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Comparison between Creatinine Clearance and eGFRcyst-crea: a real-life experience

Articoli originali

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ABSTRACT

Introduction: The evaluation of renal function is computed using the estimated glomerular filtration rate methods or the measured glomerular filtration rate. Cystatin C has been well studied as marker of renal function compared to serum creatinine, but only few studies compare Glomerular Filtration Rates estimated including both creatinine and cystatin (eGFRcyst-crea) to creatinine clearance (CrCl). This cross-sectional study compares CrCl and eGFRcyst-crea with eGFRcrea and searches for correlation with comorbidities.

Methods: This cross-sectional study consists of 78 patients hospitalized for acute and/or chronic renal disease. We performed the concordance correlation coefficient analysis between the eGFRcrea and the CrCl and eGFRcyst-crea in the whole sample and in the various subgroups.

Results: Steiger's comparison of correlations from dependent samples showed a correlation coefficient between C-reactive protein and eGFRcyst-crea stronger than between C-reactive protein and CrCl (Z: 2.51, p=0.012). Similar results were showed with the association with procalcitonin (Z: 5.24, p<0.001), serum potassium (Z: -3.13, p=0.002), and severe CKD (Z: -2.54, p=0.011). The concordance correlation coefficient test showed major differences between diagnostic methods compared to eGFR-crea in diabetic subgroup, severe CKD, and in procalcitonin higher than 0.5ng/ml.

Discussion: The demonstration of a strong concordance between the eGFRcrea and the eGFRcyst-crea allows us to diagnose and to stage CKD better than creatinine clearance in patients with high inflammatory status. Furthermore, this information opens new research scenarios, and further, larger studies are needed to confirm these hypotheses.

KEYWORDS: Phosphorus, Hemoglobin, Anemia, Chronic Kidney Disease, FGF23, Generalized estimating equation

Introduction

The association of cystatin C with renal function has been studied for more than 25 years. Cystatin C has been described to have better diagnostic performance than creatinine for assessing renal function, particularly in detecting small reductions in glomerular filtration rate (GFR).

Since cystatin C is a low-molecular-weight protein produced by all nucleated cells, it is less influenced by variables such as age, body weight or diet and it has been proposed as a more reliable marker of kidney function than serum creatinine.

From what emerges in literature, cystatin C has been reported not only as a marker of GFR measurement, but also as an independent risk factor for cardiovascular mortality among older people both with chronic kidney disease (CKD) and without renal impairment. Conversely, the hypothetical role of cystatin C as a marker of inflammation and atherosclerosis is still controversial.

Cystatin C was often compared to serum creatinine, but few studies were published comparing estimated Glomerular Filtration Rates computed with CKD-EPI formula including cystatin (eGFRcyst-crea) and creatinine clearance on 24h urine collection (CrCl).

This cross-sectional study compares CrCl and eGFRcyst-crea to estimated Glomerular Filtration Rates computed with CKD-EPI formula [eGFRcrea CKD-epi] both in the whole sample and in subgroup based on diabetes, severe CKD, inflammatory sate, bacterial inflammation, and age.

Methods

Population

The present cross-sectional study was carried out on a sample of the population admitted to the Nephrology and Dialysis Unit of the AOU Policlinico “G. Martino” Hospital of Messina from November 2020 to May 2021. The cohort consists of 78 patients hospitalized for acute and/or chronic renal failure, proteinuria, and hereditary renal diseases. We analyzed the different methods to evaluate renal function through the concordance correlation coefficient analysis of the commonly used method (CKD-EPI formula using creatinine), compared to CrCl and the formula CKD-EPIcyst-crea among the various patient subgroups. Creatinine and cystatin were analyzed, in the serum, in the central laboratory of our university hospital. Anamnestic data, domiciliary therapy, and blood chemistry values were analyzed. Laboratory tests were performed by the Pathology ward of the same hospital.

Statistics

Distributions of variables were calculated with the Kolmogorov-Smirnov test. Baseline continuous variables were reported as mean ± standard deviation or median and interquartile range in relation to their distributions. Baseline dummy variables were expressed as numbers and percentages. Positive asymmetry variables were log-transformed. Pearson’s correlation test was used to calculate the interaction between variables. Comparators of Pearson’s coefficient values were computed with Steiger’s test and reported as Z test and p. Concordant values between the two methods and our reference method (eGFR crea CKD-epi) were computed with concordant correlation coefficient both in the whole sample and in subgroups, and were expressed as coefficient and 95% confidence interval (95% CI). Stratifications were performed based on clinical and literature knowledge. ROC curve was performed for severe CKD.

Parameter	Value	Parameter	Value
M/F	43/35	C-reactive protein, *mg/dl*	0.40 (0.17 – 0.98)
Age, *years*	62 ± 17	Procalcitonin, *ng/ml*	0.14 (0.07 – 0.68)
Diabetes mellitus, *n (%)*	21 (26.9)	Parathyroid hormone, *pg/ml*	69.40 (21.10 – 216.00)
Sodium, *mmol/L*	139.22 ± 4.67	Creatinine, *mg/dl*	1.80 (0.90 – 3.95)
Potassium, *mmol/L*	4.47 ± 0.59	Cystatin C, *mg/L*	2.42 ± 1.26
Calcium, *mg/dl*	9.10 (8.42 – 9.50)	$eGFR_{creat}$, *ml/min*	36.01 (12.57 – 81.45)
Phosphorus, *mg/dl*	3.70 (3.22 – 4.77)	$eGFR_{cyst}$, *ml/min*	26.00 (14.00 – 49.75)
Haemoglobin, *g/dl*	11.49 ± 2.18	$eGFR_{cyst\text{-}creat}$, *ml/min*	35.00 (12.25 – 56.75)
Haematocrit, *%*	34.23 ± 6.16	Creatinine Clearance, *ml/min*	36.20 (18.27 – 77.67)
Transferrin saturation, *%*	23.95 ± 9.88	Proteinuria, *mg/24h*	775.00 (242.00 – 2237.00)

M=male; F=famale; eGFRcreat= estimated Glomerular Filtration Rates computed with CKD-EPI formula including creatinine; eGFRcyst= estimated Glomerular Filtration Rates computed with CKD-EPI formula including cystatine; eGFRcyst-creat= estimated Glomerular Filtration Rates computed with CKD-EPI formula including creatinine and cystatine.

Table 1: Baseline features of the whole sample. Data are reported as mean ± standard deviation or median (interquartile range) or number (%) as appropriate.

Results

Seventy-eight patients were analyzed. Baseline features of the whole sample were summarized in Table 1. Pearson's correlation test showed a correlation coefficient between C-reactive protein and eGFRcyst-crea and CrCl of 0.125 (p=0.271) and 0.002 (p=0.985), respectively; between procalcitonin and eGFRcyst-crea and between bacterial infections and creatinine clearance of 0.223 (p=0.360) and -0.032 (p=0.897), respectively; for serum potassium and eGFRcyst-crea and creatinine clearance of -0.398 (p=0.001) and -0.253 (p=0.024), respectively; and between severe CKD and eGFRcyst-crea and creatinine clearance of -0.862 (p=0.001) and -0.796 (p=0.001), respectively. Other correlations were reported in Table 2.

Steiger's comparison of correlations from dependent samples showed significant differences in the power of association with C-reactive protein (Z: 2.51, p=0.012), procalcitonin (Z: 5.24, p<0.001), serum potassium (Z: -3.13, p=0.002), and severe CKD (Z: -2.54, p=0.011) between eGFRcyst-crea and Creatinine Clearance.

The concordance correlation coefficient test, summarized in Table 3, has shown major differences (> 0.2) between diagnostic methods compared to eGFR-crea, in diabetic subgroup (Coefficient [95% CI]: 0.67 [0.38 – 0.84] for CrCl vs 0.89 [0.76 – 0.96] for eGFRcyst-crea), severe CKD (Coefficient [95% CI]: 0.52 [0.32 – 0.67] for CrCl vs 0.82 [0.68 – 0.90] for eGFRcyst-crea), not severe CKD (Coefficient 0.55 [0.30 – 0.73] vs 0.85 [0.72 – 0.91]), C-reactive protein (Coefficient [95% CI]: 0.81 [0.65 – 0.86] for CrCl vs 0.96 [0.93 – 0.98] f or eGFRcyst-crea) and in bacterial infections (Coefficient [95% CI]: 0.37 [-0.82 – 0.96]for CrCl vs 0.93 [0.86 – 0.97] for eGFRcyst-crea). No other significant differences, summed up in Table 3, were detected in the remaining subgroups.

		$eGFR_{cyst\text{-}creat}$	ClCr	$eGFR_{creat}$
$eGFR_{cyst\text{-}creat}$	Rho	1	–	–
	p	–	–	–
	n°	79	–	–
CrCl	Rho	0,908**	1	–
	p	0,000	–	–
	n°	79	79	–
$eGFR_{creat}$	Rho	0,961**	0,878**	1
	p	0,000	0,000	–
	n°	79	79	79
C-reactive protein	Rho	0,125	0,002	0,146
	p	0,271	0,985	0,198
	n°	79	79	79
Procalcitonin	Rho	0,223	-0,032	0,316
	p	0,360	0,897	0,187
	n°	19	19	19
Diabetes mellitus	Rho	-0,129	-0,121	-0,132
	p	0,262	0,293	0,248
	n°	78	78	78
Severe CKD	Rho	-0,862**	-0,796**	-0,878**
	p	0,000	0,000	0,000
	n°	79	79	79

CKD= Chronic kidney disease; CrCl= creatinine clearance; eGFRcreat= estimated Glomerular Filtration Rates computed with CKD-EPI formula including creatinine; eGFRcyst-creat= estimated Glomerular Filtration Rates computed with CKD-EPI formula including creatinine and cystatine.

Table 2: Pearson's correlation tests using $eGFR_{cyst\text{-}creat}$, ClCr and $eGFR_{crea}$ (log-transformed) as dependent variables.

Subgroups	eGFRcreat vs Creatinine clearance	eGFRcreat vs eGFRcyst-creat
Whole sample	0.84 [0.78 – 0.90]	0.95 [0.93 – 0.97]
Age < median	0.81 [0.66 – 89]	0.91 [0.85 – 0.95]
Age > median	0.78 [0.62 – 0.88]	0.94 [0.88 – 0.97]
Diabetes	0.67 [0.38 – 0.84]	0.89 [0.76 – 0.96]
No diabetes	0.82 [0.72-0.89]	0.91 [0.86 – 0.95]
Severe CKD	0.52 [0.32 – 0.67]	0.82 [0.68 – 0.90]
No severe CKD	0.55 [0.30 – 0.73]	0.85 [0.72 – 0.91]
C-reactive protein positivity	0.81 [0.65 – 0.86]	0.96 [0.93 – 0.98]
C-reactive protein negativity	0.83 [0.65 – 0.88]	0.93 [0.88 – 0.97]
Procalcitonin >0.5ng/ml	0.37 [-0.82 – 0.96]	0.93 [0.86 – 0.97]
Procalcitonin <0.5ng/ml	0.94 [0.93 – 0.98]	0.98 [0.96 – 0.99]

CKD= Chronic kidney disease; eGFRcreat= estimated Glomerular Filtration Rates computed with CKD-EPI formula including creatinine; eGFRcyst-creat= estimated Glomerular Filtration Rates computed with CKD-EPI formula including creatinine and cystatine.

Table 3: Concordant correlation coefficients.

The ROC curve for severe CKD as outcomes showed an AUC of 99,2% for eGFRcre-cyst and an AUC of 96% for ClCr (Fig. 1).

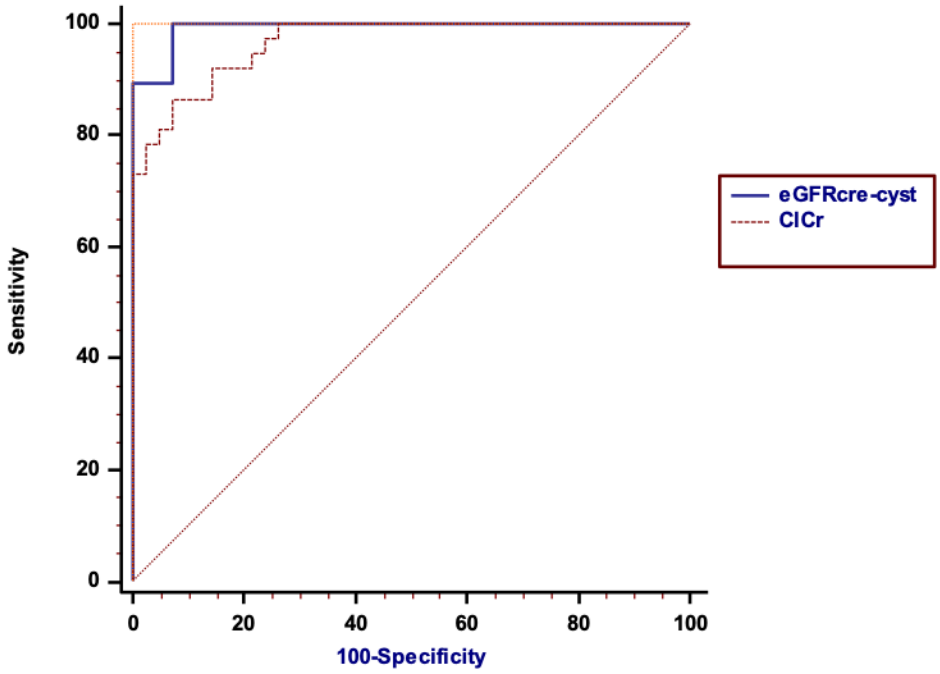

Fig. 1: ROC curve using severe CKD as outcome.

Discussion

Our study highlighted the differences between eGFRcyst-crea and CrCl compared to the eGFRcrea more evident in patients affected by diseases that increase the inflammatory state. Indeed, as summarized in Table 3, the greatest differences between these two methods were showed in the subgroups affected by diabetes or CKD or with high C-reactive Protein levels. We evaluated, differently from other published studies, the correlation between methods and comorbidity and we compared the strength of correlations among the methods. In detail, in the group of 21 diabetic patients, the concordance correlation coefficient between eGFRcrea and eGFRcyst-crea was 0.89 [95% CI, 0.76-0.96], which was higher than the concordance correlation coefficient between eGFRcrea and CrCl of 0.67 [95% CI, 0.38-0.84]. Similarly to our study, Shlipak et al. showed a higher correlation coefficient between eGFR and cystatin C than eGFR and serum creatinine (r=0.82 vs r=0.74, respectively) [1, 2].

Recent studies confirm our results, demonstrating how the GFR values estimated with cystatin-creatinine can be predictive of renal damage in patients with diabetes mellitus. In this regard, Asmamaw et al. conducted a cross-sectional comparative study, with a sample of 120 patients, for the early diagnosis of kidney disease in patients with type 2 diabetes mellitus, measuring and comparing serum levels of creatinine and cystatin C. The authors demonstrated that serum levels of creatinine and cystatin C were significantly increased in patients with type 2 diabetes mellitus compared to the control group (0.87 ± 0.44 mg / dl vs 0.63 ± 0.27 mg / dl, respectively). Similarly, the serum levels of cystatin C were also significantly higher (P = 0.0001) in the diabetic group (0.92 ± 0.38 mg / L) than in the control group (0.52 ± 0.20 mg / L). Furthermore, the means of eGFR computed by the CrCl, eGFRcys and eGFRcys-crea were 105.7 ± 27.5 mL/min /m^2, 90.4 ± 28.2 mL/min/m^2 and 100 ± 29.5 mL/min/m^2, respectively. The authors concluded that the GFR estimation equations based on cystatin C detected renal failure in patients with type 2 diabetes mellitus before the creatinine-based GFR estimation equations [3].

In our subsample of patients with severe CKD (Stage G4-5), the concordance correlation coefficient was 0.52 for CrCl, lower than that for eGFRcys-crea (0.82). As reported in a review by Redon J. et al., for GFR values less than 60 mL/min/m^2 creatinine clearance has a minor concordance with the "true glomerular filtration rate" [4].

Levely A.S. et al. highlighted as, if measured GFR is less than 20 mL/min/1.73m^2, the average CrCl overestimates the true GFR and they suggested implementing the CrCl with the urea clearance to estimate renal function [5].

Our results showed a highest concordance correlation coefficient between eGFRcrea and eGFRcys-crea (0.96 [95% CI, 0.93-0.98]) in patients with elevated C-reactive protein levels, while the concordance correlation coefficient between eGFRcrea and CrCl was 0.81 [95% CI, 0.65-0.86]. A large observational study including 8878 patients older than 45 years showed a highly significant increased mean of Cystatin C starting from 1st quartile to 4th quartile of C-reactive protein (0.95 ± 0.21, 1.00 ± 0.23, 1.02 ± 0.27, 1.10 ± 0.39; p=<0.0001 in 1st quartile, 2nd quartile, 3th quartile and 4th quartile respectively). This study also reported an increased mortality related with the association between cystatin C and C-reactive protein [6].

Another study on HIV patients was conducted by Deyà-Martínez À et al. on a pediatric sample. In this paper the authors showed a positive relationship between serum cystatin C and absence of highly active antiretroviral therapy, while it was inversely related with the years of highly active antiretroviral therapy [7].

The relationship between Cystatin C and inflammation was also evaluated in non-HIV patients. In this regard, a randomized study by Mocroft A. et al. highlighted as Cystain C was related to the serum amyloid A, RCP and IL6 at the Pearson's correlation test [8].

Analyzing other causes of high inflammatory state, in the small group of patients with positive procalcitonin we noticed a substantial difference between the concordance correlation coefficient of creatinine clearance and the CKD-EPI cyst-creaformula. According to our results, in an observational study published in 2019 cystatin C was positively and significantly related with AKI events in patients affected by bacterial infections with an OR of about 22, and the predictive value of cystatin C was higher than 90% (AUC= 0.91, 95% CI 0.74-0.99, p<0.01) [9]. The small sample size and the observational design were the limitations of this study.

Conclusions

The results of our study show the usefulness of the GFR assessment to identify impaired renal function in a simple and non-invasive way. The demonstration of a strong concordance, for some variables, between the eGFRcrea and the combined equation of cystatin C and creatinine, obtained with the statistical method of the concordance correlation coefficient, could allow us to diagnose and stage CKD better than creatinine clearance in earlier diabetic patients and in patients with high inflammatory status. Furthermore, this information opens new research scenarios from which important results can be expected in many areas, including other comorbidities often associated with CKD such as heart failure. Further studies on large populations will have to confirm these hypotheses.

BIBLIOGRAFIA

1. Shlipak MG, Mattes MD, Peralta CA, Update on cystatin C: incorporation into clinical practice, Am J Kidney Dis. 2013 Sep;62(3):595-603. https://doi.org/10.1053/j.ajkd.2013.03.027.
2. Dharnidharka VR, Kwon C, Stevens G. Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis. Am J Kidney Dis. 2002 Aug;40(2):221-6. https://doi.org/10.1053/ajkd.2002.34487.
3. Asmamaw T, Genet S, Menon M, Tarekegn G, Chekol E, Geto Z, Lejisa T, Habtu W, Getahun T, Tolcha Y. Early Detection of Renal Impairment Among Patients with Type 2 Diabetes Mellitus Through Evaluation of Serum Cystatin C in Comparison with Serum Creatinine Levels: A Cross-Sectional Study. Diabetes Metab Syndr Obes. 2020 Dec 3;13:4727-4735. https://doi.org/10.2147/DMSO.S279949.
4. Redon J., Pichler G., Martinez F. (2015) Glomerular Filtration Rate in Renal Damage. In: Agabiti Rosei E., Mancia G. (eds) Assessment of Preclinical Organ Damage in Hypertension. Springer, Cham. https://doi.org/10.1007/978-3-319-15603-3_15
5. Levey AS, Coresh J, Tighiouart H, Greene T, Inker LA. Measured and estimated glomerular filtration rate: current status and future directions. Nat Rev Nephrol. 2020 Jan;16(1):51-64. https://doi.org/10.1038/s41581-019-0191-y.
6. Shen Y, Zhang Y, Xiong S, Zhu X, Ke C. High-sensitivity C-reactive protein and cystatin C independently and jointly predict all-cause mortality among the middle-aged and elderly Chinese population. Clin Biochem. 2019 Mar;65:7-14. https://doi.org/10.1016/j.clinbiochem.2018.12.012.
7. Deyà-Martínez À, Fortuny C, Soler-Palacín P, Neth O, Sánchez E, Martín-Nalda A, Falcón-Neyra L, Vila A, Valls A, Noguera-Julian A. Cystatin C: A Marker for Inflammation and Renal Function Among HIV-infected Children and Adolescents. Pediatr Infect Dis J. 2016 Feb;35(2):196-200. https://doi.org/10.1097/INF.0000000000000960.
8. Mocroft A, Wyatt C, Szczech L, Neuhaus J, El-Sadr W, Tracy R, Kuller L, Shlipak M, Angus B, Klinker H, Ross M; INSIGHT SMART Study Group. Interruption of antiretroviral therapy is associated with increased plasma cystatin C. AIDS. 2009 Jan 2;23(1):71-82. https://doi.org/10.1097/QAD.0b013e32831cc129.
9. Zhi H, Zhang M, Cui X, Li Y. Renal echography and cystatin C for prediction of acute kidney injury: very different in patients with cardiac failure or sepsis. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. Chinise Crit Care Med 2019 Oct;31(10):1258-1263. https://doi.org/10.3760/cma.j.issn.2095-4352.2019.10.015.