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Assessment of Cystatin C–Based GFR Estimating Equations as a Novel Reliable Biomarker for Renal Pathology Diagnosis in Patients with Mild to Severe Tubular Affection

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RESEARCH

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ABSTRACT

Background and Objective

Creatinine, a commonly used biomarker in determining glomerular filtration rate (GFR) and chronic kidney disease (CKD) stage, is a highly variable biologically and does not rise until > 50% of renal function (RF) impairment, resulting in erroneous CKD grading. Applying a simple and reliable GFR estimate approach aimed at a minute evaluation of RF might be of tremendous therapeutic value. So, our investigation was aimed to assess Cystatin (Cys) -C-based eGFR equations, a novel, more sensitive biomarker in kidney pathology, and less susceptible to biological interference.

Methods

This cross-sectional study was performed on 20 CKD cases who attended the Nephrology Department at Ain Shams University, where a renal biopsy was obtained, and individuals were allocated into two categories: cases with mild tubular affection (TA) [category A] and with moderate to severe TA [category B]. All participants were referred for measurement of Cys-C Level using different GFR-estimating equations, which further compared using Multivariate Linear Regression and Bland-Altman analyses.

Result

Our results revealed a substantial statistical difference among the two studied categories regarding Hb, kidney function tests. A significant correlation between CKD-EPI CYST and mGFR was measured by Iohexol (Ioh) for category A (R=0.601, P=0.030), where there was a non-substantial relation between any of the used equations and mGFR in category B (p>0.05). There was no independent association between the eGFR results and Iohexol clearance. Stevens eGFR had the highest-level bias 33.9 compared with CKD_EPI_CYST (28) and Grubb eGFR (22.85).

Conclusion

Although cystatin-based equations have demonstrated a high level of correlation with measured Iohexol GFR, they are still deemed imprecise and cannot be established as equal to assessed GFR or as a gold standard for GFR estimate.

Key Words

Cystatin C, Chronic kidney diseases, Glomerular filtration rate, Lohexol clearance

Introduction

CKD is described as the existence of renal impairment or an estimated eGFR<60 ml/min / 1.73 m2 that lasts for 90 days or longer regardless of etiology and is graded into 6 phases depending on GFR (G1 to G5 with G3 split into 3a and 3b). It is a gradual decrease of kidney function that eventually necessitates the use of kidney dialysis or transplantation. Glomerulonephritis (GN) was once one of the most common causes of kidney disease[1].

CKD is a growing public health problem in the United States and around the universe[2]. The current disease burden may be attributed to CKD's fundamental pathogenesis shift. In 2018, the estimated annual cost of CKD upkeep was more than $81.8 billion, and treating people with end-stage kidney disease (ESRD) therapy cost an additional $36.6 billion globally, excluding kidney transplantation[3]. The high treatment costs place a significant burden on medical systems, especially in underdeveloped nations. Furthermore, CKD has a complex interrelationship with other illnesses[4]. Attributed to changes in CKD's fundamental pathogenesis.

In terms of gender, the increased CKD prevalence may be partly due to an incorrect women adjustment factor for both formulas. Furthermore, differences in shape and hemodynamics of glomerular, as well as hormone biotransformation between males and females, may play a role in the gender gap. However, significant doubts

concerning the efficacy of prediction equations persist, particularly when applied to females[5].

While the end-stage kidney illness epidemiology in Northern African nations is recognized, the epidemiology of early phases is unclear. This concern is now being addressed by a number of nationwide diagnostic tests programs, including Egypt's EGYPT-CKD initiative and Morocco's MAREMAR research. Preliminary findings from the former study indicate that proteinuria affects 10.6 per cent of relatives of dialysis patients. Regardless of the dearth of trustworthy databases, knowledge on CKD etiology was gathered by direct communication with prominent nephrologists in those countries.

It shows that GN contributes for 9–20 per cent, polycystic disease 2–3 per cent, chronic interstitial nephritis 7–17 per cent, hypertensive nephrosclerosis 10–35per cent and diabetes 11–18 per cent. Diabetes has grown more prevalent in Tunisian adults, at the cost of GN, proliferative Glomerulonephritis (PGN), and amyloidosis, whereas GN, PGN, and amyloidosis have declined in favor of Immunoglobulin A and membrane nephropathies. In Egyptians, traditional schistosomal nephropathies are giving way to hepatitis C virus (HCV) nephropathy. Focal segmental glomerulosclerosis is becoming more frequent in the region, displacing PGNs[6].

GFR and chronic renal disease grading are generally determined by monitoring the concentrations of endogenous blood indicators like albumin and creatinine. Creatinine (Cr), on the other hand, is prone to substantial biological variation, and Cr concentration doesn't really increase till almost 50% of renal function is lost, resulting in erroneous CKD grading and false negatives. In addition, in elderly people, serum Cr is not a useful indication of GFR. Moreover, to the significant influence of age on kidney structure and function, the same GFR level in various age groups may have varying pathophysiologic or non-pathophysiologic effects on renal function. Furthermore, the majority of the included studies demonstrated a gender difference in CKD prevalence. Females were more likely than males to have CKD. Females have less muscle mass than males, and muscle mass is a significant driver of blood creatinine levels[8].

To tackle these hurdles, Cystatin C, a novel GFR biomarker, has been demonstrated to be less susceptible to biological interference and more sensitive to early losses in renal function. Cystatin C is a 13-kDa protein that is generated by all nucleated cells and belongs to the cysteine proteinase inhibitor class. Its production rate remains constant from 1 to 50 years of age. It is a novel alternative GFR biomarker that has been demonstrated to be less susceptible to biological interference and more sensitive to early impairment in renal function[7]. Cystatin C has gained widespread acceptance as an endogenous biomarker of GFR and is now routinely used in the assessment of CKD[9].

Reagents and clinical assays have varied significantly over time, resulting in a plethora of cystatin C–based estimated GFR equations (eGFR) with varying coefficients to account for the variation in concentrations measured[10]. Because of the lack of consistency, it has been difficult to share or reproduce data across institutions. Concerns have also been raised about calibration changes made by individual manufacturers over the last 10–20 years. A downward drift in Siemens' particle-enhanced nephelometric immunoassay was observed, resulting in progressively higher GFR estimates[11].

The current work sought to evaluate the performance of Cystatin C–based eGFR equations evaluated by immunoturbidimetry in renal pathology Diagnosis and calibrated to the standard Cystatin C reference range in comparison to the gold stander mGFR from Iohexol.

Patients and Methods

This was a cross-sectional study performed from March 2019 to September 2019 on 20 cases with CKD who attended the Nephrology Department at Ain Shams University in Cairo, where a renal biopsy was obtained, and individuals were allocated into two categories: Cases with mild tubular affection [category A, (score 1, 2)] and cases with moderate to severe tubular affection [category B, (score 3,4)].

Prior to the start of the study, the proposed procedures were announced to all individuals who agreed to participate and satisfied the inclusion criteria. A detailed history is taken, which includes demographic information (age, weight, and body mass index kg/m2). The full general examination includes pulse, blood pressure, respiratory, cardiovascular, and abdominal.

Exclusion criteria

Demographic data and a detailed history, including a history of head trauma, drug abuse, seizures, comorbid conditions, regular medications and physical limitations was taken from the informant. Comprehensive geriatric health assessment including general physical examination, systemic examination, neurologic examination was performed.

Patients were investigated and managed as per treating physician’s protocol. Data thus collected was analyzed.

Methodology

After exclusion of non-respondents patients or with the above-mentioned exclusion criteria, informed signed consent of all study participants was taken. Ten (10 cc) of venous blood were withdrawn from every patient in each category under full aseptic condition after fasting overnight.

Blood was transferred to an Eppendorf tube at 37 °C for 30 minutes to clot and centrifuged at 4000 rpm for a further ten min. The obtained serum was put in aliquots kept at -70 º C until the analysis time to determine marker serum level.

Measurement of Cystatin C

The cyst C level in frozen-thawed serum was determined using a particle-enhanced turbidimetric immunoassay (PETIA) as reported early[12]. eGFR calculated *via* the following 3 cysteine C based equations.

Stevens: $eGFR=76.7 \times cys^{-1.19}$ [13]

Grubb: $eGFR=87.62 \times cys^{-1.693} \times (0.94 \text{ if female})$ [14]

Ckd-epi cyst:

If serum cystatin is ≤ 0.8: →133×min (s.cys/0.8)-0.499× 0.996age×0.932 if female

If serum cystatin is > 0.8: →133×max (s.cys/0.8)- 1.328× 0.996age×0.932 if female

Routine investigations

All participants were referred for routine laboratory investigation tests, including complete blood picture (CBC), coagulation profile, renal function examination (serum urea, Cr, Na, and K), hepatic function test (ALT, AST, serum albumin, uric acid) and complete urine analysis and protein/creatinine ratio.

Measurement of GFR

The gold standard for measuring GER was serum IOHEXOL clearance. A 5 mL IV bolus of Ioh (Omnipaque 300) was administered. Blood samples were collected every and 24 hrs. The specimens had been centrifuged, and the values were obtained using High-performance liquid chromatography (HPLC) and plotted into a curve to determine the area under the curve (AUC). Clearance was calculated according to the formula of one-compartment model Cl=Dose/(AUC) eq. 4.

Where Dose is the full quantity of I2 supplied during the bolus. The AUC is the area under the curve correlating to the body's time spent in contact with Ioh. Plasma clearances (Clp) were then computed using the formula of Brochner-Mortensen.

Clp=[0.990778×Cl] – [0.001218× Cl2], [16] eq. 5.

Although the blood specimen number was onerous, the 24-hour sample, when incorporated in the Clp calculation, the GFR measurement became more reliable. Earlier blood specimens (T2–T4 and T2–T6) overestimated GFR, whereas for GFR < 60 mL per min per 1.73 m2 a late timespan (24 hr) is necessary to decrease bias testing, that causes a 10 per cent overstatement of GFR[17].

Renal biopsy examination

Renal biopsy was studied under a light and electron microscope, with a focus on tubular pathology. Tubular atrophy (TA), interstitial fibrosis (IF), interstitial edema (IE), interstitial inflammation, and acute tubular damage (ATD) all were evaluated semi-quantitatively on a scale from 0 to 3 dependent on the proportion of cortex affected region (1, 1 to 25, 26 to 50, and more than 50 per cent). Arteriosclerosis and arteriolosclerosis were graded from 0 to 3 (absent, mild, moderate, and severe) based on the degree of luminal constriction and artery wall thickening, respectively.

Ethical consideration

Approval of the study design was obtained from the Institutional Review Board (IRB) unit and the Research Ethical Committee in the faculty of Medicine; Ain shams University.

Patient consent

The proposed study methods were presented to all subjects, an oral and informed written permission consent document was signed by those who agreed to participate before sample collection.

Statistical analysis

On an IBM personal computer, data was evaluated utilizing the SPSS (Statistical Package for Special Science software, Vr 25. The Spearman's rank correlation coefficient analysis is utilized to ascertain the statistical dependency of two variables[9]. The Mann-Whitney-U test is utilized to evaluate two sets of data whose distribution is unknown. Bias-Precision: the average difference between predicted and observed renal function was defined as bias, and the SD of this discrepancy was represented as precision. The Bland and Altman (BA) technique was utilized to show the discrepancies among calculated and measured GFR levels. Multivariate Linear Regression Analysis was utilized to look for an independent relationship between any of the estimated GFR outcomes and Iohexol clearance[10]. The Wilcoxon test was used to compare Iohexol clearance to other eGFR techniques.

Results

Demographic characteristics of 20 CKD cases (40 % were females), including 13 cases with mild tubular affection, and 7 cases with moderate to severe tubular affection, are presented in Table 1. The average age of all individuals involved in our current study was 35.9 ± 8.4 and 34.9 ± 16.2, respectively. Table 2 demonstrated that there is no statistically significant difference regarding age (P=0.847), gender (P=0.052), and BMI (P=0.863) among the 2 categories of the current research. Additionally, there was a non-significant difference with respect to the degree of tubular affection and virology among all studied categories (A and B), P>0.05.

The routine laboratory tests were presented in Table 3; the mean (hemoglobin) Hb value was 12.7 ± 2.9 and 8.6 ± 1.2 g/dl, for category A and B, respectively, with the same International Normalized Ratio (INR)~1.0 ± 0.1 in both categories. Our results revealed that there was a substantial

statistical difference among the two studied categories regarding Hb, kidney function test (creatinine Urea and serum uric acid), and ALT, p<0.05, Table 4.

Maximum GFRcys was calculated using different equations (Stevens, Grubb, and CKD_EPI_CYST) in comparison to GFR_iohexol. As represented in Table (3), cases with moderate to severe tubular affection had significantly lower levels for both estimated and measured GFR (82, 93, 115, or 115) ml/min / 1.73 m2, Vs. cases with mild tubular affection (200, 123, 162 or 124) ml/min / 1.73 m2, according to GFR_iohexol, Stevens, Grubb, and CKD_EPI_CYST, respectively, p<0.05[14].

The measured serum eGFRcys using Stevens, Grubb, and CKD_EPI_CYST formulas and mGFR from Iohexol were calculated for multiple correlations. Our results demonstrated a significant correlation between CKD-EPI CYST and mGFR measured by Iohexol at the mild degree of tubular affection (R=0.601, P=0.030), whereas there was non-substantial relation among any of the used equations and measured GFR at moderate to severe tubular affection (p>0.05)[16]. For all patients, a strong significant statistical correlation between all equations and measured mGFR, with comparable correlation coefficients (R=0.799, p= 0.0001) was found, as illustrated in Table 4 and Figure 1.

Table 5 presented the comparison between Iohexol clearance and different methods of eGFR in all patients and after patient's division according to the degree of tubular affection by renal biopsy. Our results revealed that eGFR by cystatin-based equations (Stevens, Grubb, and CKD_EPI_CYST) underestimate mGFR, when compared to Iohexol clearance with statistical significance in all patients (by 3.280, 2.878, 3.280 per cent, respectively) and cases with mild tubular affection (by 3.11, 2.657, 2.972 per cent, respectively) (p < 0.05), but with non-statistical significance in moderate to severe tubular affection category (B), p> 0.05.

Our results showed no independent association between any of the estimated GFR results and Iohexol clearance. Stevens eGFR had the highest-level bias 33.9 compared with CKD_EPI_CYST eGFR[28] and Grubb eGFR (22.85), Table 6, and Figure 2.

Discussion

GFR is commonly used to assess kidney function. It is most often calculated in clinical practice utilizing endogenous surrogate indicators. The most often utilized endogenous marker is serum creatinine. Serum cyst-C is a relatively recent endogenous indicator that has the benefit of being produced continuously via all nucleated body cells and being catabolized almost entirely at the proximal tubule. Serum cyst-C had been found in clinical investigations to be an accurate diagnostic of GFR[19].

The CKD Epidemiology (CKD-EPI) formula, introduced in 2009, appears to be better accurate in calculating GFR than prior ones. Because creatinine procedures were not standard throughout the intervening institutions, resulting in discrepancies in creatinine readings, all of these formulas lack appropriate validation at the GFR at that they were used. Lastly, Cr-depend GFR estimates have numerous disadvantages and are dependent on numerous variables, and the precision of these formulas is hotly debated[20].

Cyst-C has been suggested as a new endogenous GFR biomarker. Although newer research has questioned these findings, serum cyst-C level appears to be unaffected by muscle mass, gender, aging, or dietary condition. Inflammation, fever, or other factors may not affect serum cystatin C levels[15]. Furthermore, it appears to be a more accurate GFR indicator in diseases such as liver cirrhosis, diabetes mellitus, and the geriatric. Because of these qualities, several people have recommended cyst-C as a better exact measure of GFR than Cr, especially in persons of minor GFR impairment; however, these investigations are not only scarce but also conflicting and cover a small number of individuals[21].

Notwithstanding the theoretical benefits of cyst-C and the more refined formulae, the dispute persists, and no formula has been securely developed to measure GFR at any phase. As a result, the need for updated formulas is mostly owing to the lack of accuracy in estimating GFR, especially when the gold standard techniques of GFR assessment differ from one research to another[22]. Several formulae have been established based on creatinine and cystatin C. In this context, recent research wherein renal function was assessed using Iohexol clearance as the gold standard of GFR and Cr or cyst-C formulas is noteworthy[23].

In terms of demographic data, our analysis found no statistically significant difference among the 2 studied categories (A and B). eGFR estimated by Cystatin C-based equations had a strong correlation with mGFR estimated by Iohexol with comparable correlation coefficients (R), which is consistent with several studies, including one by Godwill et al., who found that cyst-C levels were substantially linked with assessed GFR[24]. Also, our findings matched those of Abdallah. Who discovered a substantial association between the Cystatin C –based formula in the examined CKD patients and the measured GFR in the same patients [25].

Stevens conducted a pooled analysis in which they estimated GFR utilizing serum Cyst-C alone and in conjunction with serum Cr, correlated significantly with GFR measured by Iothalamate but also to produce more reliable estimations, a formula combining serum cyst with serum Cr, age, gender, and race was proposed[13].

In a separate investigation, Inker evaluated the efficacy of the Cyst_CKD_EPI formula alone and in contrast to the combined Cr–cyst-C formula, finding that the combined formula provided a highly precise and accurate assessment of GFR[15].

In accordance with our findings Hojs, found that cystatin-based equations underestimated measured GFR and lacked accuracy [23]. Nevertheless, these findings contrast other research by Gupta et al., who reported cyst-based equations overestimated measured GFR[26]. Our findings also revealed a substantial degree of bias between cystatin C-based equations and Iohexol clearance, with a non-statistically significant tendency toward larger bias with Steven's equation and the least bias with Grubb's equation.

Steven's equation was compared to other several equations in a study by Harman et al. found ten research that looked at 14 different cyst-C based estimating formulae: Grubb., Arnal-Dade, Macisaac. Stevens formula demonstrated the least bias and the maximum accuracy *versus* observed GFR utilizing kidney or Clp of contrast media, radioactive elements, or inulin[26].

Another research by Chudleigh et al. evaluated the performance of multiple cystatin-based equations and discovered that all models underestimated GFR, with the Stevens equation showing less bias than the Rule and Perkins equations but higher bias than the Tan and MacIsaac equations[27].

Sharma et al. discovered that the diagnostic accuracy of several cystatin C equations varied with GFR in their investigation. This problem must be addressed when using these equations in clinical practice and in future research on eGFR equations[28].

According to Rule. The various methodologies (urinary inulin clearance, plasma 99mTc-DTPA clearance, and plasma Iohexol clearance) employed as a GFR assessments gold standard reference could potentially contribute to part of the among-investigation variations, where variations in GFR assessment procedures are likely to be a substantial origin of diversity[29].

Furthermore, Delanaye. believe that a significant cause of variance is the lack of established calibration for cyst-C testing. On comparing various cyst-C procedures, where considerable discrepancies have been recorded, and therefore when employing cystatin C-based equations, it is vital to understand that cystatin C estimations vary depending on whether the test is performed using a turbidimetric or nephelometric approach[30]. Other results of the present investigation include a strong relationship between the degree of tubular affection and Hb level, which was shown to be lower in group B patients compared to those in group A.

Patients with varied etiologies were studied, and it was shown that the prevalence of anemia was closely linked to a decline in GFR. The present investigation also demonstrated that patients in category B (moderate to severe tubular affection) had higher levels of serum uric acid, which is consistent with a study by Zhou, that found hyperuricemia to be a marker for tubulointerstitial lesions.

Conclusion

According to our findings, GFR calculated using cystatin-based equations underestimates GFR when compared to GFR evaluated using iohexol. Only in moderate tubular affection and with the CKD EPI CYST equation is there a substantial association between GFR evaluated by cystatin-based equations and gold standard GFR iohexol. The Stevens equation had the greatest bias, whereas the Grubb equation had the least bias. Although cystatin-based equations have demonstrated a high level of correlation with measured GFR, they are still regarded as imprecise and cannot be established as equal to calculated GFR or as a gold standard for GFR estimate.

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Figures and Tables

Table 1: Baseline characteristics of CKD patients distrbuation among studied categories.

characteristics of CKD patients	Category A (N=13)	Category B (N=7)	X^2	P Value
Age (Year's)	35.9 ± 8.4	34.9 ± 16.2	0.196	0.847
Gender			4.43	0.052
Male	10	2		
Female	3	5		
BMI kg/m^2	26 ± 3.1	25.7 ± 3.4	0.175	0.863
HTN	5 (38.5%)	2 (28.6%)	0.196	0.526
% of patients with active urinary sediment (AUS)	3 (30%)	4 (60%)	2.32	0.151
Virology (HCV)	5 (38.5%)	0	3.59	0.083

2 = Chi Square HTN = Hypertension

Table 2: Comparison of laboratory profile among studied categories.

	Category A (N=13)	Category B (N=7)	Z	P Value
Hg g/dl	12.7 ± 2.9	8.6 ± 1.2	2.854	0.002*
INR	1.0 ± 0.1	1.0 ± 0.1	1.468	0.157
sCreatine	1.4 ± 1.4	5.0 ± 2.2	3.058	0.001*
BUN	22.6 ± 13.1	67.6 ± 32.4	3.052	0.001*
Na	134.1 ± 3.9	135.1 ± 6.8	1.114	0.275
K	4.0 ± 0.7	4.2 ± 0.500	0.873	0.393
UA	6.0 ± 0.7	7.9 ± 1.5	2.501	0.011*
Albumin	2.2 ± 0.9	2.7 ± 0.9	1.112	0.275
TP	5.4 ± 1.1	5.6 ± 1.1	0.638	0.536
ALT	16.1 ± 6.8	11.9 ± 4.5	2.08	0.037*
Protien/ creatinine ratio	2.8 ± 1.4	5.4 ± 6	0.833	0.438

Hg = Hemoglobin INR = International Normalized Ratio

BUN = Blood Urea Nitrogen TP = Total Prot

Table 3: Comparison of categories on the basis of estimated eGFR using various methodologies.

	Category A (N=13)			Category B (N=7)				P Value
	Min	Median	Max	Min	Median	Max	Z	
GFR_iohexol	9	136	200	12	26	82	-3.051	0.001*
Stevens	17	100	123	12	22	93	-2.899	0.002*
Grubb	10	127	162	7	13	115	-2.895	0.002*
CKD_EPI_CYST	15	110	124	11	16	115	-2.736	0.005*

Table 4: Correlations among various eGFR estimate techniques and iohexol clearance as mGFR a gold standard measure: (Mild tubular affection, Moderate to severe, and all patients).

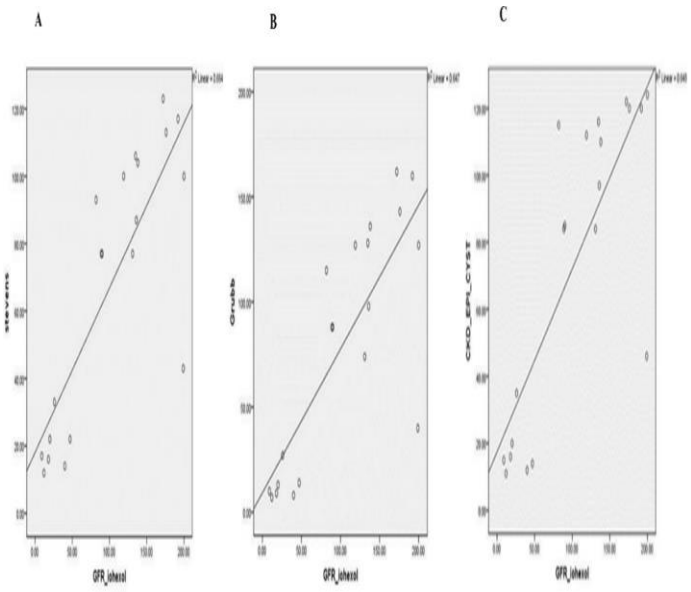
GFR_iohexol	Category A			Category B			All patients		
	S	G	ESK	S	G	ESK	S	G	ESK
R	0.49	0.485	0.601*	0.667	0.714	0.464	0.799**	0.799**	0.799**
P-Value	0.089	0.093	0.03	0.102	0.071	0.294	0.0001	0.0001	0.0001
Number	13	13	13	7	7	7	20	20	20

S=Stevens, G=Grubb, CEC=CKD_EPI_CYST, R=Spearmanns correlation coefficient

Table 5: Comparison of Iohexol clearance mGFR and various techniques of eGFR in all patients and after patient division based on degree of tubular affection (Mild tubular affection, Moderate to severe) by renal biopsy.

GFR_iohexol	Category A					Category B					All patients				
	Median	Min	Max	Z	P	Median	Min	Max	Z	P	Median	Min	Max	Z	P
Stevens	100	17	123	-3.111	0.002	22	12	93	-0.42	0.674	77	12	123	-3.28	0.001
Grubb	127	10	162	-2.657	0.008	13	7	115	-1.101	0.271	88	7	162	-2.878	0.004
CKD_EPI_CYST	110	15	124	-2.971	0.003	16	11	115	-0.42	0.674	85	11	124	-3.28	0.004

Figure 1: Correlation between eGFR estimated by A) Steven's equation B) Grubb's equation or C) CKD-EPICYST equation and iohexol clearance (mGFR) as a Gold standard measure in all patients.



Assessment of Cystatin C–Based GFR Estimating Equations as a Novel Reliable Biomarker for Renal Pathology Diagnosis in Patients with Mild to Severe Tubular Affection

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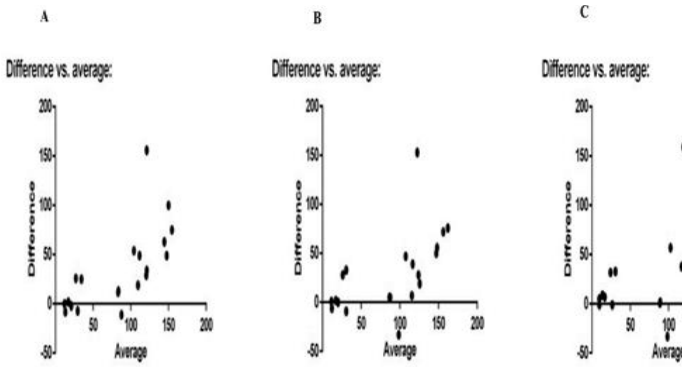
Figure 2: Bland –Altman plot comparing A) Stevens' equation, B) Grubb's equation and C) CKD-EPICYST equation with Iohexol clearance (mGFR).



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