Cystatin and glomerular filtration rate equations in old renal transplant donors

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Introduction
Early detection of renal dysfunction in live kidney donors is important and needs easy reliable tools. The aim of the study is to evaluate the cystatin level and cystatin-based equation in assessment of renal function in old healthy kidney donors.
Participants and methods
A total of 27 living kidney donors were selected in the study, where serum creatinine and cystatin C were measured. Measured glomerular filtration rate (GFR) was done by DTPA renal scintigraphy, and it was estimated by the following equations: Cockroft–Gault, Modification of Diet in Renal Disease, Chronic Kidney Disease Epidemiology Collaboration-based creatinine, cystatin, and creatinine–cystatin formulae.
Results
A total of 27 kidney donors comprised 12 (44.4%) males and 15 (55.6%) females. The mean±SD age was 61±0.14 years, and mean±SD age at the time of donation was 56.9±1.7 years. The mean of cystatin level was 1.28±0.44. Serum cystatin was negatively correlated with measured filtration rate by renal scintigraphy and estimating GFR by cystatin and creatinine–cystatin formulae. The performance of Cockroft–Gault equation was better, with the highest sensitivity (70%). Serum cystatin and cystatin-based equation had higher specificity (70%) at criterion of 1.4 and 48, respectively. Area under the curve was 0.204 and 0.839, respectively, and significance level was 0.002 and 0.009, respectively.
Conclusion
Serum cystatin and cystatin-based formulae could outperform as surrogate tools to monitor the renal function and estimating GFR in healthy older kidney donors. Chronic Kidney Disease Epidemiology Collaboration-based cystatin has better specificity, whereas Cockroft–Gault equation has better sensitivity with the best accuracy.

Keywords:
Chronic Kidney Disease Epidemiology Collaboration, creatinine, cystatin, glomerular filtration rate, old kidney donors

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Introduction

Living donor kidney transplantation is the most effective treatment for end-stage renal disease [1], yet the safety of donors is not warranted particularly in older donors [2].

Healthy young donors have the same risk as the general population to develop renal dysfunction [3]. Long-term effect of kidney donation is likely related to different ethnicity, sex, age, and comorbidities of living kidney donors (LKDs) [4].

Some research studies support the idea that living kidney donation does not increase risk of chronic kidney disease (CKD) or mortality [5,6]; however, postdonation hypertension was reported in white donors when there was more than 50% of nephron mass loss [7]. Moreover, proteinuria and loss of nocturnal blood pressure dip were found in Afro-American donors [8].

Renal assessment after donation is crucial for early detection of renal dysfunction in LKDs to maintain favorable consequence and quality of life particularly in older age group. The use of serum creatinine (SCr)-based or creatinine-based equations such as Modification of Diet in Renal Disease (MDRD) seems to be practical but is not an optimal tool owing to its fallacies through many factors such as age, sex, muscle mass, and diet [9]. Serum cystatin (Scys)-based and cystatin-based equation have been widely studied and were clearly proven to be better models in the detection of acute renal impairment [10] as well as in patients with CKD and renal transplant recipients [11,12]. Scys is superior to SCr as it is filtered and metabolized by the kidneys but not

secreted through the tubules, making it an accurate marker of renal dysfunction [13–15].

The recently emerging Chronic Kidney Disease Epidemiology Collaboration (CKD EPI) equations including CKD EPI Cys and CKD EPI creatinine–cystatin proved to have great accuracy in assessing kidney function, especially in those with glomerular filtration rate (GFR) less than 60 ml/min/1.73 m^2 [16]. Scys-based and Scys-based formulae were established in many studies as an accurate means for renal function evaluation in LKDs [17,18].

The aim of our study was to compare the performance of the aforementioned parameters with the formally measured glomerular filtration rate (mGFR) by isotope renal scan and creatinine-based equations including Cockcroft–Gault Formula (C–G), MDRD, and CKD EPI creatinine in older age renal transplant donors.

Participants and methods

Study design and selected population

This cross-sectional (pilot) study included 27 healthy living-related voluntary kidney donors who underwent kidney transplantation from July 2009 to June 2016. All participants were consecutively recruited from the Nephrology Unit of Kasr Al Aini Hospital. Participants who were above 55 years at the time of donation and those of above 1 year after nephrectomy were included in the study.

Patients with cardiovascular disorders, diabetes, and liver diseases and those with thyroid dysfunction were excluded.

The study protocol conformed to the ethical guidelines of 1975 of the Helsinki declaration and was revised and approved by the Ethical Committee of Internal Medicine, Faculty of Medicine, Cairo University. Written informed consents were obtained from all participants in this study.

Methodology

(1) All participants were subjected to full history taking and thorough clinical examination.
(2) Laboratory work was as follows: 5 ml of blood was taken under complete resting condition and pooled into a dry tube. SCr was measured by the kinetic colorimetric method using kinetic photometric equipment (Peckman; Dade Behring Company, Deerfield, Illinois, USA). Quantitative measurement of Scys was done by enzyme-linked immunosorbent assay (ELISA) using specific kits manufactured by Dade Behring Diagnostic (Marburg, Germany) after centrifuging at 3400 rpm.
(3) Estimated glomerular filtration rate (eGFR) was calculated by the following formulae [19–22]:
Cockroft–Gault:
$\text{eGFR (ml/min)} = 140 - \text{age (years)} \times \text{weight (kg)} / 72 \times \text{SCr (mg/dl)}$ ($\times 0.85$ in female).
MDRD equation:
$\text{eGFR (ml / min / 1.37m}^2) = 186 \times \text{SCr}^{-1.154} \times \text{age}^{-0.203} \times 0.742$ (if woman) $\times 1.210$ (if Afro – American).
CKD EPI creatinine:
$\text{eGFR} = 141 \times \min(\text{SCr}/\kappa,1)^{\alpha} \times \max(\text{SCr}/\kappa,1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018$ (if female) $\times$ 1.159 (if Black).
CKD EPI cystatin:
$\text{eGFR} = 133 \times \min(\text{Scys}/0.8,1)^{-0.499} \times \max(\text{Scys}/0.8,1)^{-1.328} \times 0.996^{\text{Age}} \times 0.932$ (if female).
CKD EPI creatinine–cystatin: $\text{eGFR} = 130 \times (\text{SCr}/0.7) - 0.248 \times (\text{Scys}/0.8) - 0.375 \times 0.995 \times \text{age} \times 1.08$ (if Black) $\times$ 1.03 (if male).[22].
(4) Creatinine clearance was determined by measurement of creatinine in a 24-h urine specimen, and SCr in a serum specimen was obtained during the same collection period. The creatinine clearance was then calculated by the following equation [23]:
$\text{Creatinine clearance (ml / min / 1.73 m}^2) =$ urine concentration of creatinine (mg / dl) $\times$ 24 h urine volume (ml) $\times$ 1.73 m^2 patient SA/plasma creatinine (mg / dl).
(5) Radionuclide GFR was estimated by using ^{99m}Tc-DTPA (Gate's method):
3–5 μCi of ^{99m}Tc-diethylene triaminepentaacetic acid (DTPA) was injected intravenously, and the GFR (global and differential) was calculated by a closed computer program based on Gate's method using Phillips equipment (Philips company Amasterdam, Netherlands) [24].

Statistical analysis

Data were statistically described in terms of range, mean±SD, or summary of quantitative data and frequencies used for qualitative data. A *P*-value less than 0.05 was considered statistically significant. Spearman's correlation was used to compare quantitative data. All statistical calculations were done using computer programs Microsoft Excel 2013 (Microsoft Corporation, New York, New York, USA) and statistical package for the social science, version 24 (SPSS Inc., Chicago, Illinois,

Table 1 Clinical and laboratory background of the elderly living kidney donors

Variables	Mean±SD
Age at time of study (years)	61±4
Age at time of donation (years)	56.9±1.7
Duration of donation (years)	4.6±1.9
Weight (kg)	77±8
BMI (kg/m^2)	27.6± 4
Creatinine (mg/dl)	0.75±0.14
Cystatin (mg/l)	1.28±0.44
MDRD (ml/min/1.73 m^2)	95.5±21.7
Cockroft–Gault (ml/min/1.73 m^2)	105.3±27.2
GFR renogram (ml/min/1.73 m^2)	98.36±19.60
Creatinine clearance (ml/min/1.73 m^2)	110.86±24.56
CKD EPI Cr (ml/min/1.73 m^2)	91±11
CKD EPI cystatin (ml/min/1.73 m^2)	61±22
CKD EPI Cr–Cys (ml/min/1.73 m^2)	73±16

CKD EPI, Chronic Kidney Disease Epidemiology Collaboration; Cr–Cys, creatinine–cystatin C; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.

Table 2 Correlation of measured glomerular filtration rate by DTPA-Tc99m scintigraphy with cystatin and estimated glomerular filtration rate by other formula

Variables	Measured GFR	
	r value	*P*-value
Creatinine	–0.382	0.44
Cystatin	–0.382	0.049 (S)
MDRD	0.242	0. 223
Cockroft–Gault	0. 230	0.103
Creatinine clearance	0.098	0.628
CKD EPI creatinine	0.198	0.322
CKD EPI cystatin	0.256	0.198
CKD EPI Cr–Cys	0.991	<0.01 (HS)

CKD EPI, Chronic Kidney Disease Epidemiology Collaboration; Cr–Cys, creatinine–cystatin C; GFR, glomerular filtration rate; HS, highly significant; MDRD, Modification of Diet in Renal Disease; S, significant.

USA) for Microsoft Windows. Accuracy was represented using the terms sensitivity and specificity. Receiver operating characteristic analysis was used to determine the optimum cutoff values.

Results

The study included 27 elderly LKDs [12 (44.4%) males and 15 (55.6%) females]. The mean±SD age was 61 ±0.14, ranging from 56 to 69 years. The age range at the time of donation was 55–61 years, with mean±SD of 56.9±1.7. The mean duration of donation was 4.6 ±1.9 years. The clinical and laboratory characteristic of the studied participants are shown in Table 1.

By means of DTPA renogram, about seven (25.9%) patients had decreased GFR below 90 ml/min/1.37 m^2. The results revealed a negative correlation between mGFR and Scys, whereas mGFR was positively related to CKD EPI Cr–Cys equation (Table 2).

Table 3 Correlation of cystatin and estimated glomerular filtration rate by other formulae

Variables	Cystatin	
	r value	*P*-value
Age of participants	0.214	0.238
Age at time of donation	0.120	0.552
Duration of donation	0.240	0.228
BMI	0.111	0.652
Creatinine	0.388	0.046 (S)
MDRD	–0.082	0.685
Cockroft–Gault	–0.247	0.215
Creatinine clearance	0.136	0.499
CKD EPI creatinine	–0.071	0.725
CKD EPI cystatin	–0.903	0.000 (HS)
CKD EPI Cr–Cys	–0.869	0.001 (HS)

CKD EPI, Chronic Kidney Disease Epidemiology Collaboration; Cr–Cys, creatinine–cystatin C; GFR, glomerular filtration rate; HS, highly significant; MDRD, Modification of Diet in Renal Disease; S, significant.

Regarding the age of participants, it was negatively correlated with eGFR by C–G equation (r=–0.480, P=0.011). The data showed that Scys and all other parameters did not differ by either sex or age at time of donation; however, there was an inverse relation between the duration of donation and MDRD, C–G, and CKD EPI creatinine (r=–0.434, –0.498, and –0.441 and P=0.024, 0.008, and 0.021, respectively). The correlations of cystatin level and other variables are shown in Table 3.

As revealed in Table 4 and Fig. 1, the performance of C–G equation was better with the highest sensitivity (70%) as compared with other formulae on its own. However, cystatin and CKD EPI Cys equation had the highest specificity (70%) at criterion of 1.4 and 84, respectively. Area under the curve was 0.204 and 0.839, and the significance level was 0.002 and 0.009, respectively.

From receiver operating characteristic analyses, accuracy of each was yielded for MDRD, C–G, CKD EPI Cr, CKD EPI Cys, and CKD EPI Cr–Cys at 44.6, 66.6, 48.1, 66.7, and 59.2%, respectively.

Discussion

This study verifies the role of cystatin and different equations for estimating GFR in healthy donors, especially those of older age who are more susceptible for renal deterioration after kidney donation.

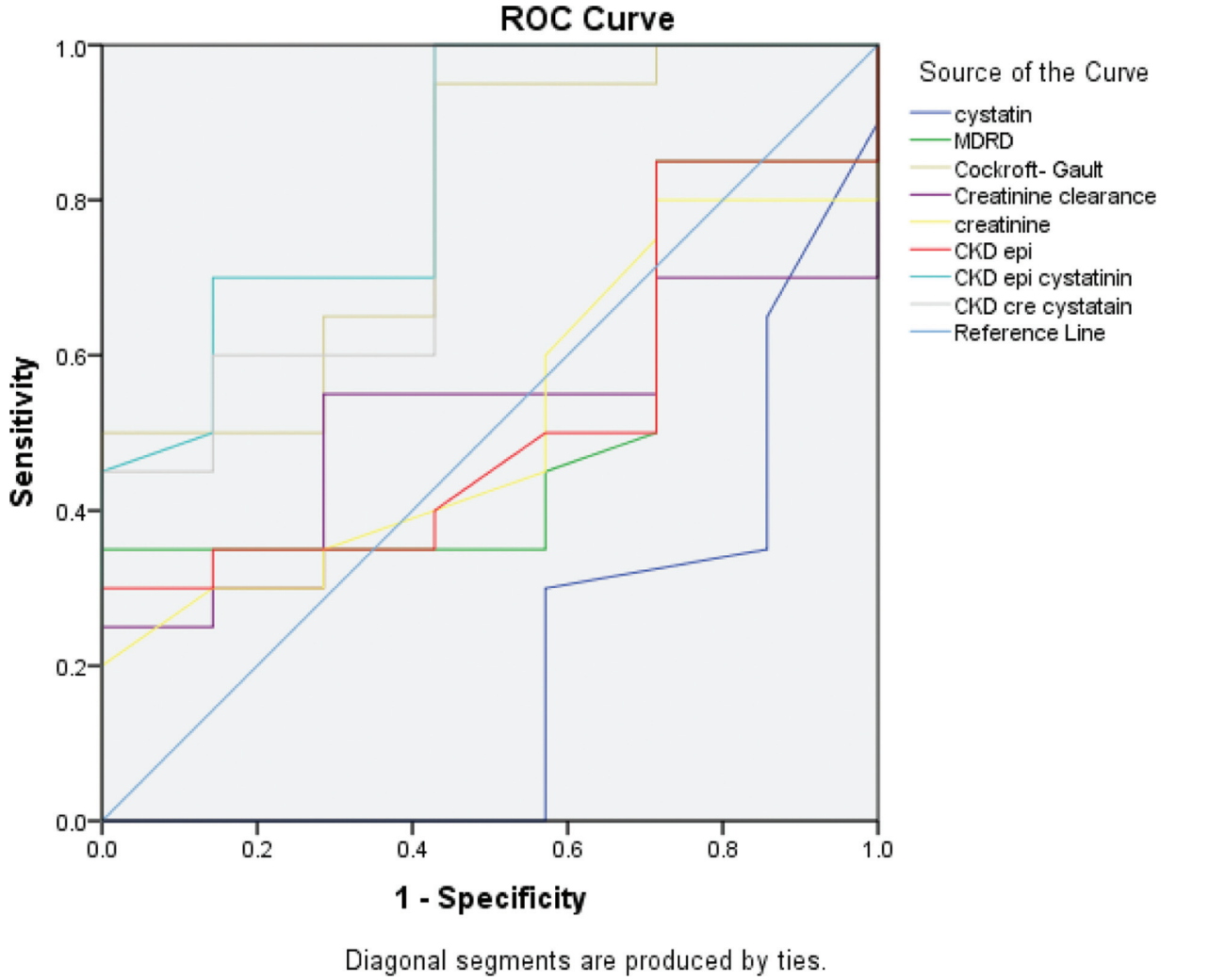
The survival and residual renal functions in LKDs are affected by filtration capacity [25]. This study revealed that seven (25.9%) patients had decreased GFR

Table 4 Results of receiver operating characteristic curve analyses of cystatin and other parameters and estimated glomerular filtration rate equations in detection of renal dysfunction (related to measured glomerular filtration rate)

Test result variable(s)	AUC	Cutoff point	*P*-value	Sensitivity (%)	Specificity (%)	Asymptotic 95% confidence interval
Cystatin	0.204	1.40	0.022	57.1	70.0	0.000–0.423
MDRD	0.511	90.50	0.934	42.9	45.0	0.276–0.746
Cockroft–Gault	0.793	97.80	0.023	71.4	65.0	0.600–0.985
Creatinine clearance	0.514	103.00	0.912	59.0	55.0	0.296–0.732
Creatinine	0.518	0.79	0.890	57.1	60.0	0.288–0.748
CKD EPI Cr	0.521	92.50	0.868	50.0	42.9	0.290–0.753
CKD EPI Cys	0.839	84.00	0.009	57.1	70.0	0.667–1.000
CKD EPI Cr–Cys	0.807	69.50	0.017	57.1	60.0	0.613–1.000

AUC, area under curve; CKD EPI, Chronic Kidney Disease Epidemiology Collaboration; Cr–Cys, creatinine–cystatin C; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.

Figure 1



Receiver operating characteristic curve analyses of cystatin, creatinine, and the various glomerular filtration rate formulae.

(mGFR) less than 90 ml/min/1.37 m^2 assessed by renal isotope scan. Regarding Scys, it was 1.28 ±0.44, and this result is similarly to earlier study, where Scys was 1.39±0.1 [26], but this was higher than reported by Ayub *et al.* [27] who found the mean level of cystatin was 0.88±0.12 mg/l. These contradictory findings might be related to different age group examined in the former study as the population was younger, and the mean age was 32.19±8.27 years.

Although SCr is the most easily used biomarker in assessing kidney function, it is unfortunate that it fails to detect early renal impairment. Interpretation of SCr values in the clinical sitting of frail elderly patients is of note. eGFR declines with age in linear pattern with

C–G equation, whereas in MDRD, there is an exponential relation between age and eGFR [28].

Creatinine-based equations were developed and modulated progressively into CKD EPI Creatinine 2009. Yet, these equations did not improve the clinical tracing of renal affection, and the different studies were controversial and elusive [17,29,30]. There is a vast knowledge suggesting that cystatin C could serve as a confirmatory test with better accuracy for kidney disease in patients with muscle wasting or chronic illness. Earlier studies reported that Scys did not offer an advantage to SCr in detecting renal impairment among LKDs [31,32]. Cystatin-based equations proved superior to those based on creatinine. Besides, CKD EPI Cystatin C formula is less effected by age or race [33], however, the evolved CKD EPI Creatinine–Cystatin C 2012 had similar bias to the creatinine or cystatin C equations but more precise of greater accuracy [34].

Attempting to find a correlation between Scys and other variables, in our study, there was a basically significant inverse correlation between Scys and eGFR by means of CKD EPI cystatin and CKD EPI Cr–Cys. Garcia-Covarrubias *et al.* [18] had confirmed a potential relation of Scys and eGFR by means of SCr-based and Scys-based equations. This difference may be due the small size sample and the older aged population comparable to this study.

In accordance to what was concluded by previous studies [22,26], our study revealed that mGFR by DTPA-Tc99m was significantly related only to CKD EPI Cr–Cys equation. This finding is inconsistent with a recent study in which a significant correlation between GFR measured by DTPA-Tc99m scan and both SCr-based and Scys-based equations, with stronger association with CKD EPI Cr followed by MDRD formulae [18].Scys was not related to C–G or MDRD, which is in contrary to Jaisuresh *et al.* [35] and Ayub *et al.* [27] who found significant correlations between Scys and CrCl, MDRD, and C–G equations.

Surprisingly, in this study, none of donors' age at the study, sex, the age at time of donation, or the duration of nephrectomy were related to Scys. These findings are in contrast to what was reported that Scys was influenced by age and sex [27,36,37], as elevated Scys was associated with older age [27]. These contradictory results may be related to different ethnicity.

The accuracy and performance of cystatin and cystatin-based equations compared with creatinine-based equation were addressed by many studies; the recorded data were conflicting. Unfortunately, there is no equation showing an absolute accuracy. A systematic review was widely conducted on many studies that considered different cystatin C-based equations and concluded that cystatin C-based equations were superior and most accurate than those based on creatinine [33]. In an another study, CKD EPI Cr equation appeared to be less accurate than MDRD in estimating GFR; moreover, CKD EPI Cys and CKD EPI Cr–Cys exhibited great bias and less accuracy than creatinine-based MDRD equation [38].

As for the performance of cystatin and other eGFR formulae in detecting renal dysfunction in donors comparable to mGFR by renogram, our study revealed that Scys and CKD EPI Cys had similar and better specificity (70%) than others variables, meanwhile C–G equation outperforms, with the best sensitivity (71.4%). The highest accuracy was yielded for CKD EPI Cys followed by C–G equations (66.7 and 66.6%, respectively).

The study emphasizes the importance of renal assessment in LKD especially elderly before and after donation. Upcoming researches should define and establish adequate protocol for following up the LKDs. Some study shortcomings make these results less generalizable. First is the small size of the sample, necessitating further studies on a larger scale. Second, we did not assess the confounding effect of morbidities like diabetes and hypertension on eGFR as we had excluded these candidates.

Conclusion

Age at time of donation has no effect on long-term outcome of LKDs. Scys and Scys-based formulae could outperform SCr-based equations as surrogate tools to monitor the renal function and estimate GFR in healthy older kidney donors. CKD EPI Cys has better specificity, whereas C–G equation has better sensitivity for determination of decline in renal filtration rate, as well the best accuracy.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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