Sensitivity and specificity of serum cystatin C and creatinine in detecting early stages of chronic kidney disease in Vietnamese patients with hypertension

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Abstract

Background: Hypertension is one of the most common diseases worldwide, especially in Viet Nam. Screening for early-stage chronic kidney disease (CKD) in patients with hypertension remains controversial. We aimed to analyze the sensitivity and specificity of serum cystatin C and serum creatinine in detecting early-stage kidney function loss as a complication in hypertensive patients.

Material and methods: From January 2013 to October 2018, 304 patients first-time diagnosed with primary hypertension at University Medical Center Ho Chi Minh City participated in this cross-sectional study. Collected data includes anthropometric indicators, measured glomerular filtration rate (GFR) by plasma 99mTc-diethylene-triaminepentaacetic clearance, serum cystatin C (ScysC), and serum creatinine (Scr).

Results: ScysC level was significantly reciprocal correlation between renal radiography ($r = 0.781$, $p < 0.001$). The cutoff value for the identification of GFR < 80 mL/min/1.73 m^2 was ScysC > 1.06 mg/L with a sensitivity of 90.8% and specificity of 90.6%, AUC was 0.90. The sensitivity and specificity of ScysC for the identification of GFR < 70 mL/min/1.73 m^2 and GFR < 60 mL/min/1.73 m^2 was 96.6%, 100% and 98.8%, 99.3%, respectively. Among 14 estimated glomerular filtration formulas used in this study, eGFR-cysC-Filler-Lepage had the highest sensitivity and specificity for identifying GFR < 80 mL/min/1.73 m^2 (79.8% and 100%, respectively). eGFR-cysC-LeBrion had the highest sensitivity and specificity for the identification of GFR < 70 mL/min/1.73 m^2 and GFR < 60 mL/min/1.73 m^2 (97.6%, 96.9% and 100%, 97%; respectively).

Conclusion: The sensitivity and specificity of ScysC were significantly higher than Scr. The eGFR-cysC-Filler-Lepage formula had the highest sensitivity and specificity in detecting the early stages of CKD.

Key words: cystatin C; creatinine; chronic kidney disease; Vietnamese

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Introduction

Hypertension is one of the most common diseases worldwide, especially in developing countries [1]. The importance of the disease is characterized by its high prevalence and serious clinical consequences, including mortality. In 2021, there were 1.13 billion patients with hypertension, which was expected to increase to 1.5 billion patients in 2025, more than two-thirds in middle and low-income countries [2]. In 2019, according to The United States Renal Data System (USRDS), there were 125,408 new cases of final-stage CKD with an increasing prevalence of 340 cases/1,000,000 people, in which hypertension was the second cause of CKD [3]. Hypertension was a risk factor for kidney damage and final-stage CKD [4, 5]. Arteriosclerosis in patients with hypertension damages the glomerular, leading to glomerulosclerosis and renal ischemia [4]. A decrease in kidney function can increase the concentration of many small protein molecules in serum. Some proteins such as lysozyme, β2-microglobulin, and cystatin C are used to measure kidney function [6–8].

GFR was accepted as the best overall measure of kidney function [8, 9]. The estimated glomerular filtration rate (eGFR) was measured by calculating the clearance of some renal excreted substances [8–10]. eGFR measured by Scr had low sensitivity for identifying the loss of kidney function early, known as 'blind point' of Scr [11, 12]. Cystatin C, a protease inhibitor, was studied as a measure of kidney function and a biomarker of cognitive impairment [10–13]. Compared to Scr, ScysC was much less affected by age, sex, and muscle mass [14, 15]. Several studies showed that ScysC could be used in a daily clinical setting to estimate glomerular filtration rate due to higher sensitivity and higher specificity than Scr [7, 10, 16]. Recent findings suggest that ScysC may more effectively estimate GFR as a supplement or replacement for Scr [17–21].

The eGFR calculated by ScysC equations has not been widely applied to clinical practices in Vietnam. Therefore, in this study, we aim to analyze the sensitivity and specificity of ScysC and Scre in measuring glomerular filtration rate by using 14 eGFR equations for 304 patients with hypertension, 3 equations measured by Scr, 1 equation measured by Scr and ScysC, 9 equations measured by ScysC.

Material and methods

Study population

Study setting

The study was conducted from January 2013 to October 2018 at University Medical Center Ho Chi Minh City 2 (HCMC). University Medical Center HCMC 2, established in 1998, is currently one of the 3 hospitals of HCMC University of Medicine and Pharmacy. The hospital has over 1000 beds, over 500 healthcare professionals, 10 functional boards, 30 specialty clinics, 5 clinical departments, and 3 subclinical departments. Over 20 years of operating, this is one of the major hospitals to serve the population of Ho Chi Minh City and the southern provinces of Vietnam.

Inclusion criteria: adult patients (≥ 18-year-old) who underwent clinically examined and were newly diagnosed primary hypertension (no previous treatment). A trained nurse measured blood pressure two times on two days after the patient had at least 15-minute rest. Patients measured blood pressure in both hands in a sitting position with an appropriate sphygmomanometer.

Exclusion criteria: patients with cancer, HIV infection, mental disorders, diabetes mellitus, hyperthyroidism, acute pathology (i.e., myocardial infarction, acute infection), endocrine pathology (Basedow's syndrome, pheochromocytoma), urinary stones, chronic pyelonephritis, kidney artery stenosis, and use of corticosteroid within 1-month before the study.

Methods

Researching process is presented in Figure 1.

Study design

The cross-sectional study was conducted on 304 patients newly diagnosed with primary hypertension. The mean age was 54.7 ± 16.2 years, and males accounted for 43.1%. Hypertension was diagnosed and classified according to the Eight Joint National Committee (JNC 8), including 31.6% stage-1 hypertension (n = 96), 68.4% stage-2 hypertension (n = 208).

Sample size

The sample size we selected by applying the following formula:

$$n = \frac{Z^2_{1-\frac{\alpha}{2}} . P(1-P)}{d^2}$$

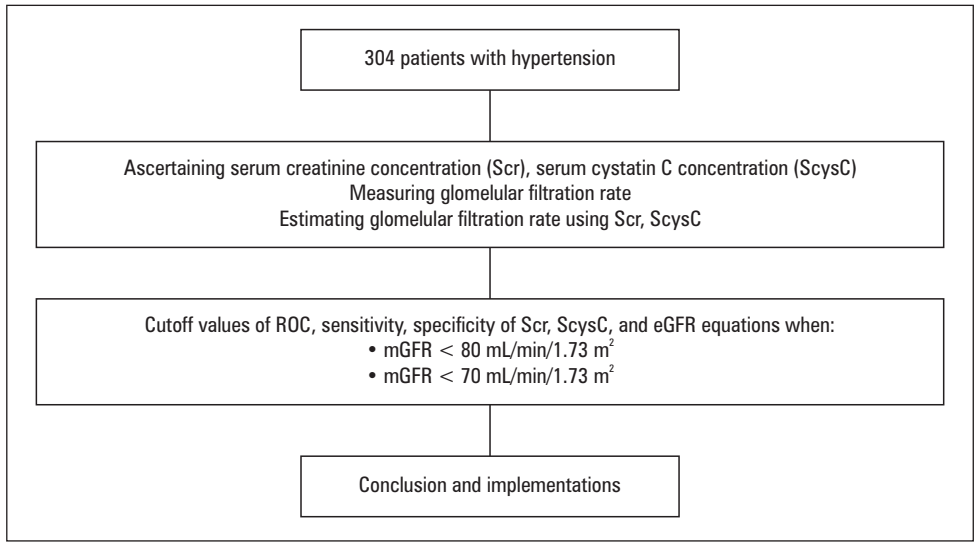

Figure 1. Study flow chart. mGFR — measured glomerular filtration rate

With: Z0.975 = 1.96; a = 0.05; d = 0.0525; p = 0.3137 is the prevalence of early stage of CKD (stage 2 and stage 3a) in patients with primary hypertension according to study of Redon et al. [16].

Data collection

Participants undergone general health examinations including clinical examinations, measuring biometric parameters (i.e., age, gender, height, weight) and performing complete blood count, serum concentration of creatinine, cystatin C, T3, T4, TSH, capillary blood glucose level, lipid profile, abdominal ultrasound, electrocardiogram, and measuring glomerular filtration rate by 99mTc-DTPA gamma-camera renography.

Blood samples were collected at patients' bed after at least an 8-hour fasting period and were immediately sent to the laboratory. Patients were taking 3 mL of intravenous blood to quantify Scr and ScysC concentrations using clotting blood.

Before measuring GFR by 99mTc-DTPA clearance, patients' weight and height were measured. To ensure adequate kidney blood flow, patients were required to drink 500 mL to 1000 mL of water (10 mL/kg) within 1 hour before measurement. The pulse rate was measured 1 minute before injection and after recording was completed (20 – 30 cm above detector surface). During the examination, the patient was lying on their backs; the probe was placed directly below the patient's back; immediately after turning on the machine, a bolus of 3–5 mCi 99mTc-DTPA was delivered into the patient's vein, then information of kidney blood flow was obtained.

Study outcomes

The glomerular filtration rate of participants was measured using 99mTc-DTPA gamma camera renography according to Gate technique by Symbia Truepoint SPECT-CT at the Department of Nuclear Medicine, radioactive units at Cho Ray Hospital. Symbia Truepoint SPECT-CT is a low-energy, high-resolution radioactive meter, parallel holes, 140 keV peak energy. The recording system was adjusted in 15–20% energy window mode, 64 x 64 pixels, zoom 1.23.

ScysC was ascertained using automated latex particle-enhanced immunonephelometry performed on Hitachi 717 automatic biochemical analyzer. ScysC concentration was determined after calibration. Briefly, 3 µL of blood was transferred with micropipette into test tubes, mixed with 230 µL incubation medium and incubated at 37°C in 5 minutes. Next, 50 µL of solution containing latex particles coated with cystatin C antibody was added. After for 4 minutes and 30 seconds the result was read on the screen at a wavelength of 571–805 nm. ScysC concentration was calculated automatically by the analyzer. Coefficient of variation (CV) of this method was 1.3–3.2% with the analysis range of 0.1–8.3 mg/L (normal range of ScysC in healthy adult: 0.56–0.95 mg/L, SD = 0.009–0.01 mg/L).

Scr was ascertained using Jaffe dynamic method with AU680 automatic biochemical analyzer. eGFRs estimated using Scr and ScysC are shown in Table 1 and Table 2.

Table 1. Estimated glomerular filtration rate (eGFR) equations using serum creatinine concentration (Scr) and serum cystatin C concentration (ScysC)

Gender	Scr (mg/dL)	ScysC (mg/L)	eGFR
CKD-EPI creatinine 2009			
Female	≤ 0.7		$eGFR = 144 \times (Scr/0.7)^{-0.329} \times 0.993^{age}$
	> 0.7		$eGFR = 144 \times (Scr/0.7)^{-1.209} \times 0.993^{age}$
Male	≤ 0.9		$eGFR = 141 \times (Scr/0.9)^{-0.411} \times 0.993^{age}$
	> 0.9		$eGFR = 141 \times (Scr/0.9)^{-1.209} \times 0.993^{age}$
CKD-EPI cystatin C 2012			
Female or male		≤ 0.8	$eGFR = 133 \times (ScysC/0,8)^{-0.499} \times 0,996^{age}$ [x 0,932 for female]
Female or male		> 0.8	$eGFR = 133 \times (ScysC/0.8)^{-1.328} \times 0.996^{age}$ [x 0.932 for female]
CKD-EPI creatinine-cystatin C 2012			
Female	≤ 0.7	≤ 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.248} x (ScysC/0.8)^{-0.375} \times 0.995^{age}$
		> 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.248} x (ScysC/0.8)^{-0.711} \times 0.995^{age}$
	> 0.7	≤ 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.601} x (ScysC/0.8)^{-0.375} \times 0.995^{age}$
		> 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.601} x (ScysC/0.8)^{-0.711} \times 0.995^{age}$
Male	≤ 0.9	≤ 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.207} x (ScysC/0.8)^{-0.375} \times 0.995^{age}$
		> 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.207} x (ScysC/0.8)^{-0.711} \times 0.995^{age}$
	> 0.9	≤ 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.601} x (ScysC/0.8)^{-0.375} \times 0.995^{age}$
		> 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.601} x (ScysC/0.8)^{-0.711} \times 0.995^{age}$

CKD-EPI — Chronic Kidney Disease Epidemiology Collaboration

Analysis and processing of data

Analyses were performed by IBM SPSS Statistics, version 20.0. Discrepancies in two average variables were assessed using Student's t-test. Student's t-test was used to compare changes in the quantitative variables between groups for independent samples with parametric distribution (Mann-Whitney test for non-parametric distribution). The correlation coefficient of two continuous variables was determined, Pearson R correlation coefficient for variables with parametric distribution and Spearman correlation coefficient for variables with non-parametric distribution. A receiver operating characteristic (ROC) curve was used to analyze the value of diagnostic tests. It evaluated the sensitivity and specificity of two or more diagnostic tests by comparing the area under the ROC curve. Diagnostic tests with a larger area under the ROC curve had higher accuracy.

Research ethics

Our research strictly adhered to ethical criteria in medical research and was approved by the Ho Chi Minh City University of Medicine and Pharmacy with decision No.256 on 4th August 2017.

Table 2. Estimated glomerular filtration rate (eGFR) equations using serum cystatin C concentration (ScysC)

Name of equation	Formula
Arnad Dade	$eGFR = 74.835/(ScysC^{1.333})$
Filler-Lepage	$eGFR = 91.62 \times (1/ScysC)^{1.123}$
Grubb et al.	$eGFR = 99.19 \times ScysC^{-1.713}$ (× 0.823 for female)
Hoek et al.	eGFR = (80.35/ScysC) – 4.32
Le Bricon et al.	eGFR = [78 × (1/ScysC)] + 4
Rule et al.	$eGFR = 76.6 \times ScysC^{-1.16}$
Larsson et al.	$eGFR = 77.24 \times ScysC^{-1.2623}$
Levey et al.	$eGFR = 76.7 \times ScysC^{-1.19}$
MacIsaac et al.	eGFR = (86.7/cystatin C) – 4.2

Results

CKD stages were defined based on eGFR according to Kidney Disease: Improving Global Outcomes (KDIGO) 2012 in 304 hypertensive patients. There were 43.7% (n = 133) patients with G1 and G2 kidney failure; the percentage of the next stages decreased to 4.3% (n = 13) patients with G4 and 0% (n = 0) patients with G5 kidney failure, the numbers are shown in Table 3.

Table 3. Stages of chronic kidney disease (CKD) in hypertensive patients according to Kidney Disease: Improving Global Outcomes (KDIGO) 2012

G {GFR category??}	All (n = 304)	Stage 1 hypertension (n = 96)	Stage 2 hypertension (n = 208)	p
1	1 (0.3)	1 (1.0)	0 (0.0)	< 0.001
2	132 (43.4)	60 (62.5)	72 (34.6)	
3a	93 (30.6)	22 (22.9)	71 (34.1)	
3b	65 (21.4)	10 (10.4)	55 (26.4)	
4	13 (4.3)	3 (3.1)	10 (4.8)	
5	0 (0.0)	0 (0.0)	0 (0.0)	

Mean Scr concentration was 1.1 ± 0.3 mg/dL (1.2 ± 0.3 mg/dL in male and 1.0 ± 0.3 mg/dL in female patients, p < 0.001). Mean CysC concentration was 1.7 ± 0.7 mg/L (1.7 ± 0.4 mg/L in male and 1.68 ± 0.8 in female patients, p > 0.05). Mean measured GFR (mGFR) was 57.5 ± 17.2 mL/min/1.73 m^2, and mean 24-hour Scr clearance was 60.03 ± 16.3 mL/min/1.73 m^2. Mean eGFR was measured using Scr, ScysC, and discrepancies between eGFR and mGFR are shown in Table 4.

Glomerular filtration rate was divided into three categories (i.e., GFR < 80 mL/min/1.73 m^2; GFR < 70 mL/min/1.73 m^2; GFR < 60 mL/min/1.73 m^2). Sensitivity and specificity of Scr and ScysC in estimating GFR was determined in each category.

The cutoff values for identification of mGFR < 80 mL/min/1.73 m^2 were ScysC = 1.06 mg/L with a sensitivity of 90.8% and a specificity of 90.6%, AUC = 0.96; Scr = 1.05 mg/dL with a sensitivity of 47.8% and specificity of 78.1%,

Table 4. The differences between estimated glomerular filtration rate (eGFR) and measured glomerular filtration rate (mGFR)

eGFR [mL/min/1.73 m^2]	Value	ΔmGFR*	p
eGFR-CG	64.2 ± 20.6	6.7 [4.9; 8.4]	< 0.001
eGFR-MDRD	81.2 ± 26.8	23.7 [20.8; 26.6]	< 0.001
eGFR-CKD-Epi Creatinine	72.9 ± 20.7	15.4 [13.4; 17.4]	< 0.001
eGFR-CKD-Epi-CysC	47.4 ± 21.5	–10.0 [–10.7; –9.4]	< 0.001
eGFR-CKD-EPI-Cre+CysC	57.6 ± 23.1	0.1 [–2.2; 2.4]	0.935
eGFR-cysC-LeBricon	56.9 ± 17.3	–0.5 [–0.8; –0.3]	< 0.001
eGFR-cysC- Levey	49.0 ± 18.7	–8.5 [–8.8; –8.2]	< 0.001
eGFR-cysC-Hoek	50.2 ± 17.8	–7.3 [–7.5; –7.0]	< 0.001
eGFR-cysC-Larsson	48.2 ± 19.4	–9.2 [–9.6; –8.9]	< 0.001
eGFR-cysC-Rule	49.4 ± 18.4	–8.1 [–8.4; –7.8]	< 0.001
eGFR-cysC-Arnad Dade	45.7 ± 19.2	–11.8 [–12.1; –11.4]	< 0.001
eGFR-cysC-Filler-Lepage	59.7 ± 21.6	2.3 [1.7; 2.8]	< 0.001
eGFR-cysC-Grubb	49.6 ± 27.1	–7.9 [–9.2; –6.6]	< 0.001
eGFR-cysC-MacIsaac	54.6 ± 19.2	–2.8 [–3.2; –2.5]	< 0.001
eGFR-CG	64.2 ± 20.6	6.7 [4.9; 8.4]	< 0.001
eGFR-MDRD	81.2 ± 26.8	23.7 [20.8; 26.6]	< 0.001
eGFR-CKD-Epi Creatinine	72.9 ± 20.7	15.4 [13.4; 17.4]	< 0.001
eGFR-CKD-Epi-CysC	47.4 ± 21.5	–10.0 [–10.7; –9.4]	< 0.001
eGFR-CKD-EPI-Cre+CysC	57.6 ± 23.1	0.1 [–2.2; 2.4]	0.935
eGFR-cysC-LeBricon	56.9 ± 17.3	–0.5 [–0.8; –0.3]	< 0.001
eGFR-cysC- Levey	49.0 ± 18.7	–8.5 [–8.8; –8.2]	< 0.001
eGFR-cysC-Hoek	50.2 ± 17.8	–7.3 [–7.5; –7.0]	< 0.001
eGFR-cysC-Larsson	48.2 ± 19.4	–9.2 [–9.6; –8.9]	< 0.001
eGFR-cysC-Rule	49.4 ± 18.4	–8.1 [–8.4; –7.8]	< 0.001

AUC = 0.69, numbers are shown in Table 5 and Figure 2.

The cutoff values for identification of mGFR < 70 mL/min/1.73 m^2 were ScysC = 1.22 mg/L with a sensitivity of 96.6% and a specificity of 100%, AUC = 1.00; Scr = 1.10 mg/dL with a sensitivity of 51% and a specificity of 68.4%, AUC = 0.66. At cutoff value of ScysC = 1.22 mg/L, the false positive value was 0%. Numbers are shown in Table 6 and Figure 3.

The cutoff values for identification of mGFR < 60 mL/min/1.73 m^2 were ScysC = 1.06 mg/L with a sensitive of 98.8% and a specificity of 99.3%, AUC = 1.00; Scr = 1.37 mg/L with a sensitivity of 67.8% and a specificity of 48.9%, AUC = 0.65. Numbers are shown in Table 7 and Figure 4.

eGFR estimated using Scr and ScysC by different equations had different sensitivity and specificity. eGFR-cysC-Filler-Lepage was the equation with the highest sensitivity and specificity for identification of mGFR < 80 mL/min/1.73 m^2. eGFR-cysC-LeBricon was the equation with the highest sensitivity and specificity for identification of mGFR < 70 mL/min/1.73 m^2 and mGFR < 60 mL/min/1.73 m^2; actual numbers are mentioned in Table 8.

Table 5. Sensitivity and specificity of serum creatinine concentration (Scr) and serum cystatin C concentration (ScysC) when measured glomerular filtration rate (mGFR) < 80 mL/min/1.73 m^2

Values	All (n = 304)		Males (n = 131)		Females (n = 173)	
	Scr	ScysC	Scr	ScysC	Scr	ScysC
Cutoff point	1.05	1.06	1.05	1.06	0.85	1.10
Sensitivity (%)	47.8	90.8	73.9	73.0	59.2	88.5
Specificity (%)	78.1	90.6	56.3	100.0	81.3	100.0
False (+) positive value	21.9	9.4	43.8	0.0	18.8	0.0
False (–) negative value	52.2	9.2	26.1	27.0	40.8	11.5
Positive predictive value (+)	94.9	98.8	92.4	100.0	96.9	100.0
Negative predictive value (–)	15.0	53.7	23.1	34.0	16.9	47.1
Diagnostic efficiency	51.0	90.8	71.8	91.6	61.3	89.6

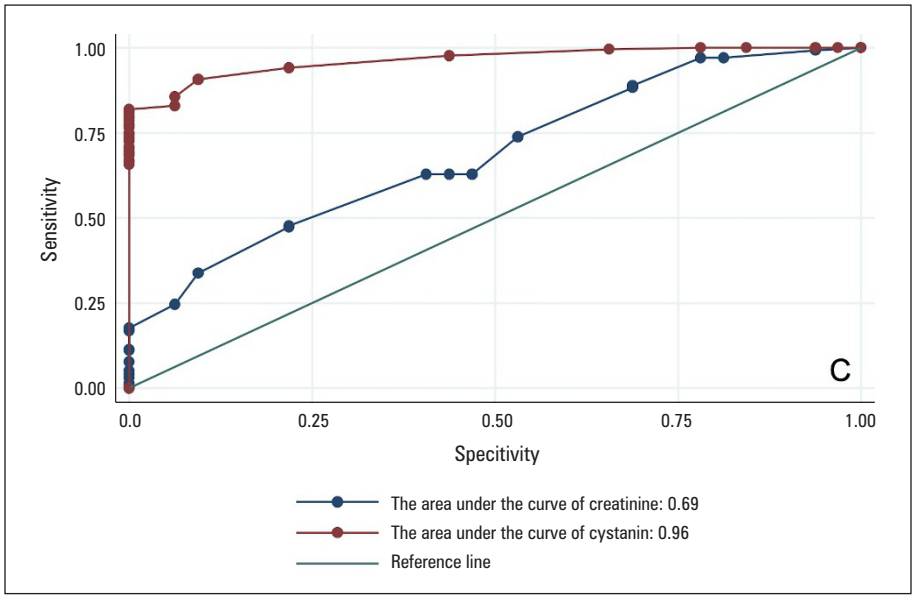

Figure 2. Area under the receiver operating characteristic (ROC) curve of serum creatinine and serum cystatin C at measured glomerular filtration rate (mGFR) < 80 mL/min/1.73 m^2

Table 6. Sensitivity, specificity of serum creatinine concentration (Scr) and serum cystatin C concentration (ScysC) when measured glomerular filtration rate (mGFR) < 70 mL/min/1.73 m^2

Values	All (n = 304)		Males (n = 131)		Females (n = 173)	
	Scr	ScysC	Scr	ScysC	Scr	ScysC
Cutoff point	1.10	1.22	1,15	1.22	0.85	1.22
Sensitivity (%)	51.0	96.6	62,2	96.0	67.4	97.0
Specificity (%)	68.4	100.0	73,7	100.0	82.9	100.0
False (+) positive value	31.6	0.0	26,3	0.0	17.1	0.0
False (–) negative value	49.0	3.4	37,8	4.1	32.6	3.0
Positive predictive value (+)	77.2	100.0	75,4	100.0	92.7	100.0
Negative predictive value (–)	39.9	93.3	60,0	95.0	44.2	91.1
Diagnostic efficiency	56.6	97.7	67,2	97.7	71.1	97.7

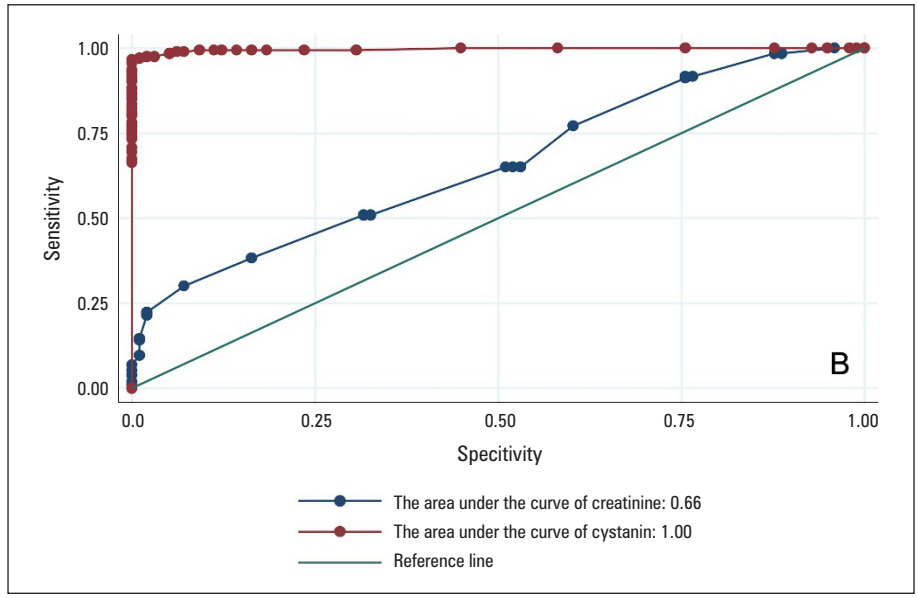

Figure 3. Area under the receiver operating characteristic (ROC) curve of serum creatinine and serum cystatin C at measured glomerular filtration rate (mGFR) < 70 mL/min/1.73 m^2

Table 7. Sensitivity, specificity of serum creatinine concentration (Scr) and serum cystatin C concentration (ScysC) when measured glomerular filtration rate (mGFR) < 60 mL/min/1.73 m^2

Values	All (n = 304)		Males (n = 131)		Females (n = 173)	
	Scr	ScysC	Scr	ScysC	Scr	ScysC
Cutoff value	1.37	1.42	1.27	1.44	1.45	1.42
Sensitivity (%)	67.8	98.8	51.7	98.3	71.2	99.1
Specificity (%)	48.9	99.3	83.1	100.0	72.6	98.4
False (+) positive value	51.1	0.8	16.9	0.0	27.4	1.6
False (–) negative value	32.2	1.2	48.3	1.7	28.8	0.9
Positive predictive value (+)	63.0	99.4	72.1	100.0	82.3	99.1
Negative predictive value (–)	54.2	98.5	67.1	98.6	58.4	98.4
Diagnostic efficiency	59.5	99.0	68.7	99.2	71.7	98.8

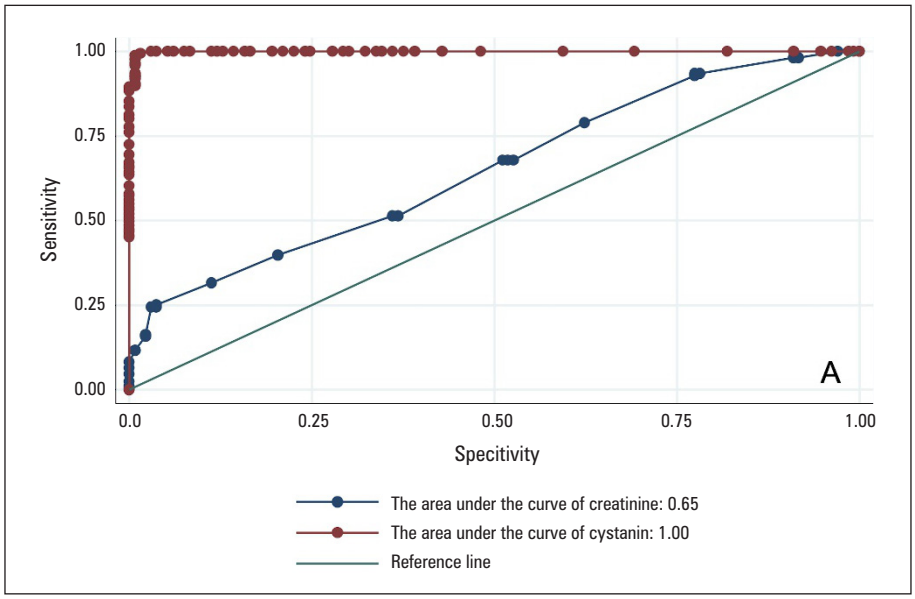

Figure 4. Area under the receiver operating characteristic (ROC) curve of serum creatinine and serum cystatin C at measured glomerular filtration rate (mGFR) < 60 mL/min/1.73 m^2

Table 8. Sensitivity and specificity of estimated glomerular filtration rate (eGFR) equations

eGFR equations	mGFR < 80 mL/min/1.73 m^2		mGFR < 70 mL/min/1.73 m^2		mGFR < 60 mL/min/1.73 m^2	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
eGFR-CG	82.7	87.5	78.6	85.7	66.1	88.0
eGFR-MDRD	60.7	62.5	48.5	83.7	30.4	93.2
eGFR-CKD-Epi Crea	68.0	90.6	61.2	89.8	45.0	94.0
eGFR-CKD-Epi-CysC	97.4	61.3	99.5	71.4	100.0	78.2
eGFR-CKD-EPI-Cre+CysC	85.3	73.1	85.4	68.2	77.2	85.4
eGFR-cysC-LeBricon	99.6	34.4	97.6	96.9	100.0	97.0
eGFR-cysC- Levey	100.0	3.1	99.5	69.4	100.0	79.0
eGFR-cysC-Hoek	100.0	3.1	99.5	76.5	100.0	83.5
eGFR-cysC-Larsson	100.0	3.1	99.5	76.5	100.0	79.0
eGFR-cysC-Rule	100.0	3.1	99.5	76.5	100.0	80.5
eGFR-cysC-Arnad Dade	100.0	3.1	100.0	55.1	100.0	75.2
eGFR-cysC-Filler-Lepage	79.8	100.0	91.3	100.0	96.5	99.3
eGFR-cysC-Grubb	86.8	62.5	98.1	91.8	100.0	82.0
eGFR-cysC-MacIsaac	99.6	34.4	99.0	93.9	100.0	94.0

mGFR — measured glomerular filtration rate; Scr — serum creatinine concentration; ScysC — serum cystatin C concentration

Discussion

Participant characteristics

In 304 participants of our study, the men/women proportion was 43.1%/56.9%, and the mean age was 54.7 ± 16.2 years (the lowest age of 21 and the highest age of 95). The mean age of the female group was 3.7 years higher than that of the male group. The difference in blood pressure between the male and female groups was insignificant. In Olzer et al.'s study on 51 patients with hypertension, in which 47% were men (n = 24) and 53% were women (n = 27), the mean age was 48.47 ± 0.77 years (from 35 to 56 years) [22]. Although all participants were < 60 years old, the mean BMI value was high (27.50 ± 0.59 kg/m^2). In Salgado et al.'s study on 279 primary hypertensive patients with a mean age of 60 ± 11.8 years, the men/women proportion was 26.6%/73.4%, with a mean BMI value of 27.5 ± 4.8 kg/m^2 [23]. Patients in both studies had higher

weight, height, and BMI values than patients in our study. Comparing the mean age, the patients included in Olzer et al.'s study were younger and the participants in Salgado et al.'s study were older compared with our study [22, 23]. These differences were explained by races and inclusion and exclusion criteria.

Gender was a dependent risk factor for hypertension; the effect of gender was significant in the menopause female group, in which endocrine disorders in women over 65 years of age increase blood pressure. From 45 to 54 years old, the prevalence of hypertension in men and women was 36.2%. Among patients aged 55 to 64, hypertension was found in 54.4% patients in the female group compared to 50.2% in the male group. In the 65 to 74 years old group, hypertension in the female group accounted for 70.8% compared to 64.1% in the male group [24]. Some studies found that the prevalence of patients with hypertension was equal between women of childbearing age and men but this proportion was higher in the menopause female group [19]. The mean blood pressure was higher in women in our study, although it was not statistically significant.

Sensitivity, specificity, positive predictive value, negative predictive value, diagnostic efficiency of Scr and ScysC in early-stage kidney function loss

In our study on 304 patients with hypertension, at the cutoff value of ScysC > 1.23 mg/L, the sensitivity and specificity of ScysC in identification of mGFR < 80 mL/min/1.73 m^2 were 97.79% (95% CI: 90–100), 98.82% (95% CI: 89.5–99.7), respectively. These values were significantly higher than the sensitivity and specificity of Scr. Thus, ScysC concentration was more effective than Scr concentration in estimating GFR in the early stage of CKD. Although Scr had been the longstanding biomarker of choice in estimating the loss of kidney function, we found ScysC was a well-investigated biomarker with clear advantages over Scr in asymptomatic patients with the early CKD stage.

In Olzer et al.'s study on hypertensive patients at GFR < 80 mL/min/1.73 m^2, sensitivity, specificity, and AUC of ScysC were significantly higher than Scr [22]. Therefore, an early decrease in kidney function in patients with hypertension can be assessed by estimating eGFR using ScysC. In Toan's study study on patients with type 2 diabetes complicated by kidney damage with albuminuria and/or GFR < 60 mL/min/1.73 m^2), ScysC was more effective in diagnosing the loss of kidney function than Scr ($p < 0.05$) [25]. In Mussap et al.'s study on 52 patients with type 2 diabetes mellitus, sensitivity and specificity of ScysC were higher than Scr at the patients' cut-point of GFR < 80 mL/min/1.73 m^2 (97%, 81% of ScysC, and 62%, 89% of Scr, respectively) [26, 27].

Another study by MacIssac et al. on 251 diabetic patients found that ScysC was an effective biomarker for screening early-stage of CKD at GFR < 90 mL/min/1.73 m^2 with a sensitivity of 98.1% and a specificity of 89.8%, AUC = 97.9% at a cutoff value of ScysC > 0.89 mg/L. At GFR < 60 mL/min/1.73 m^2, the cutoff value of ScysC > 1.1 mg/L had a sensitivity of 90.2%, a specificity of 79.8%, AUC = 92.3% [28]. These values demonstrate the benefits of using ScysC as a biomarker of filtration in eGFR estimating equations to diagnose early-stage CKD in patients with hypertension and/or diabetes mellitus.

Current studies on CKD as a complication of hypertension or diabetes, kidney transplant, or cirrhosis demonstrated the clear advantages of ScysC in screening early-stage CKD over Scr [17–20]. ScysC concentration increased, although urine microalbumin was detectable and eGFR estimated by Scr in the normal range. In contrast, ScysC concentration increases stepwise with the decrease in GFR at late-stage renal failure. Thus, recent research considered ScysC a biomarker of choice to screen for the loss of kidney function in hypertensive patients with urine microalbumin values in the normal range [29].

Sensitivity and specificity of eGFR equations using ScysC and/or Scr

eGFR estimated using ScysC was considered a biomarker of choice in diagnosing glomerulopathy in patients with normal urine albumin and staging, prognosis, and treatment in patients with glomerulopathy [10, 30]. In our study, eGFR-Filler-Lepage equation using ScysC had highest sensitivity (79.8%) and specificity (100%) in estimating early GFR reduction (GFR < 80 mL/min/1.73 m^2), followed by Cockcroft-Gault equation (82.7% and 87.5%), CKD-Epi-Creatinine equation (68% and 90.6%), CKD-Epi-Creatinine-Cystatin C equation (90.4% and 31.3%), Grubb equation (86.8% and 62.5%). Whereas, at cut-point of GFR < 70 mL/min/1.73 m^2 and GFR < 60 mL/min/1.73 m^2, eGFR-LeBricon had the highest sensitivity and specificity (97.6% and 96.9%; 100% and 97%, respectively).

At the cut-point of GFR < 80 mL/min/1.73 m^2, Olzer et al. showed in their study on hypertensive patients that the AUC of eGFR estimated by ScysC (= 0.90) was higher than eGFR estimated by Cockcroft-Gault equation using Scr and BUN [22]. Comparing the AUC of all eGFR equations

in our study, eGFR-Filler-Lepage equations had the highest value in three mGFR cut-point values atmGFR<80mL/min/1.73m^2,mGFR<70mL/min/1.73m^2, and mGFR < 60 mL/min/1.73 m^2 (AUC = 0.9; 0.96; 0.98, respectively), followed by eGFR-Lebricon equation, e-GFR-Cockcroft-Gault equation.

Cystatin C alone, or in combination with creatinine, had been shown to strengthen the diagnostic efficiency of early-stage CKD as a complication of hypertension and/or diabetes. In contrast, due to its clear advantages over creatinine, cystatin C was considered the biomarker of choice in estimating eGFR in patients with early kidney function loss.

Limitations and implementations

The obtained results in our study and recent studies considered the use of cystatin C in addition to creatinine to determine the severity of CKD, especially early-stage of CKD in hypertensive patients. When ScysC concentration is > 1.06 mg/L, we suggest the need to perform other investigations such as urine microalbumin to diagnose, stage, and plan treatment for CKD as a complication of hypertension. The present study design had several limitations. First, there was a lack of long-term follow-up of kidney function in hypertensive participants by ascertaining cystatin C and creatinine. Long-term observation gives a better perspective on kidney function changes related to ScysC concentration. Second, this single-center study leads to a partial understanding of the collected data. Nevertheless, comparing our study to recent studies in the discussion compensated for the limited time and resources. We suggest the need for multicenter studies and long-term follow-up to comprehensively evaluate the advantages and disadvantages of cystatin C in screening, diagnosis, staging, prognosis, and treatment of the loss of kidney function in hypertensive patients.

Conclusions

Cystatin C was more sensitive and specific than creatinine in identifying early loss of kidney function. In our study, eGFR was estimated using the Filler-Lepage equation, and cystatin C had the highest sensitivity and specificity at three cutoff values of mGFR.

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