A comparative study between Cystatin C based equations in relation to other estimated Glomerular Filtration Rate equations for patients with chronic kidney disease in Mosul city

Article information

Mohammed Khalid J. Nori Al-Nori[1]   **Akram J. Ahmed**[2]

Abstract:

Background and objectives: Chronic kidney disease (CKD) is a common problem in public health. Its prevalence has been studied using the estimated glomerular filtration rate (eGFR) by the creatinine-based equations developed in Modified Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) study. Recently, new equations based either on cystatin C alone (Cystatin C_1) or cystatin C with the age (Cystatin C_3), or estimating equation including all of Cystatin C, serum creatinine and age (Cystatin C_4) have been proposed by the CKD-Epidemiology collaboration. The aim of this study was to measure the differences between these estimating equations to achieve the closest one to the gold standard 24 hours corrected creatinine clearance (Corrected CrCl).

Methods: Corrected 24 hours urine creatinine clearance from 185 patients with different stages of CKD was compared with eGFR derived from six equations which are Cockcroft–Gault (CG), (4-MDRD), CKD-EPI, Cystatin C4, Cystatin C3, Cystatin C1 equations, the results were analyzed using Receiver Operating Characteristics Curve (ROC) and correlation analysis by SPSS computerized statistical analysis program.

Results: the result revealed depending on corrected 24h creatinine clearance as a gold standard that the most accurate eGFR equation was in the following order Cystatin C1 and Cystatin C3, Cytatin C4, CKD-EPI, 4MDRD, then Cockcroft–Gault respectively.

Conclusions: Cystatin C dependent eGFR equations are good, reliable, simple and accurate method for estimating renal functions.

---

[1] Lecturer, Department of clinical laboratory sciences, College of Pharmacy, University of Mosul. E.mail**:alnorimkj@Yahoo.com. alnorimkj@gmail.com**

[2] Professor of chemical pathology, Department of Biochemistry, College of Medicine, University of Mosul. E.mail:**Akramj1948 @yahoo.com.**

Recommendations: Physician involved in diagnosis and treatment of patients with kidney diseases are better to be advised to use Cystatin C eGFR equations rather than the other previously known eGFR equations which were less accurate.

Key Words: CKD, Cystatin C, eGFR

Background:

Many studies still consider the corrected 24hour creatinine clearance as the gold standard for the assessment of GFR (Villa *et al, 2005*). Unfortunately this method is time consuming and annoying for the patients. Efforts were attempted to avoid the obstacles of 24h urine collection by different calculated equations which can save time and help the doctors to gain rapid and accurate results for their estimation but this is faced by fact that these equations shows only relative correlation with the gold standard 24h creatinine clearance

(Morín *et al*, 2007) on the other hand, Cystatine C is a reliable biochemical marker with very promising results worldwide. Different studies showed good correlation with 24h creatinine clearance (Wee *et al*, 2012) unfortunately it is not used in our locality to our knowledge.

The objective of the current study is to estimate the role of Cystatine C equations in comparison with other conventional equations using 24h creatinine clearance as a gold standard.

Methods:

Test of diagnostic accuracy design was used in this research.

This study included 185 patients suffering from or under the risk of CKD. Both blood samples and 24h urine samples were collected. Volume of urine samples were measured and recorded for each patient. The studied patients were classified according to the National Kidney Disease Education Program (NKDEP) Classification (Levey *et al*, 2005). Patients with the following criteria were excluded from the study:

1. Patients with thyroid diseases.

2. Patients with impaired renal function who are receiving corticosteroids.

3. Patients with recent attack of coaggulopathic conditions.

4. Patients on therapies affecting the measured parameters.

5. Pregnant and lactating women.

Serum Cystatin C was measured by atandard cup automated immunoassay pack (ST AIA-PACK) which is designed for the quantitative measurement of cystatin c in human serum on TOSOH AIA System Analyzers.

The included eGFR equations are the following:

1. Corrected creatinine clearance CrCl=CrCl x $(1.73m^2/$ Body Surface Area $m^2)$.

CrCl(ml/min) =(Urine Cr(mg/dl)/sCr(mg/dl)) x Urine volume(ml/min).
Creatinine was measured spectrophotometrically (bishop *et al*, 2010)

$$BSA\ (m^2) = \sqrt{\frac{Height\ (cm) \times Weight\ (kg)}{3600}}$$

2. Cockckroft – Gault: eGFR (ml/min) = [(140-age) x body weight (kg)]/[72 x Serum creatinine (mg/dL)]
(x 0.85 if female.

3. MDRD4: eGFR (ml/min/1.73m^2) = 175x sCr (mg/dL) $^{-1.154}$ x age (years) $^{-0.203}$ x (0.742 if female).

4. CKD-EPI eGFR (ml/min/1.73m^2) for female=144(sCr/0.7)$^{-0.329(-1.209\ if\ sCr>0.7)}$ x 0.993^{age}.
eGFR (ml/min/1.73m^2) for male=141(sCr/0.9)$^{-0.411(-1.209\ if\ sCr>0.9)}$ x 0.993^{age}.
5. Cystatin C1-based equation: GFR (mL/min) = 76.7 X Cys C$^{-1.19}$.

The current result as shown in the following figures (1-6) revealed that the higher specificity and sensitivity obtained by Cystatin C1 followed by Cystatin C3, Cystatin C4, CKD-EPI, 4MDRD and

6. Cystatin C3 equation: eGFR (mL/min) = 127.7 X Cys C$^{-1.17}$ Xage$^{-0.13}$ X0.91 if female.
7. Cystatin C4 equation: eGFR (mL/min) = 177.6 X sCr$^{-0.65}$X Cys C$^{-0.57}$ Xage$^{-0.2}$ X0.82 if female. (Kirwan *et al*, 2013)
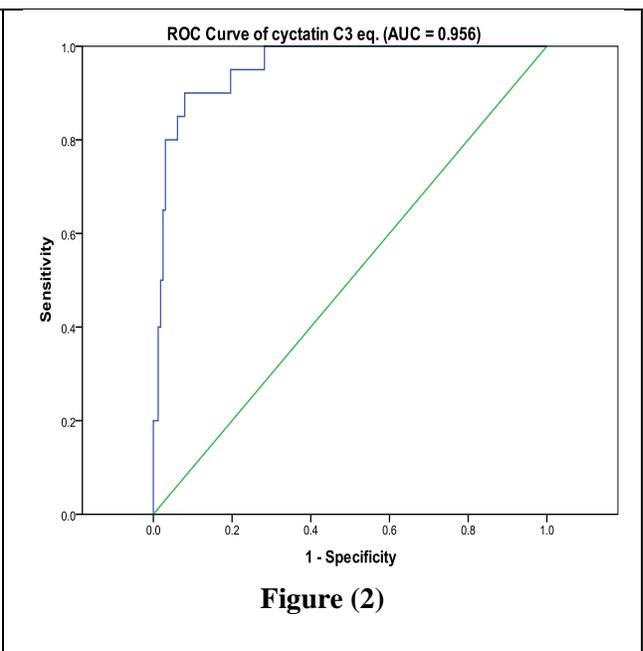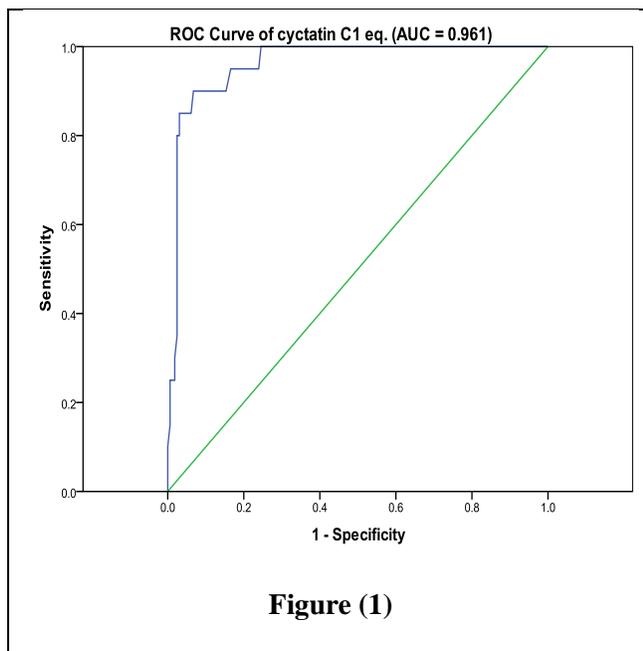
Statistical Analysis:
Calculations and statistical analyses were performed according to standard formulae for ROC plots, in which the optimal point was defined as the point having the greatest sum of sensitivity plus specificity at the maximum area under the curve (AUC). The data obtained in the current study was analyzed using Statistical Package for Social Sciences (SPSS) program.
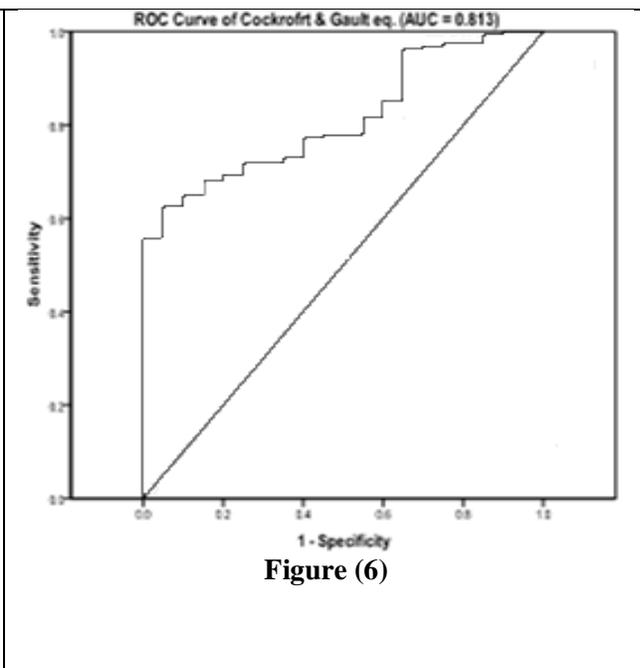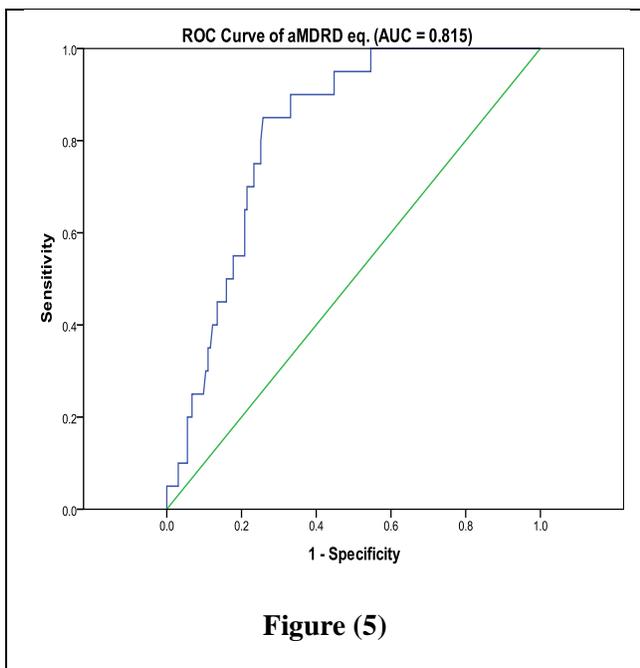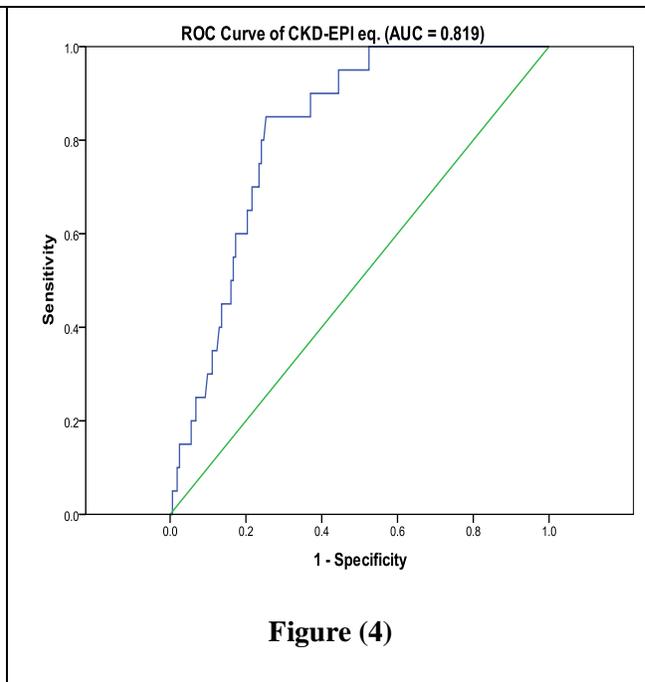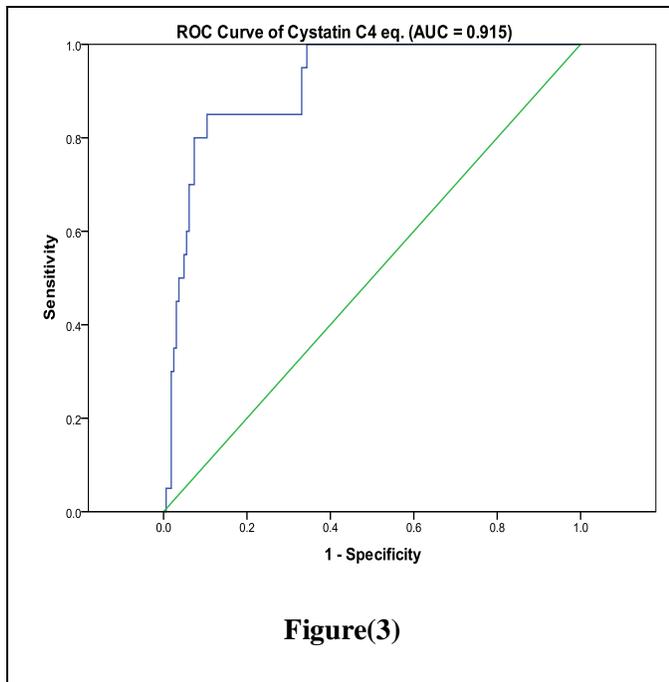**Results:**
the lowest one was Cockckroft – Gault equations respectively.

The result shows that the equation which have the maximum (AUC) was the Cystatin C1 which mean it's the most accurate equation.
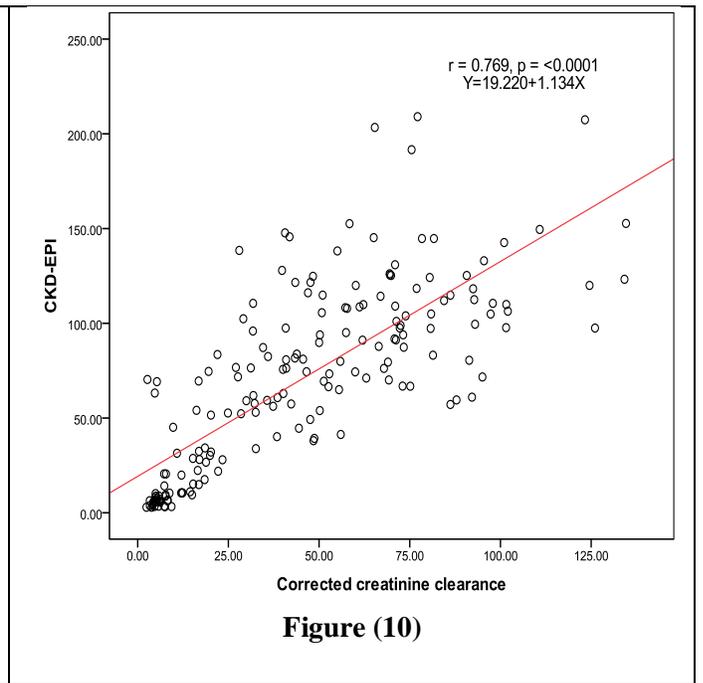

Figure (1)

Figure (2)

Figure(3)

Figure (4)

Figure (5)

Figure (6)

In the correlation analysis result when considering the corrected 24h creatinine clearance as independent variable analyzed with the studied estimated equations as the dependent variables, the result shows that the highest correlation was obtained by Cystatin C1 with highest R value equal to 0.932 followed by Cystatin C3, Cystatin C4, CKD-EPI, 4MDRD and the lowest R value obtained by Cockckroft – Gault equation equal to 0.616 as shown by figures (7-12).

Figure (7)

Figure (8)
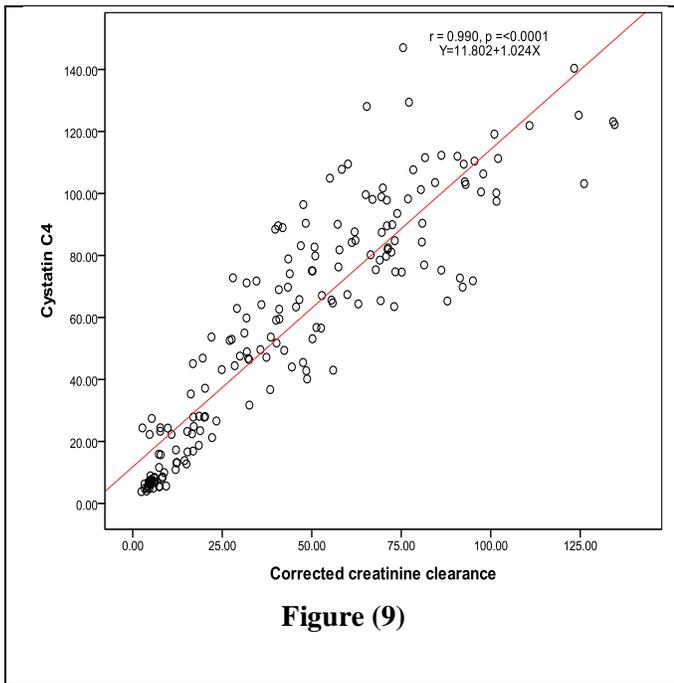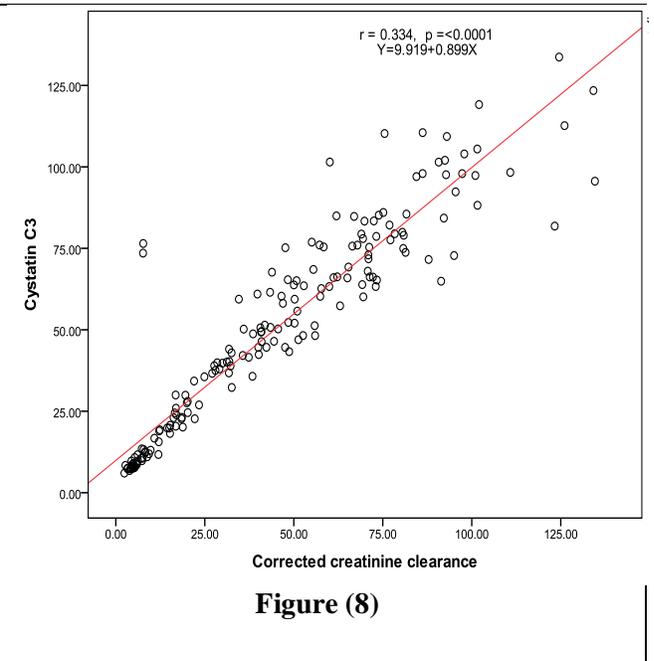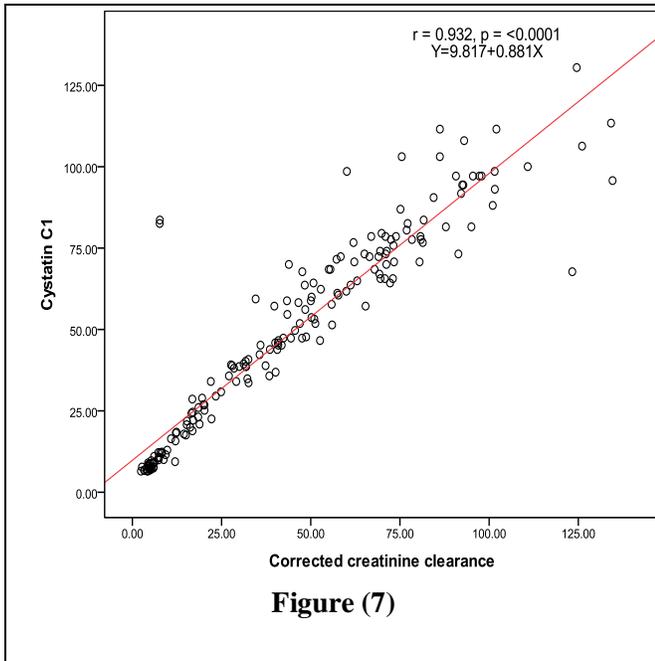
Figure (9)

Figure (10)

Figure (11)

Figure (12)

Discussion:

In this study, we pooled data from 185 patients with CKD, comparing GFR calculated by estimating equations using serum creatinine, cystatin C alone or Cystatin C in combination with creatinine.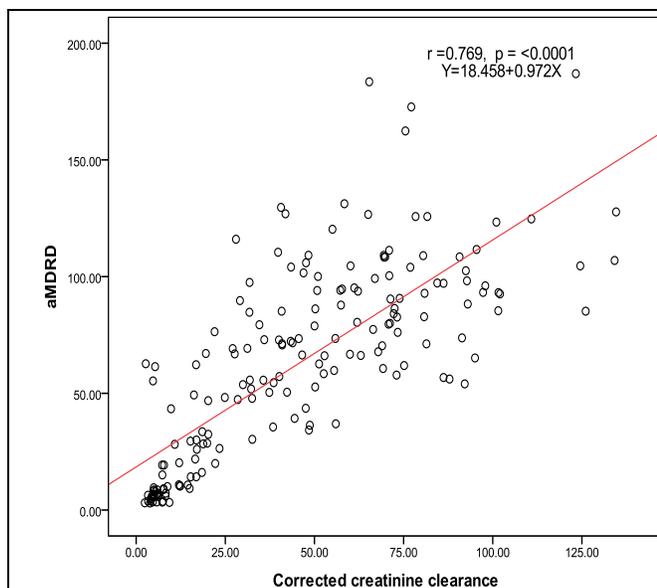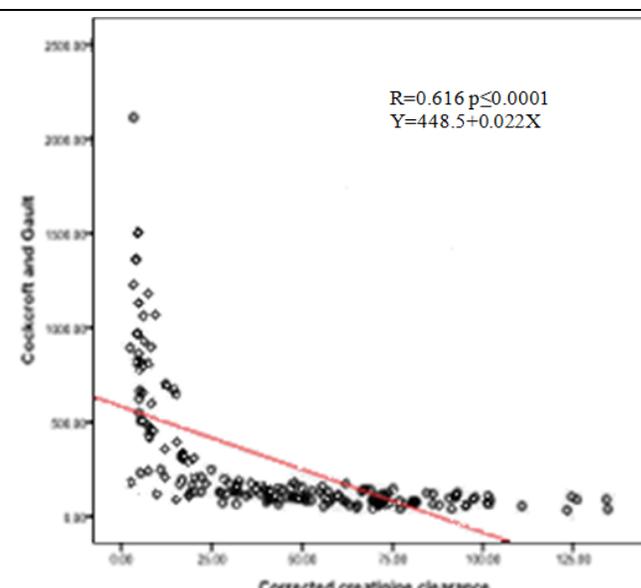 The cystatin C alone may be a better predictor for the assessment of kidney disease than cystatin C with creatinine. Use of cystatin C may also help physicians for better identification of patients with CKD who need intense monitoring or treatment.

A study conducted a meta-analysis of 11 general population involving 90,750 participants and 5 studies involving 2960 participants with CKD, effectively showed that the cystatin C–based eGFR offers the best means of predicting rates of death and end-stage renal disease across diverse populations, (Shlipak *et al,* 2011).

Other studies reported cystatin C alone to provide GFR estimates that are nearly as accurate as serum creatinine adjusted for age, sex and race thus providing an alternative GFR estimate that is not linked to muscle mass. An equation including cystatin C in combination with serum creatinine, age, sex and race provide more accurate estimates (Stevens *et al,* 2008).

Whereas others concluded that although the cystatin C assay is acceptable for routine clinical laboratory monitoring, none of the existing cystatin C-based equations were ideal for estimating GFR in Chinese CKD patients (Sun *et al,* 2010).

Most researchers revealed that Cystatin C is more accurate in detecting the decline in renal function than creatinine-based methods in the studied population of subjects with type 1 diabetes and a normal mean baseline GFR (Prematne *et al,* 2008).

Others reported cystatin C as a more reliable measure of GFR than creatinine clearance and is highly correlated with iohexol clearance than plasma creatinine, and is worthy for further investigation as a clinical measure of GFR in type 1 diabetes (Tan *et al,* 2002).

In a study conducted on diabetic type 2 population, reported that the simple cystatin C formula could be a useful tool for the evaluation of renal function in overweight patients with DM2 and impaired kidney function in daily clinical practice in hospital and especially in outpatients, despite the advantages of the simple cystatin C formula, cystatin C-based equations cannot completely replace the "gold standard" for estimation of the GFR in a population of DM2 patients with CKD, but may contribute to a more accurate selection of patients requiring such invasive and costly procedures. (Bevc *et al,* 2012)

In a study conducted at Malaysia, the researchers showed that cystatin C-based eGFR equation was more accurate, sensitive and specific in overweight and obese subjects compared to the creatinine based eGFR equations (Marwyne *et al,* 2011).

Another study conducted on intensive care unit patients, showed that plasma cystatin C was more sensitive than serum creatinine in detecting kidney failure in intensive care patients. Patients in intensive care frequently presented with decreased muscular mass. Therefore serum creatinine, which depends on the muscular protein creatinine, may remain abnormally low and thus overestimate true

Conclusion

Creatinine clearance remains the most widely used test for estimating GFR in clinical practice despite its many disadvantages and problems. Appreciating the limitations, GFR can be estimated

GFR. The increased sensitivity of plasma cystatin C can be explained by this phenomenon (Delanaye *et al,* 2004). In Germany (Poge *et al,* 2006) in a study conducted on cirrhotic patients showed a significant improvement of GFR estimation in liver cirrhotics by means of the Cystatin C-based equations formulae. However, all estimates remain as crude approximation of true GFR and thus cannot replace the gold standard method. Finally in study conducted on 100 Caucasian CKD patients and 15 voluntaries, showed no superiority of combination of both s-creatinine and s-cystatin C formulae over cystatin C alone formulae for GFR estimation (Urbaniak *et al*, 2008).

with reasonable accuracy and precision from serum Cystatin C_1 formula. Cystatin C could well enter the clinical field in our locality as a routine method for estimating GFR.

Refrences:

Bevc S, Radovan H, Robert E, *et al*.(2012), Simple Cystatin C Formula for Estimation of Glomerular Filtration Rate in Overweight Patients with DM Type 2 and CKD, *Experimental Diabetes Research.* 2012(10), 1155-1163.

Bishop ML, Fody EP, Schoeff LE, editors.(2010). *Clinical Chemistry Techniques, Principles, Correlations*. 6th ed. Philadelphia: Lippincott Williams and Wilkins, 300-302.

Delanaye P, Bernard L, Jean-Paul C, *et al.* (2004), Plasmatic cystatin C for the estimation of glomerular filtration rate in intensive care units, *Intensive Care Medicine,* 30(5), 980-983.

Morín JD, Serafín M, Nuria F, Corsino R, María D, Gonzalo S, Andrés C and Alberto M(May 2007). Cystatin C and beta2-microglobulin: markers of glomerular filtration in critically ill children, *Critical Care.* 11(3),1-7.

Kirwan CJ, Barbara JP, Iain AP (2013) Estimated Glomerular Filtration Rate Correlates Poorly with Four-Hour Creatinine Clearance in Critically Ill, *Critical Care Research and Practice*. 2013, 1-8.

Levey AS, Eckardt KU, Tsukamoto Y, *et al* (2005): Definition and classification of chronic kidney disease: A position statement from Kidney

Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 67, 2089-2100.

Marwyne MN, Loo CY, Halim AG, *et al*. (2011). Estimation of Glomerular Filtration Rate using Serum Cystatin C in Overweight and Obese Subjects, *Med J Malaysia* Vol 66(4), 313-317.

Poge UG, Stoffe W, Klehr H, *et al.* (2006), Calculation of glomerular filtration rate based on Cystatin C in cirrhotic patients, *Nephrol Dial Transplant* 21, 660–664.

Premartene S, Richard JM, Sue F, Sianna P, Elif E, *et al*.(2008) Serial Measurements of Cystatin C Are More Accurate Than Creatinine-Based Methods in Detecting Declining Renal Function in Type 1 Diabetes. *Diabetes care*,31(5).

Shlipak MG, Weekley CC, Li Y *et al*. (2011) Comparison of cardiovascular prognosis by 3 serum cystatin C methods in the Heart and Soul Study. *Clin Chem*; 57:737–745.

Stevens L A, Josef C, Christopher HS, *et al*. (2008) Estimating GFR using Serum Cystatin C Alone and in Combination with Serum Creatinine: A Pooled Analysis of 3418 Individuals with CKD. *Am J Kidney Dis*. March; 51(3): 395–406.

Sun Y, Tang J, Zeng Z, Peisong C (2010). Performance evaluation of a particle-enhanced turbidimetric cystatin C assay using the Abbott Aeroset analyser and assessment of cystatin C-based equations for estimating glomerular filtration rate in chronic kidney disease. *Nephrol Dial Transplant* 25: 1489–1496.

Tan GD, Lewis A, JamesT, *et al*. (2002) Clinical Usefulness of Cystatin C for the Estimation of Glomerular Filtration Rate in Type 1 Diabetes. *Diabetes care*. 25(11).

Urbaniak J, Weyde W, Zagocka E, *et al*. (2008) S-cystatin C formulae or combination of s-cystatin C 457.

and s-creatinine formulae do not improve prediction of GFR. Nephrol Dial Transplant 23: 2425-2426

Villa p, Manuel J, Maria-Cruz S, Jesus M and Pilar C (February, 2005). Serum cystatin C concentration as a marker of acute renal dysfunction in critically ill patients, C*ritical care*,9(2) p139-143.

Wee BT, Hui X,Danhua W, Jialiang L, Arvind KS, Borys S, Sunil S, and Evan JC. (2012) Estimating Glomerular Filtration Rates by Use of Both Cystatin C and Standardized Serum Creatinine Avoids Ethnicity Coefficients in Asian Patients with Chronic Kidney Disease*, Clinical Chemistry*. 58(2) 450–