Concordance of Serum Creatinine to Estimated Glomerular Filtration Rate in Determining Early Chronic Kidney Disease in Malaysia

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Abstract: Little is known about the accuracy of serum creatinine (SCr) in identifying early chronic kidney disease (CKD) in the primary care setting. Thus, this study aims to examine the concordance of SCr to estimated glomerular filtration rate (eGFR) in detecting early CKD. This is part of a randomly selected 10-year retrospective, observation cohort study of patients registered with the Department of Primary Care Medicine Clinic at the University of Malaya Medical Centre. A SCr ≥ 132µmol/L and eGFR < 60 ml/min are used as the cut-off points for impaired renal function. Kappa statistic is used to test the inter-rater agreement of SCr with eGFR. A total of 1100 subjects were recruited. The mean age, SCr and eGFR were 66±9 years, 86±42 µmol/L and 70±30 ml/min respectively. The concordance between SCr and eGFR was poor as 363 (35.5%) patients had normal SCr but abnormal eGFR. Kappa value was 0.022 (p<0.001). Screening for CKD using SCr fails to detect an additional third of patients with impaired renal functions. Hence using eGFR is a better way to identify early CKD.
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1. Introduction

Chronic kidney disease (CKD) is an independent risk factor of cardiovascular disease (1, 2, and 3) where a majority dies from cardiovascular disease before succumbing to end stage renal failure (4). Detection of early asymptomatic stage of CKD is important because intervention can retard the progression of CKD to end stage renal disease (5, 6). Furthermore, drug adjustment is important for those with the later stages of or more advanced but yet asymptomatic CKD. This is important in order to prevent adverse drug events and minimize additional renal injury (7). This is particularly important in view of the rapidly increasing prevalence of CKD in Asia and throughout the world (8-11).

In Malaysia, there has been an exponential increase in the incidence of CKD and the number of ESRD patients needing renal dialysis . The reported dialysis prevalence rate increased from 4 per million population in 1980 to 365 per million in 2002 and 391 per million in 2003 (10). This increase in the rate of dialysis is partly due to rapid economic growth in Malaysia, leading to a more sedentary lifestyle and obesity in both adults and children. As a result of this there has been an escalating increase in the incidence of diabetes and hypertension, which are major causes of CKD. (10, 12, and 13).

Currently, most clinicians use serum creatinine (SCr) as a measure to determine the presence or absence of CKD as it is convenient and does not require any mathematical manipulation. However, it is well known that SCr can still remain within the normal range in spite of the glomerular filtration rate (GFR) being less than 60mL/min per $1.73m^2$ and it can also be within normal even when half or more of the normal adult kidney function has been lost (14,15).

A complete review of the literature did not show any studies that have been done to examine the difference in diagnosis of CKD using serum creatinine compared to using estimated GFR in a multi-ethnic population in Malaysia. Thus, the aim of the study was to examine the prevalence and predictors of patients with CKD, who are missed by using SCr instead of eGFR at a primary care multi-ethnic population setting.

2. Material and Methods

The current research is part of a 10-year retrospective cohort study of patients registered with the Department of Primary Care Medicine Clinic at the University of Malaya Medical Centre. The data presented here is that for the year 2007. The original cohort consists of a total of 1547 adult patients who were randomly selected based on the systematic randomisation sampling number generated by a computer programme. Baseline data was collected in 1998, and follow-up data collected in 2002 and 2007 at five-year intervals. All the patients with complete data on the serum creatinine and eGFR were selected for this study. Patients with incomplete

data for serum creatinine or eGFR were excluded.

Age, weight, serum creatinine and socio-demographic variables were obtained from patient records. SCr was measured as part of the routine medical care for patients with diabetes and hypertension in this hospital-based primary care clinic. A SCr $\geq$ 132µmol/L and eGFR based on the Cockcroft-Gault (C-G) formula of < 60 ml/min are used as the cut-off points for impaired renal function (14,16, and 17). The Modification of Diet in Renal Disease (MDRD) and C-G formula are the two most common formulae used to classify the severity of CKD. There is consensus on the accuracy in assessing CKD by using the MDRD and C-G formula amongst multiethnic Asian population. However the MDRD formula has been shown to be less accurate than the C-G formula in assessing early CKD (18). Thus, the C-G formula was used in this study as we believe that outpatients are usually in the early stages of CKD rather than at the more advanced stages

In order to compare the difference in the prevalence of CKD using serum creatinine or the eGFR, patients were divided into four categories in the following manner; overt normal renal function (normal SCr and normal eGFR), covert normal renal function (abnormal SCr but normal eGFR), covert renal dysfunction (normal SCr but abnormal eGFR) and overt renal dysfunction (abnormal SCr and abnormal eGFR).

All analysis and calculations were performed using the SPSS version 19 (SPSS IBM New York, United States). Continuous data are described as mean and SD or median and interquartile range (25-75th percentiles). Chi square test and t-test were used to analyse the categorical and continuous data. The kappa test statistics was used to test the inter-rater agreement of serum creatinine to eGFR where the kappa value is interpreted as in Box 1 (19).

Box 1. Interpretation of kappa value in our study

Kappa value	Interpretation *
< 0.20	Poor agreement
0.21 – 0.40	Slight agreement
0.41 – 0.60	Moderate agreement
0.61 – 0.80	Substantial agreement
0.81 – 1.00	Almost perfect agreement

* The level of significance was set at $p<0.05$

3. Results

Out of the 1547 original cohort entered into the study, 1100 remained for follow-up at the end of 10 years. Only those with complete records for this aspect of the study were included. 65% were women and the ethnic distribution was 43% Chinese, 31% Indian and 25% Malay. The mean age and weight were 66 ± 9 years and 64.9 ± 0.4kg respectively. The median SCr and eGFR was 77.0 (range 30 to 586) µmol/L and 65.9 (range 10 to 285) ml/min respectively

Table 1. Concordance of serum creatinine to estimated glomerular filtration rate in year 2007

		eGFR 2007*		
		Abnormal renal function (<60ml/min)	Normal renal function (≥60ml/min)	Total, N
Creatinine 2007	Abnormal renal function (≥132umol/L), n (%)	96(99)	1(1)	97
	Normal (<132umol/L), n (%)	356(35.5)	647(64.5)	1003
Total, N, (%)		452(41.1)	648(58.9)	1100

* eGFR: Estimated Glomerular Filtration Rate

Table 2. Concordance of serum creatinine to estimated glomerular filtration rate stratified by age in year 2007

	Age (years) of patients				
	40-49 (n=49)	50-59 (n=214)	60-69 (n=423)	70-79 (n=318)	80 and above (n=96)
Overt normal renal function, n (%)	46 (97.9)	188 (91.7)	278 (71.6)	126 (45.2)	9 (10.7)
Covert renal dysfunction, n (%)	1 (2.1)	17 (8.3)	110 (28.4)	153 (54.8)	75 (89.3)
Kappa value, n	0.79	0.482	0.295	0.159	0.029

Table 3. Concordance of serum creatinine to estimated glomerular filtration rate stratified by body mass index in year 2007

	BMI (kg/m2) of patients		
	Underweight (BMI<18.5) *	Normal (18.5≤BMI<23)	Overweight (BMI>23)
	n=168, mean age 66.9 years	n=153 mean age 68.1 years	n=574 mean age 64.9 years
Overt normal renal function, n (%)	93 (62.0)	68(48.2)	380 (72.8)
Covert renal dysfunction, n (%)	57(38.0)	73 (51.8)	142 (27.2)
Kappa value, n	0.238	0.127	0.327

* BMI: Body Mass Index

The prevalence of CKD based on SCr was 8.8% and 41.1% based on eGFR. Table 1 shows the concordance of SCr to eGFR. More than one third (35.5%) of those with normal SCr actually had abnormal eGFR. All except for one patient who had an abnormal SCr had an abnormal eGFR. The kappa coefficient was 0.022, which shows poor inter-rater agreement between the SCr and eGFR and this poor inter-rater agreement is significant ($p<0.001$). There was a big difference in renal function between the overt normal renal function group where the eGFR was normal(88 ± 27)ml/min compared to the covert renal dysfunction group which was "true" impaired function (eGFR was 48 ±9) ml/min. This difference is statistically significant ($p<0.001$). This discordance is further confirmed by the sensitivity of only 21.2% of SCr in detecting renal impairment despite its high specificity (99.8%). In other words, when the SCr is abnormal, it is almost certain that the patient truly has renal impairment (20). The positive predictive value of the SCr in this study population is 98.9% while the negative predictive value is 64.5%.

The prevalence of covert renal dysfunction increases with age. Furthermore, the kappa value was worse in older people (Table 2).

Table 4. Predictors of covert renal dysfunction in multivariate analysis in year 2007

Variables	Adjusted OR*	95% CI**
Age, year	1.07	1.050,1.099
Weight, Kg	0.95	0.939,0.969
eGFR C-G, ml/min	1.06	0.934,0.955

* OR: Odds Ratio,
** CI: Confidence Interval
* Adjusted for age, weight, estimated glomerular filtration rate, diastolic blood pressure, systolic blood pressure, ethnicity, sex and serum creatinine.

The prevalence of covert renal dysfunction increased with body weight amongst patients who are

The prevalence of covert renal dysfunction dropped from 51.8% in the normal weight to 27.2% in the overweight group. Overall, it can be seen that the prevalence of covert renal dysfunction is lower in the overweight group than in the normal or underweight group (Table 3). A multivariate logistic regression analysis (Table 4) shows a significant association between age, weight, eGFR and covert renal dysfunction. For every increase of one year in age, the odds of developing covert renal disease was 1.07 (Odds ratio (OR) 1.07, 95% confidence interval (CI) 1.050-1.099). An increase of one kilogram in weight will reduce 0.95 odds (OR 0.95, 95% CI 0.939-0.969) and a reduction
in eGFR of 1ml/min will increase 1.06 times odds (OR 1.06, 95% CI 0.934-0.955) of developing covert renal dysfunction. However, there was no significant association between covert renal dysfunction and ethnicity, nor with sex, systolic blood pressure, and SCr level

4. Discussion

The prevalence of CKD based on SCr in this study population was low where else the prevalence of CKD based on eGFR was nearly five times higher. Furthermore, this study shows that the concordance of SCr with eGFR is rather poor. Using SCr, instead of the eGFR will fail to detect as many as a third (35.5%) of patients with seemingly normal SCr but who, in fact, have impaired renal function. This is much higher than that reported in another study, which was also done on outpatients, where the it was 13.9% (21). This difference could be due to the lower cut-off points for abnormal eGFR that was used in the other study (50ml/min in other study vs. 60ml/min in our study). The other reasons could be our study population were older (66 ± 9 versus 57 ± 9 years and thinner (64.9 ± 0.4kg versus 74 kg ± 0.4kg). A further reason could be due to presence of other co-morbidities like hypertension and diabetes seen in our study population as these conditions further compromise renal function.

Despite that eGFR is not the gold standard to measure actual renal function, it serves as a reliable surrogate, particularly in a primary care setting, as it is less expensive and easier to do than the gold standard inulin test. Furthermore, several studies have supported the use of the eGFR as a reliable measure of renal function (16, 17, and 22). Primary care physicians can play an important role in identifying CKD early in order to slow down the progress of CKD by early nephrology referral or implementing interventions that can delay the progression of renal impairment (23-27). As can be seen from this study, the eGFR is better than the SCr in identifying CKD particularly in thin and older patients, age 60 years or older. This can be explained by the fact that muscle bulk is the main contributor of SCr levels and older individuals have less muscles giving a seemingly low SCr (16). Hence, the eGFR should be used to determine renal functions especially if patients are older and also thin.

The limitation of this study is that there was no comparison of eGFR against the goal standard of inulin testing. However, there are enough studies that have consistently supported the use of eGFR in its place as it closely mirrors the "true" renal function that uses the gold standard inulin test (22, 28). The alternative is to use the MDRD formula which is more accurate than C-G equation and does not require knowing the patient's weight (29, 30, AND 31). However, it was not used in this study as the applicability of the MDRD equation in adjusting medication doses has not been validated in many countries (30, 32). Furthermore, the MDRD cannot be calculated using a conventional calculator.

In summary, the finding of this study shows that there is a wide discordance between SCr and eGFR. Screening for CKD using SCr fails to detect an additional third of patients with impaired renal function. Therefore, eGFR rather than the traditional SCr should be used as a measure of renal function, particularly in the elderly and thin patients. There is no difference amongst the ethnic group in terms of usage of this formula. The higher rate of of detection of early CKD using eGFR indicate that routine evaluation of kidney function should include reporting the eGFR rather than the Scr alone.

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