C (mg/L), and Uric acid (mg/dL) were the independent influencing factors for prostate cancer patients. A multifactor Cox proportional risk regression model and ROC curve diagram were established. As shown in Fig. 4 Fig. 5, AUC=0.945 in the ROC curve graph.

Table 1. Patient baseline characteristics

	Prostate cancer status		
Characteristics	No prostate cancer	Has prostate cancer	P (for z-test)
Patients(n)	689	56	
Age (years) (%)			
40_49	124 (18.00)	0 (0.00)	<0.001
50_59	82 (11.90)	0 (0.00)	
60_69	234 (33.96)	15 (26.79)	
70_79	162 (23.51)	22 (39.29)	
80_85	87 (12.63)	19 (33.93)	
Race/Ethnicity (%)			
Mexican American	130 (18.87)	2 (3.57)	0.027
Other Hispanic	19 (2.76)	0 (0.00)	
Non-Hispanic White	415 (60.23)	41 (73.21)	
Non-Hispanic Black	108 (15.67)	12 (21.43)	
Other Race	17 (2.47)	1 (1.79)	
Education (%)			
Less than high school	235 (34.11)	16 (28.57)	0.532
High school	156 (22.64)	16 (28.57)	
More than high school	298 (43.25)	24 (42.86)	
Body mass index(kg/m2) (%)			
<25	160 (23.22)	16 (28.57)	0.251
25-30	323 (46.88)	29 (51.79)	
>30	206 (29.90)	11 (19.64)	
Smokinghistory (%)			
current	146 (21.19)	2 (3.57)	0.006
former	315 (45.72)	31 (55.36)	
never	228 (33.09)	23 (41.07)	
Cystatin C (mg/L)	1.057±0.454	1.22±0.456	0.010
Creatinine (mg/dL)	132.771±70.103	126.073±62.814	0.493
Blood urea nitrogen (mg/dL)	16.875±7.25	19.768±8.67	0.005
Cholesterol (mg/dL)	198.808±40.618	192.411±42.962	0.259
Uric acid (mg/dL)	6.147±1.427	6.162±1.836	0.941

3.3. Univariate and Multivariate Logistic Regression Models

The constructs are shown in Table 2. Divided into three models, all of the above models showed a positive correlation between Cys-C and PCa, with all p-values less than 0.05. The ratio of ratios (95% confidence intervals) for models I, II and III were 1.6117 (0.0412,0.9144), 1.5841 (-0.0192, 0.8819) 1.3357 (-0.3876,0.8454). For further sensitivity analysis and to assess trends, Cys-C was divided into quartiles in Table 2. In Model III, when comparing the Q2, Q3, and Q4 groups to

the reference Q1 group, the corrected ratio ratios (95% confidence intervals) for the risk of PCa were 3.4785 (0.2200,2.4306), 3.4700 (0.2097,2.4348), and 4.879 (0.5202,2.8063), respectively (p for trend=0.0100). Again, these trends persisted in Model I (p=0.0006 for trend) and Model II (p=0.0021 for trend). The multi-model ROC curves are shown in Figure 6f, with AUCs of 0.652, 0.736, and 0.741 in M1, M2, and M3, respectively.

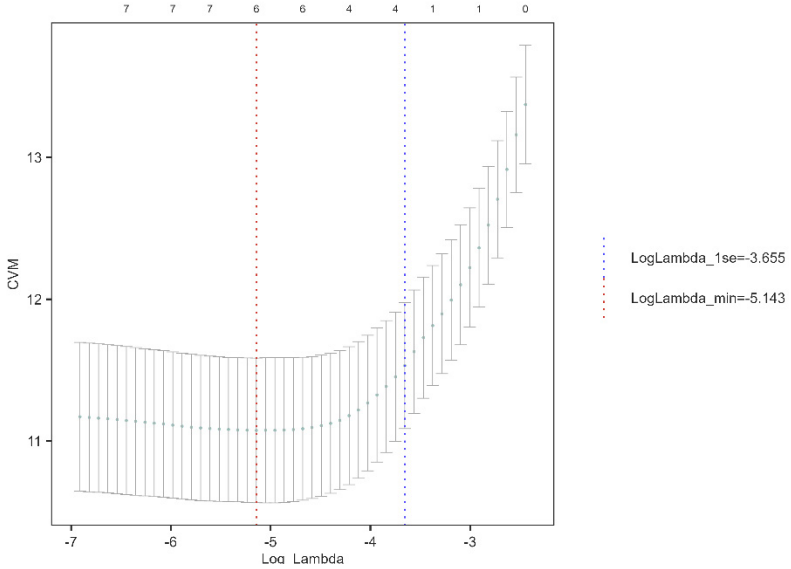

fig 2. Log Laaso Regression lambda and CVM Plot

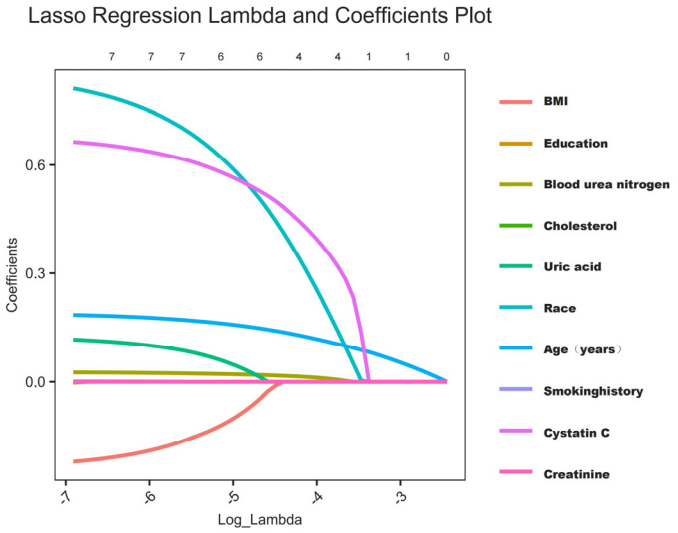

fig 3. Coefficients Plot

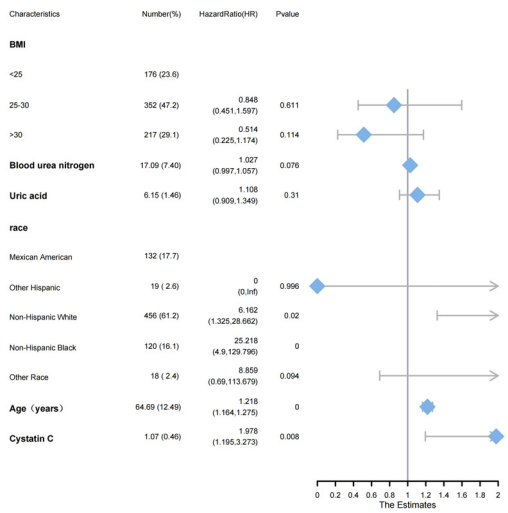

fig 4. COX Regression HR Forest Plot

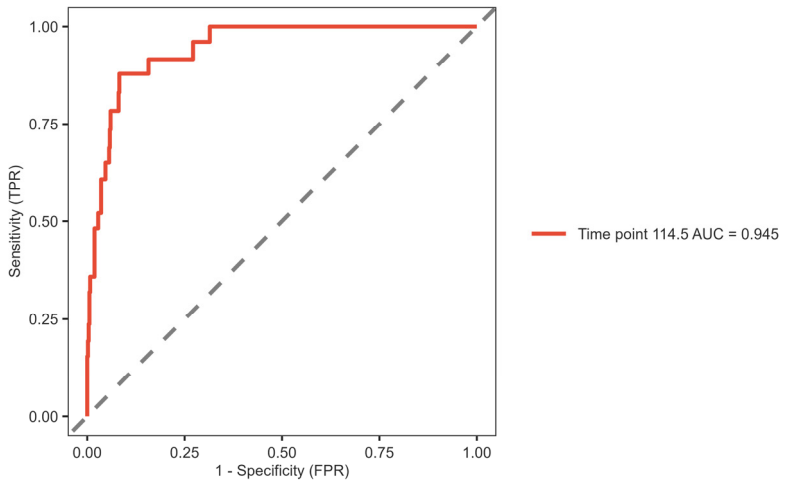

fig 5. COX Regression ROC Curve Plot

Table 2. Regression models for univariate and multivariate analysis

Exposure	**Model**		**Mode2**		**Mode3**	
	OR	Pvalue	OR	Pvalue	OR	Pvalue
Cystatin C	1.6117 (0.0412,0.9144)	0.0251	1.5841 (-0.0192, 0.8819)	0.0366	1.3357 (-0.3876,0.8454)	0.3302
Cystatin C(quartile)						
Q1	reference		reference		reference	
Q2	3.0253 (0.1235,2.2534)	0.0373	3.3842 (0.1988,2.3977)	0.0267	3.4785 (0.2200,2.4306)	0.0242
Q3	3.1521 (0.1641,2.2948)	0.0308	3.4421 (0.2090, 2.4206)	0.0255	3.4700 (0.2097,2.4348)	0.0255
Q4	5.4050 (0.7747,2.7963)	0.0008	5.2955 (0.7005,2.8194)	0.0017	4.8798 (0.5202,2.8063)	0.0057
p for trend		0.0006		0.0021		0.0100

Unadjusted models 1 will be adjusted for none.

Minimally adjusted models 2 adjust for BMI (kg/m ^{2}), race/ethnicity, Smokinghistory, education level

Fully adjusted models 3 adjust for BMI (kg/m ^{2}), age, race/ethnicity, education level, Smokinghistory, Creatinine (mg/dL), Blood urea nitrogen (mg/dL), Cholesterol (mg/dL) and Uric acid (mg/dL).

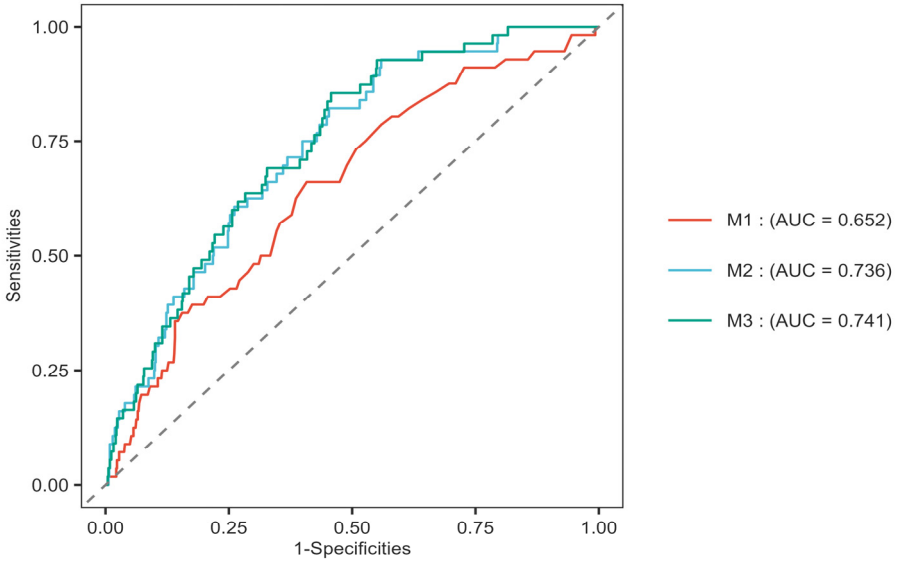

fig 6. Mulit-logistic Regression Model ROC Curve Plot

To identify and visualize the nonlinear relationship between Cys-C and PCa, the data were fitted by a restricted cubic spline regression model (Fig 7). The results showed a nonlinear correlation between Cys-C and PCa (nonlinear p=0.007) and the corrected ORs for PCa increased with increasing Cys-C.

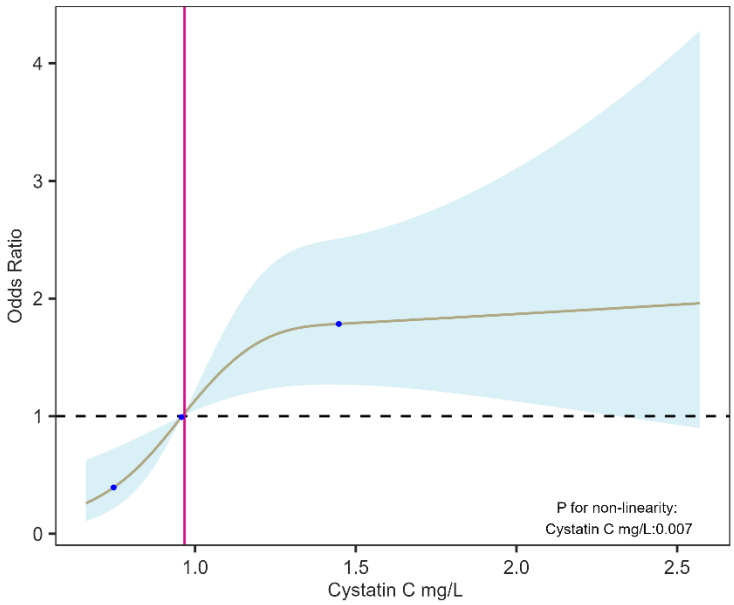

fig 7. RCS Prediction Plot

3.4. One-way Subgroup Cox Analysis

Cys-C one-way subgroup cox analysis showed (Figure 8) that all associations were positive across subgroups, except for the subgroup of other races, which was negative. Age, education water, race, BMI, and smoking history were statistically different on average (P < 0.05).

Variable	Count	Percent	Point_Estimate	Lower	Upper	P_value	P_for_interaction
Overall	745	100	1.89	1.71	2.08	<0.001	
years							<0.001
40_49	124	16.6	3.29	1.75	6.17	<0.001	
50_59	82	11	1.36	0.74	2.48	0.317	
60_69	249	33.4	5.15	3.4	7.8	<0.001	
70_79	184	24.7	1.6	1.35	1.89	<0.001	
80_85	106	14.2	3.08	1.8	5.27	<0.001	
race							<0.001
Mexican American	132	17.7	1.76	1.41	2.19	<0.001	
Other Hispanic	19	2.6	13.08	1.03	165.57	0.047	
Non-Hispanic White	456	61.2	4.27	3.49	5.21	<0.001	
Non-Hispanic Black	120	16.1	1.41	1.02	1.94	0.036	
Other Race	18	2.4	0.14	0	299.03	0.617	
ducation							<0.001
Less than high school	251	33.7	1.58	1.37	1.83	<0.001	
High school	172	23.1	3.24	2.33	4.51	<0.001	
More than high schoo	322	43.2	5.22	3.81	7.16	<0.001	
BMI							<0.001
<25	176	23.6	1.6	1.35	1.91	<0.001	
25-30	352	47.2	2.18	1.84	2.57	<0.001	
>30	217	29.1	4.03	2.78	5.84	<0.001	
smokinghistory							0.001
current	148	19.9	6.29	3.73	10.6	<0.001	
fomer	346	46.4	2.05	1.72	2.46	<0.001	
never	251	33.7	1.79	1.54	2.08	<0.001	

fig 8. Univariate Subgroup COX Regression Analysis Plot

3.5. Analysis of the Correlation between Serum CystatinC Levels and Age

Age was tested for normality using Lilliefors test (Fig9). The percentile of the variable was D = 0.077, p <= 0.05, indicating that the variable did not conform to the normal distribution was tested, the age of the patients collected in this study was not normally distributed. The correlation between serum Cys-C level and age was analyzed by Spearman correlation analysis. Spearman correlation analysis showed (Fig 10), serum Cys-C level was significantly correlated with age and the difference was statistically significant (r=0.476, P<0.01), suggesting that serum Cys-C level increased with age.

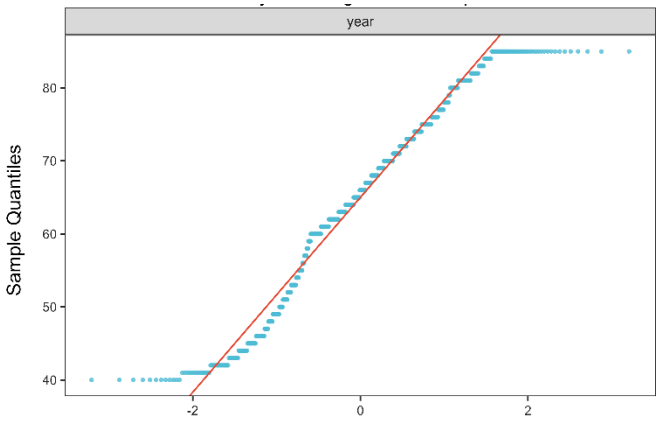

fig 9. Theoretical Quantiles

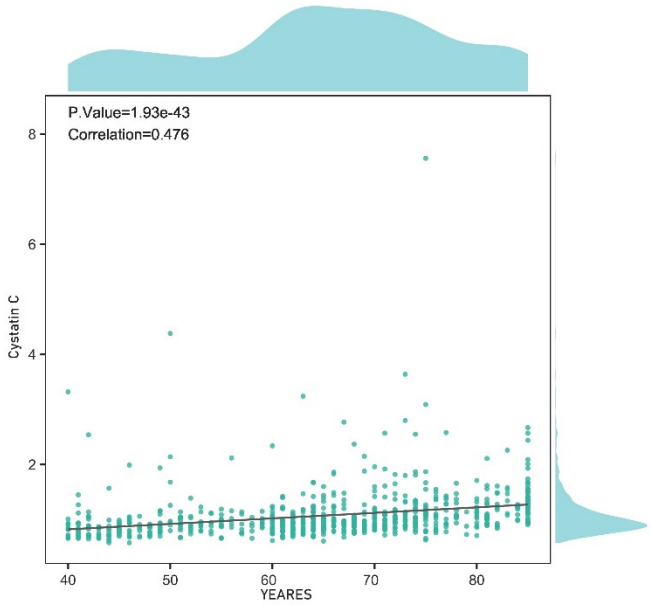

fig 10. Linear Correlation Analysis Scatter Plot

3.6. Univariate Analysis of Survival in Prostate Cancer Patients

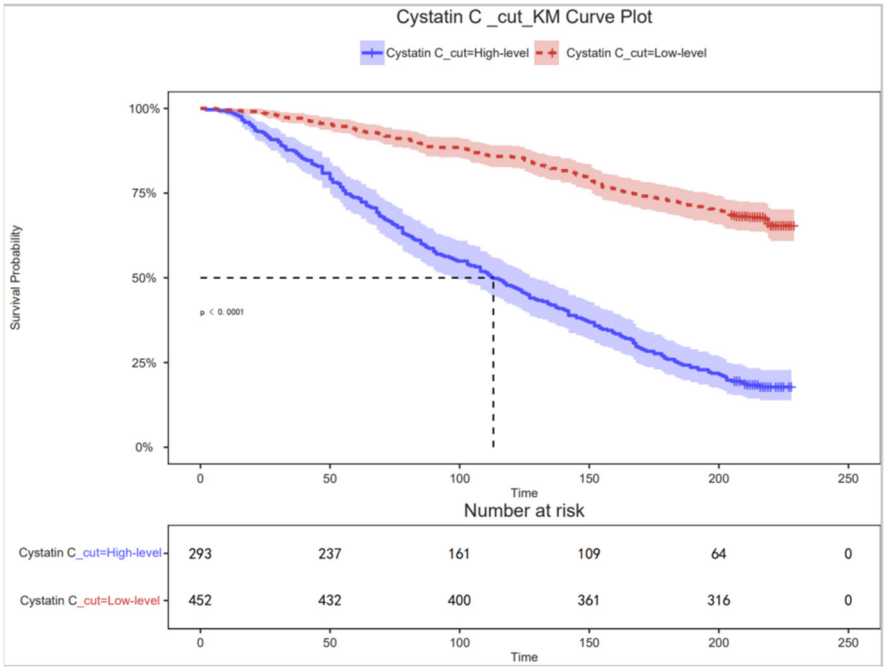

fig 11. Cystatin C cut KM Curve Plot

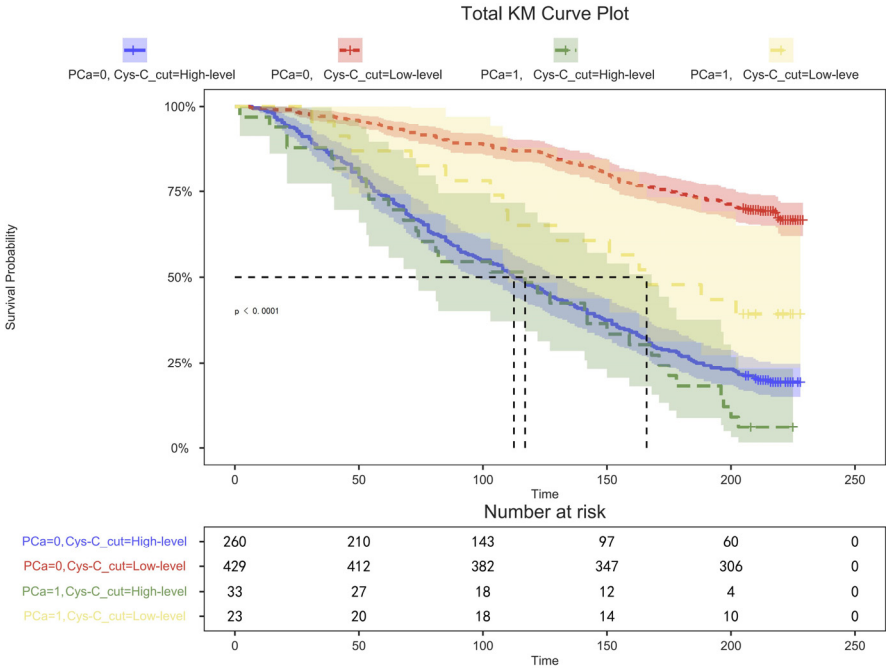

fig 12. Total KM Curve Plot

Kaplan-Meier survival curves were plotted (Figs. 11k and 12l), and the survival time was measured in months, and a simple comparison was made between the survival rates of the High-level and Low-level groups of patients with Cys-C and whether they were groups of patients with prostate cancer or not. As can be seen from the figure, the Kaplan -Meier survival curves of patients with high levels of Cys-C are closer to the horizontal axis, and the survival curves have a faster decreasing trend, and the overall survival of patients with low levels of Cys-C expression is higher than that of patients with high levels of Cys-C expression, and the survival curves of patients with high levels of Cys-C are faster decreasing than those of patients with low levels of Cys-C expression, and the survival curves of patients with low levels of Cys-C are faster decreasing than those of patients with low levels of Cys-C expression. The survival curves of patients with high levels of Cys-C showed a faster decreasing trend. This suggests that prostate cancer patients with high Cys-C levels will have shorter survival time and lower survival rate than those with low Cys-C levels.

4. Discussion

In this cross-sectional study, we observed that the average level of Cys-C in prostate cancer patients was significantly higher than that in normal subjects, suggesting that Cys-C plays an important role in the pathogenesis of prostate cancer and can be used as a potential diagnostic indicator of prostate cancer; at the same time, we also found that the serum Cys-C level of the patients increased gradually with age, suggesting that age affects serum Cys-C level of prostate cancer patients, suggesting that Cys-C can be a supplementary diagnostic indicator for regular monitoring of patients of different ages and normal subjects. Meanwhile, the present study also found that the serum Cys-C level of patients increased gradually with age, indicating that age affects the serum Cys-C level of prostate cancer patients, which suggests that Cys-C can be used as an auxiliary diagnostic index for the regular monitoring of patients with prostate cancer of different ages and normal people.

Serum Cys-C, also known as cysteine protease inhibitor C, is usually regarded as an ideal marker reflecting the early impairment of renal function [15], and also as an endogenous inhibitor of lysosomal cysteine proteases inhibits the activity of tissue proteases B, H, K, L, and S, regulates the level of intracellular protein hydrolysis, and plays an important role in a number of physiological and pathological processes [16]. In recent years, many studies have shown that serum Cys-C is closely related to the prognosis of malignant tumors [17]. Guo et al. [18] found that in renal clear cell carcinoma, the overall survival of patients with low levels of serum Cys-C was higher than that of patients with high levels of Cys-C, which suggests that serum Cys-C can be used as an ideal prognostic biomarker of tumors [19, 20]. Relevant literature has demonstrated the high clinical value of Cys-C in the diagnosis and prognosis of PCa.

The most important feature of malignant tumors is the uncontrolled growth of abnormal cells in the human body, because cystatin C can be expressed in almost all nucleated cells [20], and thus it is hypothesized that cystatin C will be highly expressed in tumor tissues. In recent years, there is increasing experimental and clinical evidence that cysteine protease inhibitors may also be involved in the pathogenesis of various human pathological conditions, including cancer. Therefore, Cys-C is important for the monitoring of tumorigenesis, progression and recurrence.

The limitations of this study are similar to those inherent in all case-control studies. Because the NHANES database only has 2 cycles of Cys-C records (1999-2000 and 2001-2002), the 1999-2000 cycle has many missing data, so the number of cases was not used, and the number of cases was small. In addition, due to the small number of cases and false-negative situation, the diagnosis of prostate cancer was not based on the use of penetrating pathology, and we did not use the diagnosis of prostate cancer. Instead, we used the questionnaire “Have {you/he} ever been told by a doctor or health professional that {you/he} has prostate cancer?” to diagnose prostate cancer. The exclusion of patients with Prostate Specific Antigen (PSA) >= 4 (ng/mL), which can be found in patients who have not been told they have prostate cancer, reduces the false-negative rate, and we therefore

expect that any effect of the referral on the report will be equivocal. The main effect of this misclassification may therefore be an OR attenuation of zero.

Selection bias is a common problem in case-control studies. Selection bias may result when neither cases nor controls are representative of the same target population, or when voluntary subjects are not representative of the entire target population because of "self-selection." First, NHANES did not collect imaging and pathology data from its participants; therefore, we relied on self-reported physician-diagnosed PCa cases to define PCa patients. Some recall bias should be considered. Second, our study was a cross-sectional analysis, which inherently limits the ability to establish clear causal relationships. In addition, the lack of NHANES follow-up data on Cys-C and PCa patients further contributes to the uncertainty of the temporal relationship between Cys-C alterations and PCa prognosis. Third, due to limitations of the NHANES database, we were unable to obtain clinical data on grading, staging, and treatment of PCa in our subjects, thus hindering stratified assessment of potential changes in the association between Cys-C and PCa risk or progression. Fourth, the potential impact of modifications in prostate cancer screening strategies, which could lead to changes in PCa incidence at that particular stage, was overlooked.

In summary, the role of serum Cys-C levels as a potential molecular marker of prostate cancer with high expression in the clinical management of prostate cancer provides a new theoretical basis for the development of prostate cancer prevention and treatment strategies.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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