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Serum Triglycerides Are Related to Chronic Kidney Disease (CKD) Stage 2 in Young and Middle-Aged Chinese Individuals During Routine Health Examination

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

AEF Ning Xue
CEF Yi Fang
BC Xiaoqiang Ding
DF Li Wang
BD Linghan Xu
AD Xiaotian Jiang
CDF Xiaoyan Zhang

Department of Nephrology, Zhongshan Hospital, Fudan University, Shanghai, P.R. China

Corresponding Authors: Yi Fang, e-mail: fang.yi@zs-hospital.sh.cn, Xiaoqiang Ding, e-mail: ding.xiaoqiang@zs-hospital.sh.cn
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Background: The aim of this study was to determine the risk factors for early chronic kidney disease (CKD) (GFR 60–89 ml/min/1.73 m^2; CKD stage 2) in asymptomatic Chinese individuals undergoing routine health examination.

Material/Methods: This cross-sectional study enrolled 9100 individuals who received voluntary medical examinations between 10/01/2011 and 09/30/2017. Demographic data, clinical history, clinical examination, medication, smoking, alcohol, blood biochemistry, urinalysis, and carotid ultrasound were extracted from the medical records. All laboratory analyses were performed routinely. Multivariable logistic regression for factors predicting CKD stage 2 was performed.

Result: A total of 9100 individuals were enrolled (age of 18-65 and 65.4% male). CKD stage 2 was found in 1989/9100 individuals (21.9%). Male gender (OR=6.711, 95%CI: 5.376–8.403, P<0.001), older age (OR=1.077, 95%CI: 1.068–1.086, P<0.001), hemoglobin levels (OR=1.051, 95%CI: 1.046–1.057, P<0.001), triglycerides levels (OR=1.174, 95%CI: 1.067–1.292, P=0.001), HDL-C (OR=0.539, 95%CI: 0.380–0.763, P<0.001), Lp(a) levels (OR=1.000, 95%CI: 1.000–1.001, P=0.03), and carotid atherosclerosis (OR=1.248, 95%CI: 1.005–1.550, P=0.045) were associated with CKD stage 2 among all subjects. Serum triglycerides levels were associated with CKD stage 2 in the 18-45 and 45-65 years of age subgroups.

Conclusions: Factors that are routinely assessed during routine health examinations (male gender, age, hemoglobin levels, triglycerides levels, HDL-C, Lp(a) levels, and carotid atherosclerosis) can help identify individuals at higher risk of having CKD stage 2. The Chinese dyslipidemia is characterized by high triglycerides and low HDL-C and occurs in young and middle-aged individuals. Those factors could help identify individuals at higher risk for CKD stage 2 and who could benefit from preventive treatments.

MeSH Keywords: Fontan Procedure • Renal Insufficiency, Chronic • Risk Factors

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Background

Chronic kidney disease (CKD) is characterized by abnormalities of kidney structure or function that have been present for >3 months and have implications for health [1]. CKD can be defined based on the glomerular filtration rate (GFR) and CKD is defined as GFR <60 ml/min/1.73 m^2 (or stage >3) [1]. The prevalence of stage 3–5 CKD is 7–15% worldwide [2]. In China, the prevalence of CKD is 10.8% [2,3], roughly representing over 100 million patients, imposing a serious burden to the health care system and society and reduced quality of life [4].

Stage 2 CKD (GFR 60–89 ml/min/1.73 m^2), although non-clinically significant in the absence of other pathological signs of CKD [1], can suggest the beginning of the disease process. Since therapies are available to slow the progression of CKD stage 2 to advanced stages requiring dialysis or kidney transplantation, early management can improve patient prognosis, with reduced morbidity and mortality [5–7].

The main issue is how to predict CKD stage 2 in patients who are asymptomatic and who only undergo routine clinical examinations. Indeed, any disease screening process has to balance optimal disease detection with costs and inconvenience to the individuals. A number of programs are available worldwide [8–10], but they require formal settings and processes, or target high-risk populations. Optimal screening should be automatic and based on routine parameters that are readily available and obtained during routine health examinations [11]. A number of studies examined predictive factors and models for CKD stage 2 in various populations [12–20]. Nevertheless, since CKD is related to environmental factors such as diet, stress, and population [21,22], population-specific studies are necessary to identify the factors adequately. The main manifestation of dyslipidemia in China is high triglycerides and low high-density lipoprotein cholesterol (HDL-C) levels [23–25]. The Chinese diet has been associated with high blood triglycerides levels [26]. In Asian countries such as Japan, hypertriglyceridemia and low HDL-C are associated with the decline of GFR [27–29]. Carotid atherosclerosis is a marker of the cardiovascular risk associated with high triglycerides and low HDL-C, and has also been associated with GFR decline [30,31].

Therefore, the aim of the present study was to determine the risk factors for CKD stage 2 (GFR 60–89 ml/min/1.73 m^2) in asymptomatic Chinese individuals undergoing routine health examination.

Material and Methods

Study design and patients

This was a cross-sectional study of people who received voluntary medical examinations between October 1st, 2011 and September 30th, 2017. This study was approved by the ethics committee of our hospital. All subjects provided a written informed consent.

The inclusion criteria were: 1) 18–65 years of age; 2) voluntarily received physical examination; and eGFR >60 ml/min/1.73 m^2. The exclusion criteria were: 1) refused to provide medical history; 2) acute and active infection within 1 week of the physical examination; 3) women during menstrual period; 4) pregnant or lactating; 5) acute cardiac insufficiency, acute or chronic respiratory failure, or acute kidney injury; 6) cancer; 7) life expectancy <12 months; or 8) severe mental disorders.

Data collection

Demographic data, clinical history, clinical examination, medication, smoking, drinking, urinalysis, and carotid ultrasound were extracted from the patient charts. All laboratory analyses were performed routinely. Blood pressure was measured after a 10-min rest in the sitting position; both arms were measured and the highest value was kept. eGFR was calculated using the Modification of Diet in Renal Disease equation, modified for Chinese individuals [32,33].

Statistical analysis

Continuous data were tested for normal distribution with the Kolmogorov-Smirnov test and presented as means ± standard deviation or median (range), as appropriate, and analyzed using the Student t test or the Mann-Whitney U test. Categorical data were presented as frequencies and analyzed using the chi-square test. Multivariate logistic regression for factors predicting stage 2 CKD was performed using the enter method. SPSS 16.0 (IBM, Armonk, NY, USA) was used for analysis. Two-sided P-values <0.05 were considered statistically significant.

Results

Characteristics of the subjects

A total of 10,277 individuals were screened for eligibility and 9100 finally met the eligibility criteria: 1989 with eGFR 60-89 ml/min/1.73 m^2 and 7111 with normal renal function (eGFR >90 ml/min/1.73 m^2). Table 1 presents the characteristics of the patients. Compared with individuals with normal eGFR, those with CKD stage 2 showed a lower frequency of male,

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Table 1. Characteristics of the subjects.

Baseline data	eGFR 60–89 ml/min/1.73 m² (n=1989)		eGFR >90 ml/min/1.73 m² (n=7111)		P
Gender, Male, n (%)	1050	(52.8)	4902	(68.9)	<0.001
Age (years)	48.00	[21.00–60.00]	45.00	[18.00–60.00]	<0.001
History of hypertension, n (%)	537	(27.0)	1621	(22.8)	<0.001
History of diabetes mellitus, n (%)	210	(10.6)	752	(10.6)	0.983
History of coronary heart disease or stroke, n (%)	138	(6.9)	400	(5.6)	0.028
History of chronic kidney disease, n (%)	95	(4.8)	337	(4.7)	0.945
History of cancer, n (%)	62	(3.1)	139	(2.0)	0.002
Body mass index (kg/m²)	24.28	[14.86–42.41]	24.44	[14.33–45.52]	0.091
Hemoglobin (g/L)	150.00	[81.00–194.00]	142.00	[63.00–207.00]	<0.001
Proteinuria, n (%)	33	(1.7)	141	(2.0)	0.351
Hematuria, n (%)	64	(3.2)	400	(5.6)	<0.001
Blood uric acid (μmol/L)	389.00	[124.00–821.00]	331.00	[100.00–716.00]	<0.001
Total cholesterol (mmol/L)	4.84	[1.90–11.17]	4.72	[1.83–14.70]	<0.001
Triglycerides (mmol/L)	1.61	[0.40–16.23]	1.42	[0.31–21.56]	<0.001
High-density lipoprotein cholesterol (mmol/L)	1.14	[0.38–3.15]	1.22	[0.28–10.70]	<0.001
Low-density lipoprotein cholesterol (mmol/L)	2.82	[0.33–8.64]	2.68	[0.35–8.02]	<0.001
Lipoprotein (a) (mg/dL)	124.00	[0.00–2534.00]	119.00	[0.00–4643.00]	0.324
Carotid atherosclerosis, n (%)	172	(8.6)	580	(8.2)	0.482

older age, and higher frequencies of hypertension, history of cardiovascular disease, history of cancer, and negative hematuria. The levels of hemoglobin, uric acid, total cholesterol, triglycerides, and low-density lipoprotein cholesterol (LDL-C) were higher in the eGFR 60–89 ml/min/1.73 m² group compared with the eGFR >90 ml/min/1.73 m² group, while HDL-C and the frequency of hematuria were lower.

Related factors to CKD stage 2

Table 2 shows that male gender, older age, hemoglobin levels, triglycerides levels, HDL-C, Lp(a) levels, and carotid atherosclerosis were associated with eGFR 60–89 ml/min/1.73 m² among all subjects.

Predictive factors for CKD stage 2 in males

Table 3 shows that age, history of hypertension, hemoglobin levels, and triglycerides levels were associated with eGFR 60-89 ml/min/1.73 m² among males.

Predictive factors for CKD stage 2 in females

Table 3 shows that age, hemoglobin levels, triglycerides levels, HDL-C, and Lp(a) levels were associated with eGFR 60–89 ml/min/1.73 m² among females.

Predictive factors for CKD stage 2 in individuals 18–45 years of age

Table 4 shows that male gender and triglycerides levels were associated with eGFR 60–89 ml/min/1.73 m² among individuals 18–45 years of age.

Predictive factors for CKD stage 2 in individuals 45–65 years of age

Table 4 shows that male gender, carotid atherosclerosis, and triglycerides levels were associated with eGFR 60–89 ml/min/1.73 m² among individuals 45–65 years of age.

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Table 2. Logistic regression analysis of factors predicting for eGFR of 60–89 ml/min/1.73 m^2.

Variables	OR	95% CI	P
Male	6.711	5.376–8.403	<0.001
Older age	1.077	1.068–1.086	<0.001
History of hypertension (yes *vs.* no)	1.049	0.873–1.26	0.609
History of diabetes mellitus (yes *vs.* no)	0.863	0.691–1.078	0.194
History of coronary heart disease or stroke (yes *vs.* no)	1.057	0.836–1.338	0.642
History of cancer (1=yes *vs.* 0=no)	1.074	0.747–1.544	0.702
Body mass index	1.046	0.868–1.26	0.639
Systolic blood pressure (high *vs.* normal)	1.069	0.793–1.441	0.662
Diastolic blood pressure (high *vs.* normal)	1.052	0.753–1.47	0.768
Hemoglobin	1.051	1.046–1.057	<0.001
Triglycerides	1.174	1.067–1.292	0.001
High-density lipoprotein cholesterol	0.539	0.38–0.763	<0.001
Low-density lipoprotein cholesterol	0.955	0.726–1.256	0.74
Lp(a)	1.000	1.000–1.001	0.028
Carotid atherosclerosis (yes *vs.* no)	1.248	1.005–1.550	0.045

Table 3. Logistic regression analysis of factors predicting for eGFR of 60–89 ml/min/1.73 m^2 in male and female subjects.

Variables	Males			Females		
	OR	95% CI	P	OR	95% CI	P
Age	1.073	1.058–1.089	<0.001	1.085	1.072–1.097	<0.001
History of hypertension (yes *vs.* no)	1.6	1.078–2.373	0.02	0.914	0.74–1.129	0.404
History of diabetes mellitus (yes *vs.* no)	0.936	0.599–1.463	0.773	0.836	0.645–1.084	0.177
History of coronary heart disease or stroke (yes *vs.* no)	1.095	0.662–1.811	0.723	0.999	0.762–1.309	0.993
History of hepatitis (yes *vs.* no)	0.808	0.587–1.112	0.191	0.988	0.821–1.188	0.895
History of cancer (1=yes *vs.* 0=no)	1.477	0.867–2.515	0.151	0.835	0.48–1.452	0.523
Body mass index	0.618	0.375–1.02	0.06	1.392	0.996–1.946	0.053
Hemoglobin	1.07	1.06–1.079	< 0.001	1.031	1.024–1.038	< 0.001
Triglycerides	1.443	1.065–1.955	0.018	1.229	1.078–1.401	0.002
High-density lipoprotein cholesterol	0.789	0.409–1.52	0.479	0.47	0.282–0.784	0.004
Low-density lipoprotein cholesterol	1.086	0.606–1.943	0.782	0.838	0.548–1.282	0.415
Lp(a)	1.000	1.000–1.001	0.225	1.001	1–1.001	0.006
Carotid atherosclerosis (yes *vs.* no)	0.71	0.4–1.26	0.241	0.799	0.631–1.012	0.063

Discussion

A number of studies examined the predictive factors and models for CKD stage 2 (GFR 60–89 ml/min/1.73 m^2) in various populations [12–20], but they are still controversial. Therefore, this study aimed to determine the risk factors for CKD stage 2 in asymptomatic Chinese individuals undergoing routine health examination. The results suggest that demographic, clinical,

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Table 4. Logistic regression analysis of factors predicting for eGFR of 60–89 ml/min/1.73 m^2 in subjects 18–45 and 45–65 years of age.

Variables	18–45 years			45–65 years		
	OR	95% CI	P	OR	95% CI	P
Male gender	10.526	7.143–15.625	< 0.001	5.025	3.831–6.579	< 0.001
Older age	0.988	0.654–1.492	0.953	1.194	0.974–1.463	0.088
History of hypertension (yes *vs.* no)	1.039	0.555–1.943	0.906	1.247	0.965–1.612	0.092
History of diabetes mellitus (yes *vs.* no)	0.968	0.282–3.33	0.959	1.161	0.77–1.751	0.476
History of coronary heart disease or stroke (yes *vs.* no)	0.925	0.548–1.561	0.769	1.011	0.731–1.396	0.949
History of chronic kidney disease (yes *vs.* no)	0.853	0.644–1.131	0.269	---	---	---
History of cancer (1=yes *vs.* 0=no)	1.051	0.755–1.465	0.767	1.156	0.952–1.404	0.144
Body mass index	0.864	0.346–2.155	0.754	0.984	0.642–1.51	0.942
Hemoglobin	0.989	0.589–1.661	0.966	0.992	0.73–1.349	0.96
Blood cholesterol	0.895	0.64–1.253	0.52	---	---	---
Triglycerides	1.389	1.042–1.851	0.025	1.193	1.000–1.423	0.0498
High-density lipoprotein cholesterol	0.994	0.755–1.309	0.965	0.875	0.718–1.068	0.189
Low-density lipoprotein cholesterol	0.89	0.624–1.271	0.521	0.838	0.654–1.073	0.161
Lp(a)	0.946	0.682–1.31	0.737	1.066	0.843–1.347	0.595
Carotid atherosclerosis (yes *vs.* no)	1.76	0.751–4.125	0.194	1.495	1.063–2.103	0.021

and biochemical factors that are routinely assessed during routine health examinations can help identify individuals at higher risk of having CKD stage 2, in whom preventive interventions (such as drugs) could be started early and before symptoms appear [5–7].

The progression of CKD is inevitable [34,35]. GFR declines as a normal process of aging, but the rate of decline is heterogeneous among different individuals and a number of environmental and genetic factors are associated with this decline [20]. A community-based study of individuals >65 years of age showed a decline of 0.8–1.4 ml/min/1.73 m^2 per year [36], while another study showed that about 67% of healthy older individuals have significant loss of GFR over 10 years [37]. Hence, many patients with CKD stage 2 will probably progress to stage >3, hence the importance for proper identification of the patients.

In 2012, the US Preventive Services Task Force (USPSTF) and the American College of Physicians (ACP) stated that the evidence for CKD screening in asymptomatic individuals were inadequate and that there was no universal tool for CKD screening [38], but patients with diabetes or hypertension were not included in their analysis. The ACP later recommended against screening in asymptomatic adults without risk factors of CKD [39], mainly because of the lack of high evidence level clinical trials on the risks and harms of CKD screening. On the other hand, the American Society of Nephrology (ASN) "strongly recommends regular screening for CKD, regardless of risk factors" [11]. Other organizations also support screening in individuals at higher risk of CKD [40–42]. Nevertheless, therapies are available to slow the progression of CKD stage 2 and delay the need for dialysis or kidney transplant and it has been shown that early management can improve patient prognosis [5–7], supporting the need for early diagnosis of even mild kidney impairment (CKD stage 2).

Kshirsagar et al. [43] reported that age, gender, anemia, hypertension, diabetes, history of cardiovascular disease, history of heart failure, and peripheral vascular disease could be used to predict the risk of GFR <60 ml/min/1.73 m^2. Using the Framingham Offspring Study, O'Seaghdha et al. [1] showed that age, diabetes, hypertension, proteinuria, and eGFR could be used to predict stage >3 CKD. The SCORED model uses age, gender, anemia, hypertension, diabetes, history of cardiovascular disease, history of heart failure, peripheral artery disease, and proteinuria to predict CKD [44]. Another clinical prediction model, based on age, body mass index, diastolic blood pressure, history of diabetes, and history of stroke, has been shown to predict CKD [45]. A previous study by our group showed that age, gender, and HDL-C were associated with eGFR <60 ml/min/1.73 m^2, while routine urinalysis showed

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poor performance [46]. Nevertheless, these models can be used to predict stage >3 CKD, i.e. when CKD becomes symptomatic and significant kidney damage has already occurred.

In the present study, it was found that male gender, age, hemoglobin levels, triglycerides levels, HDL-C, Lp(a) levels, and carotid atherosclerosis were associated with eGFR 60–89 ml/min/1.73 m^2 among all subjects. When considering the gender and age subgroups, some variations were observed but cardiovascular risk factors, especially triglycerides levels, were globally associated with the risk of CKD stage 2. Those factors are generally associated with the metabolic syndrome, which has been shown to be associated with CKD [47–49]. Nevertheless, those results are generally supported by the previous models used to predict stage >3 CKD since a number of risk factors appears to be shared [1,43–45].

Previous studies examined the risk factors for CKD stage 2 in various populations worldwide [12–20]. Again, the identified factors were similar to those identified for more advanced CKD. In a Taiwanese population, Chang et al. [15] showed that the risk factors for CKD stage 2 were proteinuria, age, anemia, and poor blood pressure control for men, and poor glycemic control, poor blood pressure control, and family income for women. Another Taiwanese study showed that the presence of occult urine blood could predict the risk of CKD [18].

Importantly, diet and lifestyle factors are associated with the development of CKD and some of those factors are population-specific. Indeed, dyslipidemia among Chinese individuals is mainly manifested as high triglycerides and low HDL-C [23–25], and this pattern has been associated, among other factors, with the high consumption of peppers [26]. Previous studies from Japan showed that high triglyceride and low HDL-C levels were associated with declining eGFR [27–29]. This association was also observed in Chinese individuals [50,51]. Furthermore, carotid atherosclerosis has been shown to be associated with lower eGFR [30,31]. Taken together, those previous studies and the results presented here suggest that cardiovascular risk factors that are easily and routinely measured can predict declining eGFR in an Asian population. Nevertheless, since the exact patterns seem to vary among subgroups, additional studies are necessary to identify those patterns.

The present study is not without limitations. Although the sample size was large, it was from a single hospital serving a single geographical region of China. Since lifestyle and genetic factors vary considerably among different regions of China, additional studies are necessary to determine the exact risk factors for CKD in China. In addition, future studies should consider use of food questionnaires and additional biomarkers (such as inflammatory markers).

Conclusions

Factors that are routinely assessed during routine health examinations (male gender, age, hemoglobin levels, triglycerides levels, HDL-C, Lp(a) levels, and carotid atherosclerosis) can help identify individuals at higher risk of having CKD stage 2. The Chinese dyslipidemia is characterized by high triglycerides and low HDL-C and occurs in young and middle-aged individuals. Those factors could help identify individuals at higher risk for CKD stage 2 and who could benefit from preventive treatments.

Conflicts of interest

None.

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