ANALYSIS OF SERUM CYSTATIN C LEVELS IN HEALTHY INDIVIDUALS IN NANCHONG (SICHUAN PROVINCE, CHINA)

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ABSTRACT

Objective*: The aim of the present study was to investigate the distribution and abnormal detection rate of serum cystatin C (CysC) levels in healthy individuals in Nanchong (Sichuan Province, China).*

Methods*: A group of healthy individuals undergoing physical examinations at a tertiary A hospital in Nanchong City from January to August 2018 was studied to compare serum CysC levels and their abnormal detection rates as a function of age, sex, blood pressure, blood glucose, blood lipids, and body mass index (BMI).*

Results*: Serum CysC levels and their abnormal detection rate in healthy individuals were 0.79±0.25 mg/L and 8.5%, respectively, which gradually increased with age. At different ages, the abnormal detection rate was significantly higher in males than in females (P<0.05). For individuals under 60 years old, serum CysC levels were higher in males than in females (P<0.05). Individuals who were overweight or obese, had high blood pressure, or had abnormal blood lipids had higher serum CysC levels and abnormal detection rates than those with normal or low BMIs, normal or low blood pressure, or normal blood lipids, respectively (P<0.05).*

Conclusions*: Serum CysC levels and abnormal detection rates were high in our Nanchong cohort. Hence, public health departments should strengthen the prevention and treatment of chronic kidney disease, especially in individuals who are overweight/obese or have high blood pressure, abnormal blood lipids, or high blood glucose.*

Keywords: *cystatin C, physical check-ups, Renal impairment, chronic kidney disease.*

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Introduction

With the increase in population and aging and the epidemiological trend of chronic diseases, such as diabetes and hypertension in recent years, the incidence, prevalence, mortality, and disability-adjusted life years (DALYs) of chronic kidney disease (CKD) have gradually increased and become a globally recognized public health issue[(1)]. CKD exhibits a covert onset, atypical early symptoms, low awareness rate, high end-stage renal disease (ESRD) medical costs, many complications, and irreversible properties. Early diagnosis of the disease and standardized management of CKD patients effectively slows the decline of renal function, delays the development of more CKD patients to ESRD, improves the quality of life of affected patients, and saves family and social medical resources[(2,3)]. Therefore, early screening of CKD is particularly important. Blood creatinine is the most commonly used indicator for CKD screening, but it is easily affected by extrarenal factors, such as diet and muscle mass. Furthermore, blood creatine will only increase when the glomerular filtration rate

(GFR) decreases by more than 50%, limiting the early diagnosis of CKD[4,5]. Serum cystatin C (CysC) is a new indicator for detecting renal function. It has favorable characteristics in terms of a constant production rate and quantity, as well as a small molecular weight. CysC is almost entirely filtered in glomeruli, reabsorbed and catabolized in the proximal tubule, and is less affected by other factors, such as diets, weight, and drugs. Changes in CysC levels are easily detected when kidney function is mildly or moderately impaired, indicating that it is a reliable indicator for early screening of CKD[4,6].

The present study analyzed serum CysC levels to determine their relationships with gender, age, body mass index (BMI), blood pressure, blood glucose, and other indicators to initially understand the prevalence of CKD in Nanchong (Sichuan Province, China) and to provide a basis for the improved prevention and treatment of CKD.

Data and methods

Data source

This study included a group of healthy individuals who underwent routine physical examinations at a health management center of a tertiary A hospital in Nanchong during January-August of 2018, during which we collected their generation information and blood biochemical indicators. The generation information included gender, age, body height, body weight, and blood pressure. The BMI of each individual was calculated by dividing one's body weight in kilograms by one's body height in meters squared (i.e., BMI=body weight [kg]/body height 2 [m^2]). The blood biochemical indicators included serum CysC, fasting blood glucose (FBG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C).

The inclusion criteria consisted of the following for each individual:

- ≥18 years old;
- living in Nanchong for ≥6 months;
- with complete data collection of research indicators.

The exclusion criteria were as follows for each individual:

- confirmed to have a kidney lesion or kidney transplantation;
- had recently used nephrotoxic drugs and steroid hormones;
- had thyroid dysfunction.

Measurement of CysC levels

Fasting venous blood samples (4-5 ml) were collected from each participant, through the elbow, in the morning, and samples were then stored in sodium heparin (anticoagulant) tubes. Individuals were fasted and had no liquid consumption for 12 h before blood collection. Venous blood samples were centrifuged within 2 h of collection at 3,000 rpm (centrifugation radius of 20 cm) for 10 min to separate plasma, followed by reading samples via an automatic biochemical analyzer (Beckman Coulter UniCel DxC 800 system) within 8 h to detect CysC immune-turbidimetry according to the instrument and reagent operating procedures.

Indicators and definitions

According to the National Clinical Laboratory Procedures (Fourth Edition)[7], the reference values of adult serum CysC levels ranged from 0.51–1.09 mg/L. Because there was no clinical diagnostic value below the lower limit of the reference value range, the present study defined serum CysC levels outside the normal reference value range as abnormal CysC levels. According to the Guidelines for the Prevention and Treatment of Type II diabetes in China (2017 version)[8], ≥6.1 mmol/L FPG levels were defined as elevated blood glucose. According to the Guidelines for Prevention and Treatment of Adult Dyslipidemia in China (2016 revised version) [9], the presence of any of the following indicators-including ≥5.2 mmoL/L TC, ≥3.4 mmol/L LDL-C, ≥1.7 mmoL/L TG, and <1.0 mmol/LHDL-C-was considered to indicate abnormal blood lipids. According to the Guidelines for the Prevention and Treatment of Hypertension in China (2018 revised version)(10), ≥140 systolic blood pressure (SBP) or ≥90 diastolic blood pressure (DBP) was considered as elevated blood pressure. According to the Guidelines for the Prevention and Control of Overweight and Obesity in Chinese Adults[11] and the purpose of the present study, individuals that were <24 kg/m2 were considered to be of normal weight, whereas individuals that were ≥24 kg/m2 were considered to be overweight or obese.

Statistical analysis

SPSS22.0 software (SPSS IBM Inc., Chicago, IL) was used for statistical analysis of the data in this study. The statistical indicators included rates, mean values, and standard deviations. Count data were analyzed using chi-square tests. Measurement data between two groups were compared using t-tests.

Multi-sample mean comparisons were performed using the Fisher's least-significant-difference (LSD) method. The trend changes were analyzed by analyses of variance and chi-square trend tests. A P<0.05 was considered statistically significant.

Results

General conditions

A total of 11,258 individuals were included in this study, with their age ranging from 18 to 94 (46.61±13.37) years, including 7,221 (64.1%) males with a mean age of 47.66±13.38 years and 4,037 females with a mean age of 44.73±12.56 years. Individuals in this study were divided into eight groups according to age: 18-29 years, 30-39 years, 40-49 years, 50-59 years, 60-69 years, 70-79 years, and ≥80 years (See Table 1 for the number of individuals in each group). In addition, there were 1,053 (9.4%) individuals with elevated FBG, 2,663 (23.7%) individuals with elevated blood pressure, 6,200 (55.1%) individuals with abnormal blood lipids, and 5,161 (45.5%) individuals who were overweight/obese.

Comparative analysis of serum CysC levels in different gender and age groups

Among all participants, the average serum CysC level was 0.79±0.25 mg/L, with the average serum CysC level of males (0.83±0.27 mg/L) being significantly higher than that of females (0.72±0.21 mg/L) (t=23.964, P<0.001). The serum CysC levels of males <60 years old were higher than those of females <60 years old (P<0.05). However, there was no significant difference in serum CysC levels was found between males and females ≥60 years of age (P>0.05). The variance and trend analyses showed that the overall serum CysC levels, as well as the serum CysC levels of both males and females, gradually increased as a function of age (P<0.05) (Table 1).

Age (year)	Male		Female		Total	
	n	CysC level (mg/L, $\bar{x}$ ±s)	n	CysC level (mg/L, $\bar{x}$ ±s)	n	CysC level (mg/L, $\bar{x}$ ±s)
18–	670	0.75±0.19*	502	0.66±0.17	1172	0.71±0.18
30–	1352	0.78±0.20*	913	0.66±0.18	2265	0.73±0.20
40–	2121	0.80±0.23*	1291	0.69±0.19	3412	0.76±0.22
50–	1746	0.83±0.25*	771	0.75±0.21	2517	0.81±0.24
60–	823	0.90±0.32	410	0.84±0.25	1233	0.88±0.30
70–	368	1.03±0.37	123	0.96±0.30	491	1.01±0.36
≥80	141	1.27±0.42	27	1.04±0.22	168	1.23±0.40
Total	7221	0.83±0.27	4037	0.71±0.21	11258	0.79±0.25
F_{trend}		788.052		221.659		1206.560
P		<0.001		<0.001		<0.001

Table 1: Comparison of serum CysC levels as a function of gender or age.
*Note: CysC: cystatin C; * represents a significant difference in serum CysC levels between males and females*

Comparative analysis of abnormal detection rates of serum CysC levels in different genders and ages

Among all participants, there were 962 individuals with abnormal serum CysC levels, yielding an abnormal detection rate of 8.5%. There were 816 males and 146 females detected with abnormal serum CysC levels, yielding abnormal detection rates of 11.3% and 3.6%, respectively, indicating that the abnormal detection rate of serum CysC in males was significantly higher than that in females (χ^2=195.7, P<0.001). The results of chi-square analysis for trend showed that the abnormal detection rate of serum CysC levels gradually increased with age, regardless of gender (P<0.05) (See Table 2 for specific details).

Age (year)	Male		Female		Total	
	n	Number of individuals with abnormal CysC level (rate)	n	Number of individuals with CysC level (rate)	n	Number of individuals with CysC level (rate)
18–	670	16 (2.4)	502	0	1172	16 (1.4)
30–	1352	65 (4.8)	913	7 (0.8)	2265	72 (3.2)
40–	2121	170 (8.0)	1291	17 (1.3)	3412	187 (5.5)
50–	1746	189 (10.8)	771	33 (4.3)	2517	222 (8.8)
60–	823	141 (17.1)	410	45 (11.0)	1233	186 (15.1)
70–	368	139 (37.8)	123	34 (27.6)	491	173 (35.2)
≥80	141	96 (68.1)	27	10 (37.0)	168	106 (63.1)
Total	7221	816 (11.3)	4037	146 (3.6)	11258	146 (3.6)
χ^2_{trend}		592.554		226.434		905.876
P		<0.001		<0.001		<0.001

Table 2: Comparison of the abnormal detection rates of serum CysC levels as a function of gender or age.
Note: CysC: cystatin C

Analysis of serum CysC levels and abnormalities in BMIs, blood pressure, blood lipids, and blood glucose

Table 3 shows the serum CysC levels and abnormal conditions under different BMIs, blood pressures, and blood glucose conditions. Among them, serum CysC levels were significantly higher in the following: the overweight/obese group compared to those in the normal BMI group (t=8.053, P<0.001); the elevated blood pressure group compared to those in the low/normal blood pressure group (t=14.340, P<0.001); the dyslipidemia group compared to those in the normal blood lipid group (t=9.322, P<0.001); and the hyperglycemic group compared to those in the normal/hypoglycemic fasting group (t=1.558, P>0.05). The abnormal detection rate of serum CysC levels was significantly higher in the following: the overweight/obese group than in the normal BMI group (χ^2=47.622, P<0.001); the elevated blood pressure group than in the low or normal blood pressure group (χ2=242.899, P<0.001); the dyslipidemia group than in the normal blood lipid group (χ^2=34.140, P<0.001); the hyperglycemic group than in the normal or hypoglycemic fasting group (χ^2=11.291, P<0.05).

Group	Number of individuals	CysC level (mg/L, $\bar{x}$ ±s)	Number of individuals with abnormal CysC level (rate)
BMI			
Overweight or obese	5161	0.81±0.27	543 (10.52%)
Normal	6097	0.77±0.24	419 (6.87%)
Elevated blood pressure			
Yes	2663	0.86±0.32	429 (16.11%)
No	8595	0.76±0.22	538 (6.26%)
Blood lipids			
Abnormal	6200	0.81±0.26	616 (9.94%)
Normal	5058	0.76±0.25	346 (6.84%)
Elevated blood glucose			
Yes	1053	0.80±0.30	119 (11.30%)
No	10205	0.79±0.25	843 (8.26%)

Table 3: Analysis of abnormal CysC levels as a function of blood glucose, blood pressure, blood lipids, and BMI.
Note: BMI: body mass index; CysC: cystatin C

Discussion

The present study analyzed serum CysC levels and their abnormal detection rates in individuals with physical check-ups at a health examination center of a highest-rank 3A hospital in Nanchong, China, and revealed that serum CysC levels and their abnormal detection rates were increased as a function of age, regardless of gender. In addition, the abnormal detection rate of serum CysC levels in males was higher than in females. Serum CysC levels and abnormal detection rates in overweight/obese individuals with elevated blood pressure and dyslipidemia were higher than those with normal or low BMIs, normal or low blood pressure, and normal blood lipids. The abnormal detection rate of serum CysC levels in individuals with hyperglycemia was higher than that in individuals with normal blood sugar levels or hypoglycemia.

The results of the present study showed that the average serum CysC level of healthy individuals undergoing physical examinations in Nanchong was 0.79±0.25 mg/L, which was higher than the CysC levels of a healthy population reported by Wang and Gu[12]. The difference in serum CysC levels between the two studies may be due to differential gender and/or age compositions. Most studies[12,13] have shown that serum CysC levels of males are higher than those of females. In the present study, the percentage of males (64.1%) was higher than that (47.3%) reported by Wang and Gu[12], and this higher proportion of males may have contributed to higher overall CysC levels in our present study. In addition, the age range of individuals in the present study was 18-94 years old, including 570 individuals (5.1%) over 70 years of age; in contrast, the age range of participants by Wang and Gu was 20-70 years old, suggesting that this factor may have contributed to our average serum CysC levels being higher than those reported by Wang and Gu[12]. In addition, the abnormal detection rate of serum CysC levels of the present study was 8.5%, which was higher than that reported by Yin et al. in the analysis of healthy populations with physical check-ups from Shihezi, which is a sub-prefecture-level city in northern Xinjiang, China[14]. We speculate that renal damage in individuals from Nanchong may be more serious than that in individuals in Shihezi. However, our abnormal detection rate of serum CysC levels was still lower than that reported by Wang and Gu[12], suggesting that this difference may have been due to the abnormal standard of serum CysC levels being defaulted as 1.09 mg/L in our present study, while the abnormal standard of serum CysC levels reported by Wang and Gu[12] was 1.03 mg/L. Currently, uniform standards for the testing methods and reagents for serum CysC levels are still lacking[15], and, therefore, the reference range of serum CysC levels also varies. According to the above analysis, the serum CysC levels and abnormal detection rates in Nanchong were higher than those in other regions of China, indicating that kidney damage in individuals living in Nanchong may be more severe and that the prevalence of CKD may also be higher. Hence, public health departments should pay more attention to high-risk populations in terms of screening and health education.

Many studies have shown that[12,14,16] adult serum CysC levels and abnormal detection rates show a significant increase with age, regardless of gender, which is consistent with our present findings. The reason for this phenomenon may be that kidney function of individuals gradually declines with age, and that serum CysC levels and their abnormal detection rates also tend to increase with age[14]. In addition, in the present study, serum CysC levels in males under 60 years old were significantly higher than those in females. However, there was no significant difference in serum CysC levels between males and females ≥60 years old, suggesting that this phenomenon may be related to the protective effect of female sex hormones on kidneys before menopause[17].

A previous study[18] has shown a gender difference in serum CysC levels of individuals under 50 years old, while this difference was not found in individuals ≥50 years old, which is different from the findings of our present study. We suspect that this difference may be related to the continuous decline in the age of menarche in Chinese adolescent females, leading to more years post-menopause[19,20]. Our present study also showed that the abnormal detection rates of CysC levels in males were higher than those in females

at all age groups and that the abnormal detection rate after 60 years old increased with age. Therefore, males and individuals ≥60 years old represent the key populations who most require CKD screening.

Guidelines of different groups-such as the Kidney Disease Improvement Global Outcome (KDIGO), the National Institute for Health and Care Excellence (NICE) in the United Kingdom, and the Kidney Health Australia-Caring for Australasians with Renal Impairment (KHA-CARI)-also recommend that individuals with high risk of CKD should be screened and monitored[20-22]. A previous study has shown that serum CysC is produced by all nucleated cells at a constant rate and is freely filtered by the kidney through the glomerulus. Serum CysC is completely secreted and degraded by renal tubular reabsorption and is highly sensitive and specific for early screening of damage to kidney function caused by various factors[6]. In the present study, serum CysC levels and abnormal detection rates of individuals who were overweight/obese and had elevated blood pressure, elevated blood glucose, and dyslipidemia were relatively high, which further verifies that serum CysC may be useful for screening high-risk populations, such as individuals with hypertension or diabetes, as well as those who are overweight/obese. However, clinical healthcare professionals still only use traditional indicators-such as serum creatinine, urea nitrogen, and uric acid-to evaluate kidney function. Therefore, publicity, seminars, and various methods to raise the awareness and the importance of testing for serum CysC levels are necessary. In addition, it is recommended that serum CysC levels be included in routine medical examinations to facilitate the early detection of CKD.

The present study also has some limitations. Data collected in this study were collected from the medical examination database of physical check-ups in 2018 and focused on employees or retired employees of enterprises and public institutions, who were mostly urban residents and did not fully represent the general population. As such, this bias may affect the generalizability of the conclusions of the present study. Further research in this aspect should be expanded to verify the accuracy of the results of the present study before generalizing our conclusions.

In conclusion, serum levels and abnormal detection rates of CysC in individuals from Nanchong were high, suggesting that the prevention and screening of CKD should be strengthened in this area. In particular, individuals who were males, over 60 years old, overweight/obese, and with hypertension, diabetes, and/or dyslipidemia represent high-risk populations that should receive additional healthcare attention.

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