Determination of a new constant to estimate glomerular filtration rate in pediatrics

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ABSTRACT

Introduction. In pediatrics, glomerular filtration rate (GFR) may be estimated by measured corrected creatinine clearance (mcCrCl) (mL/min/1.73 m^2) or the Schwartz formula (eGFR = height/plasma creatinine x *k*). The constant *k* depends on the plasma creatinine determination method: *k* = 0.55 for the Jaffe colorimetric method and *k* = 0.413 for the enzymatic method. Our laboratory uses the compensated kinetic colorimetric assay (CKC), and differences are observed between the estimated and measured GFR.

Hypothesis: The proposed values of *k* do not adjust to the CKC method for plasma creatinine.

Objective. To calculate a *k* value that allows to estimate GFR through creatinine measurement with CKC.

Methods. Correlational, descriptive design. Patients aged 3-18 years seen at the Division of Pediatric Nephrology between July 2017 and January 2018 with normal or altered GFR, bladder and bowel control, and signed consent were included. Malnourished and myelomeningocele patients were excluded. Studied variables were plasma and urine creatinine, height, and 24-hour urine output.

Results. A total of 184 patients were analyzed, their mean age was 10 years. Median mcCrCl was 123 mL/min/1.73 m^2. The linear correlation between height and plasma creatinine and mcCrCl resulted in a *k* value of 0.499 (r = 0.974 and r^2 = 0.949). The linear correlation between the estimated GFR (*k* = 0.499) and mcCrCl resulted in a 0.999 ß coefficient (r = 0.951 and r^2 = 0.903).

Conclusion. According to this study, the constant that allows to estimate GFR when measuring plasma creatinine with the CKC method is 0.499.

Key words: *glomerular filtration rate, colorimetric assay, creatinine.*

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Acronyms and abbreviations

CKC: Compensated kinetic colorimetric assay.
eGFR: Estimated glomerular filtration rate.
EM: Enzymatic method.
GFR: Glomerular filtration rate.
IDMS: Isotope dilution mass spectrometry method.
JCM: Jaffe colorimetric method.
mcCrCl: Measured corrected creatinine clearance.
PCr: Plasma creatinine.

INTRODUCTION

The measurement of kidney function, both in adults and children, underwent several changes since the development of the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines in 2002[1] and their subsequent update, Kidney Disease: Improving Global Outcomes (KDIGO), in 2012.[2]

These guidelines, in addition to reaching a consensus on the definition, evaluation, and classification of stages of chronic kidney disease (CKD), recommend assessing kidney function not only through plasma creatinine (PCr) determination but also through glomerular filtration rate (GFR). The latter may be performed by measuring the clearance (Cl) of endogenous substances (such as creatinine) or exogenous ones (such as inulin, iothalamate or iohexol) or may be estimated through predefined formulas.[3] Despite being specific, exogenous markers are not routinely used in clinical pediatrics given their complex measurement. For this reason, GFR in pediatrics may be estimated with the well-known formula of measured creatinine

clearance corrected (mcCrCl) for 1.73 m^2 of body surface area with a 24-hour urine sample[4] or with the formula developed by Schwartz in 1976,[5] known as estimated glomerular filtration rate (eGFR), which allows to calculate GFR using plasma creatinine and patient height:

eGFR = height (cm) x *k*/PCr (mg/dL)

By using a linear correlation between the height and creatinine values versus mcCrCl, Schwartz obtained an initial constant *k* of 0.55.

This constant allows to correct methodological errors and is intrinsically related to the measurement method used for creatinine. The formula was developed using the Jaffe colorimetric method (JCM).[6] In this formula, in order to measure plasma creatinine, an orange-colored reaction that occurs when creatinine combines with picrate is used. This reaction is non-specific because there are positive and negative interferences with other chromogens which result in an overestimation or underestimation of creatinine.

Later on, some laboratories started measuring plasma creatinine using an enzymatic method (EM), which is more specific and accurate, and is not subject to marked interferences with other substances.[7] A new correlation was performed with this method in 2009 (called bedside) through which the *k* value was determined at 0.413.[8]

Nowadays, in several health care facilities, including our hospital, creatinine levels are determined using a third method, known as compensated kinetic colorimetric assay (CKC), also called the Jaffe kinetic method, which minimizes the interferences of the JCM.[9]

Unfortunately, there are few studies in the bibliography regarding the value of *k* suggested to estimate GFR with the CKC.[10-13] In short, there are 3 methods to measure plasma creatinine, which should use different *k* values to estimate GFR based on the Schwartz formula. For the JCM, since 1976, a *k* value of 0.55 has been used;[5] for the EM, since 2009, a *k* value of 0.413 has been used;[8] however, for the CKC there is no strong suggestion regarding the adequate *k* value.[11]

Since 2010, our facility has been using the CKC. In routine practice, there is an overestimation of the eGFR when using a *k* value of 0.55 and an underestimation when using a value of 0.413 (mcCrCl is considered to be the gold standard).

OBJECTIVES

- To investigate which is the adequate *k* value for the measurement method used in our laboratory (CKC) in patients younger than 18 years, validating the pre-existing mathematical model proposed by Schwartz in 1976.
- To assess the correlation between eGFR and mcCrCl using the new *k* value obtained.

MATERIALS AND METHODS

This was a descriptive and correlational study conducted between July 1st, 2017 and January 30th, 2018. The initial hypothesis was that none of the *k* values proposed to date allows to estimate the GFR more accurately when plasma creatinine is measured through CKC.

Patients aged 3-18 years with normal GFR or any stage of chronic kidney disease (CKD), with bladder and bowel control, seen at the Division of Nephrology of the Department of Pediatrics of Hospital Nacional Profesor A. Posadas were included in the study.

Malnourished patients according to the guidelines of the Sociedad Argentina de Pediatría[14] and patients diagnosed with myelomeningocele were excluded.

Participants who did not undergo all requested lab tests or did not have an adequate 24-hour urine sample collection were left out. In order to determine if urine collection was adequate, the measurement of daily urinary creatinine excretion per kilogram of body weight (UCr/kg/day) was used taking as reference values those between the 5th and 95th percentiles according to age and sex.[15]

The following variables were analyzed: sex, weight, height, plasma creatinine, and mcCrCl (expressed as mL/min/1.73 m^2). Plasma creatinine was measured using the Jaffe modified method (CKC) and processed in a Cobas 6000 C501® autoanalyzer (Roche, Basel); this test has been standardized against the reference isotope dilution mass spectrometry method (IDMS). The other variables necessary to estimate mcCrCl based on the formula described above[4] were urinary creatinine, measured as per the Jaffe kinetic method, and total urinary output, corrected for 1.73 m^2 of body surface. Body surface area was determined using the DuBois formula.[16]

This study was approved by the Clinical Research Ethics Committee of our facility. All included patients signed the informed consent or assent, as applicable.

The SPSS® statistical package, version 22.0, and the XLSTAT 2018.2® complement were used for the statistical analysis.

Given the multivariate model with 9 regressor variables, a minimum of 90 patients were included in the protocol. Continuous variables were expressed as mean or median based on their distribution, with their corresponding standard deviation (SD) or interquartile range (IQR). Categorical variables were described as absolute or relative values (percentage).

Two linear regression models were developed:

- **First model**: height/PCr and mcCrCl for 1.73 m^2 of body surface area.[5]
- **Second model**: GFR estimated by formula (with the new *k* value obtained) and mcCrCl for 1.73 m^2. Once correlations were established, Pearson's correlation coefficient (r) and the coefficient of determination (r^2) were estimated.

RESULTS

In the study period, 242 patients were included; of these, 58 (31 %) were excluded: 38 for having pending lab results and 20 due to an inadequate 24-hour urine sample collection. Out of the 184 studied patients (*Table 1*), 92 (50 %) were males and 23 were older than 13 years.

The median age was 10.5 years (range: 3.2-18) with an abnormal distribution. The most common diagnoses among studied patients were uropathy and dysplasia (33.5 %) (*Table 2*).

Regarding studied variables related to kidney function, the median plasma creatinine value was 0.5 mg/dL, and the mcCrCl showed a normal distribution (*Figure 1*), with a mean value of 123 mL/min/1.73 m^2 (SD: 46.3 mL/min/1.73 m^2). In addition, it was observed that 57 % of patients (105/184) had a mcCrCl higher than 90 mL/min/1.73 m^2 (*Table 2*).

Table 1. *Characteristics of the studied population (n = 184)*

Variables	Data
Number of patients	184
Age (years): M (IQR)	10.5 (5.8)
Boys: n (%)	92 (50)
Weight (kg): M (IQR)	35.7 (24)
Height (cm): M (IQR)	139 (34)
BSA (m^2): M (IQR)	1.2 (0.6)
PCr (mg/dL): M (IQR)	0.5 (0.2)
mcCrCl (mL/min/1.73 m^2): X (SD)	123 (46.3)

M: median, IQR: interquartile range, n: number, X: mean, SD: standard deviation, BSA: body surface area, PCr: plasma creatinine, mcCrCl: measured corrected creatinine clearance (mL/min/1.73 m^2).

First model: Correlation between mcCrCl and the height/plasma creatinine ratio

In order to assess the correlation between mcCrCl and the height/plasma creatinine ratio, a univariate linear regression model (first model) through the origin (without an intercept term) was developed. mcCrCl was considered the dependent variable or response and the height/plasma creatinine ratio, the independent o regressor variable.

An unstandardized β coefficient (constant *k*) of 0.499 was obtained; with a 95 % confidence interval (CI) ranging from 0.482 to 0.515. This regression presents a Pearson's correlation coefficient (r) of 0.974 and a $r^2 = 0.949$, showing the direct relation between studied variables (*Figure 2*).

Second model: Correlation between mcCrCl and eGFR with the new *k* value

In order to assess the correlation between mcCrCl and eGFR using the new *k* value (0.499 x height/plasma creatinine) proposed, a

Table 2. *Classification of included patients*

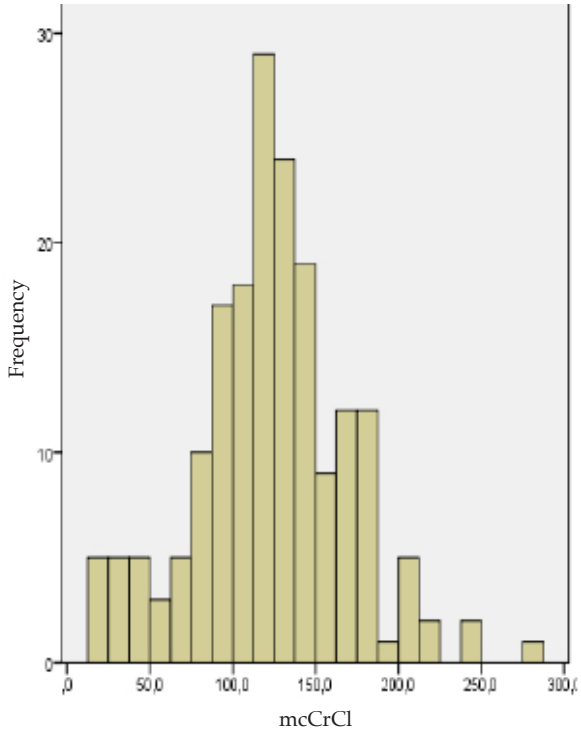
By diagnosis		By chronic kidney disease stage by mcCrCl (mL/min/1.73 m^2)	
Diagnoses	**N (%)**	**Stage***	**N (%)**
Uropathy and dysplasia	62 (33.5)	S1 (≥ 90)	149 (81)
Glomerulopathies	31 (17)	S2 (60-89)	17 (9.23)
Solitary kidney	23 (12.5)	S3 (30-59)	10 (5.43)
Hematuria	14 (7.5)	S4 (15-29)	8 (4.34)
Hemolytic uremic syndrome	12 (6.5)	S5 (< 15)	0 (0)
Arterial hypertension	7 (4)		
Lithiasis	6 (3)		
Urinary tract infection	4 (2)		
Other	25 (14)		

mcCrCl: measured corrected creatinine clearance.

univariate regression model through the origin was developed. mcCrCl was considered the dependent variable or response and eGFR, the independent o regressor variable (*Figure 3*).

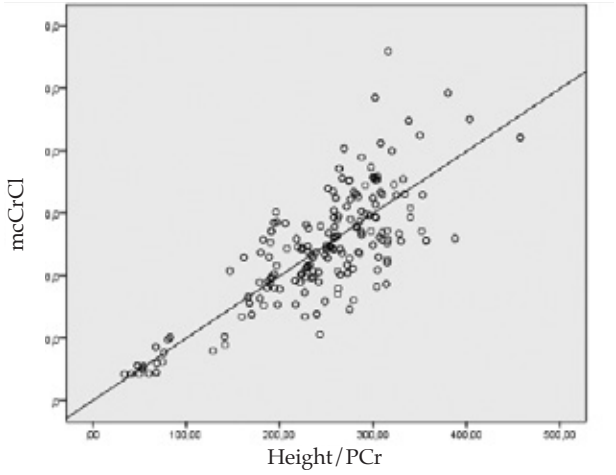
In this case, the β coefficient was 0.999 (95 % CI: 0.965-1.033). A direct relation was again demonstrated between the dependent variable and the independent variable (r = 0.974 and $r^2 = 0.949$).

FIGURE 1. *Histogram of distribution of measured corrected creatinine clearance (mL/min/1.73 m²)*



The mean mcCrCl is 123 mL/min/1.73 m² (n = 184).
Standard deviation: 46.3 mL/min/1.73 m². mcCrCl: measured corrected creatinine clearance (mL/min/1.73 m²).

FIGURE 2. *Linear correlation between height (cm)/plasma creatinine (mg/dL) and measured corrected creatinine clearance (mL/min/1.73 m²)*



β coefficient of 0.499 with r = 0.974 and r2 = 0.949 (n = 184).
PCr: plasma creatinine, mcCrCl: measured corrected creatinine clearance (mL/min/1.73 m²).

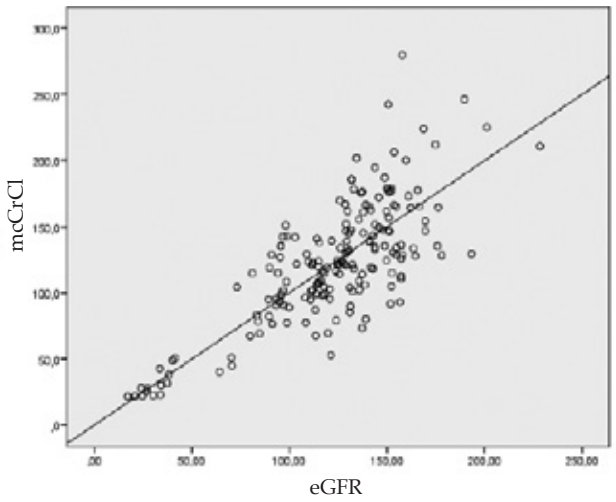
Comparison between the median values of mcCrCl and eGFR using the new *k* value

If the median eGFR (129 mL/min/1.73 m²) using the constant found for the CKC is compared to the median mcCrCl (123 mL/min/1.73 m²) (*Figure 4*), an eGFR overestimation of 5.8 mL/min/1.73 m² is observed.

Comparison between median eGFR estimates using the different *k* values

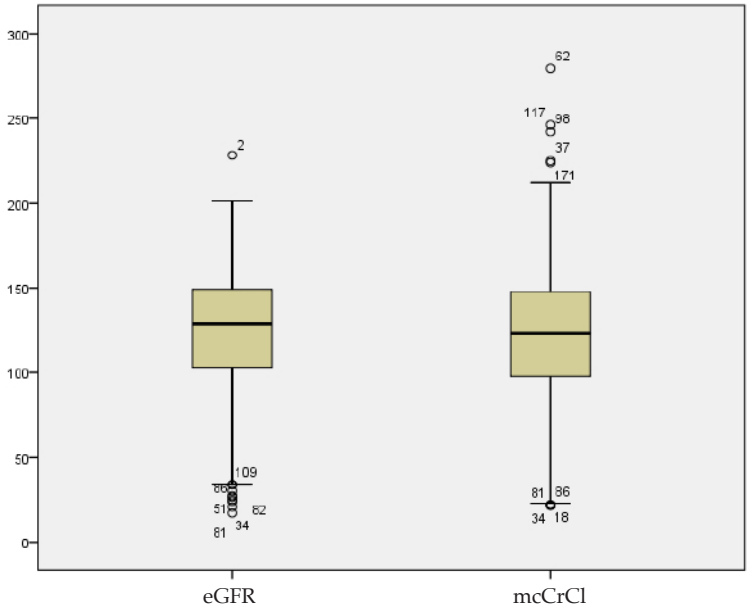
If the two values of the constant *k* previously suggested by Schwartz[5,8] were used in the formulas to estimate GFR in our group of patients, the following would be observed: an overestimation of 13.2 mL/min/1.73 m² with the

FIGURE 3. *Linear correlation between the estimated glomerular filtration rate (with a k value of 0.499) and the measured corrected creatinine clearance*



β coefficient of 0.999 with r = 0.974 and r2 = 0.949 (n = 184).
eGFR: estimated glomerular filtration rate, mcCrCl: measured corrected creatinine clearance (mL/min/1.73 m²).

FIGURE 4. *Box plot: Comparison between the median values of the estimated glomerular filtration rate (with a k value of 0.499) and the measured corrected creatinine clearance*



Median values of eGFR and mcCrCl of 128.9 and 123 mL/min/1.73 m², respectively.
eGFR: estimated glomerular filtration rate, mcCrCl: measured corrected creatinine clearance (mL/min/1.73 m²).

k value of 0.55 (JCM) and an underestimation of 22.22 mL/min/1.73 m^2 with the *k* value of 0.413.

DISCUSSION

Pediatricians and pediatric nephrologists have always calculated eGFR based on height. However, after modifying the measurement method for plasma creatinine, we observed a wide variability of eGFR levels depending on whether the *k* value adjusted to the JCM or the EM is used. These differences could affect the correct and rapid decision-making on treatment based on the eGFR level, for instance, to adjust the dose of medication in a patient with acute kidney injury.

The determination of serum creatinine is based on the Jaffe reaction, whose advantages include its simple analysis and low cost, but its main problem is the lack of specificity with interferences, both positive and negative. In order to minimize interferences, the CKC has 3 modifications: a) it performs a kinetic-colorimetric reading, b) it performs a sample blank (to reduce the negative interference of bilirubin), and c) it introduces a negative correction factor of -0.3 mg/dL (to minimize the positive interference of pseudochromogens, such as proteins, glucose, ascorbic acid, ketoacids, uric acid, among others). This compensation assumes that the interference is constant in all samples and that it may be excessive in patients with a low creatinine production rate and the variable presence of pseudochromogens, as is the case in the pediatric population.[17]

The CKC method used has been standardized against the IDMS method. Standardization is a method that allows to reduce differences between creatinine values obtained through different methods and their impact on the GFR results obtained through an equation.

In pediatrics, the most commonly used equation since 1976 has been that proposed by Schwartz, which uses plasma creatinine, patient height, and a constant (*k*); the selection of the latter depends on the method used to measure creatinine and the study population.

For non-IDMS-traceable Jaffe methods, a *k* value of 0.55 is used, and for IDMS-traceable EM, a *k* value of 0.413.[17]

Schwartz conducted several studies; in 1976 he assessed 186 patients with plasma creatinine measurement through JCM and GFR ranging between 10 and 140 mL/min/1.73 m^2, and found no differences between sexes nor between prepubertal and postpubertal patients using the same *k* value.[5] In a subsequent study, the same author determined different constants according to age and sex; he defined a *k* value of 0.7 and 0.55 for adolescent boys and girls, respectively.[18] In 2009,[8] Schwartz modified the constant ($k = 0.413$) due to the change in the method used to measure creatinine (EM) and included patients with mcCrCl ranging from 15 to 75 mL/min/1.73 m^2. In 2016, there was a proposal to modify that formula based on normalized serum creatinine using a coefficient (*Q*) obtained from the median plasma creatinine from a healthy population for age and sex using the enzymatic method, which is why it does not apply to our population nor to our measurement method for plasma creatinine.[19] In 2019, the adequate formula to calculate eGFR in adolescent and young adults[8] proposed by the KDIGO guidelines was questioned.[20,21]

Our study was conducted in a population with a wider range of kidney function than that of patients initially studied by Schwartz;[5] in addition, more than half of our patients (57 %) had a mcCrCl within reference values, with a small proportion of children (18 %) with advanced CKD (< 60 mL/min/1.73 m^2).

Afterwards, few studies have analyzed the correlation between eGFR and mcCrCl with CKC.[10-13]

In 2012, Hari also used CKC to measure plasma creatinine. The patients included in that study had a lower median mcCrCl than that of our participants (85.5 versus 123 mL/min/1.73 m^2); in addition, those authors found a different *k* value (0.42 versus 0.499) and a lower r^2 (0.61 versus 0.949) compared to our findings.[11]

A 2014 consensus proposes that the *k* value should be adapted locally due to the great variation among laboratories in relation to the method used for creatinine determination.[3] In agreement with this, we suggest using a *k* value of 0.499 when plasma creatinine is measured with CKC.

When estimating the GFR using this new *k* value, we tried to assess it in different study subgroups, and we noticed an underestimation in boys older than 13 years and an overestimation in patients with advanced CKD in relation to mcCrCl. Therefore, we believe that, given the characteristics of the studied population, in the future we should plan a new study including a higher number of adolescent patients with mcCrCl < 60 mL/min/1.73 m^2, so as to draw more appropriate conclusions regarding these subgroups.

When comparing eGFR with mcCrCl with a *k* value of 0.499, we observed a slight eGFR overestimation of 5.8 mL/min/1.73 m^2.

One of the limitations of this study is that we used mcCrCl as the gold standard of GFR, knowing that it overestimates the real value of kidney function by 10-20 % as a consequence of tubular creatinine secretion, which is even higher in pediatric patients with a drop in GFR.[1]

In relation to the statistical method used, despite the excellent correlation observed between the related and studied variables, we face the same difficulties as the original studies by Schwartz and his group: the analyzed variables do not show normality or homoscedasticity in their distribution. For this reason, conclusions drawn from this correlation should be assessed in the clinical setting, given that they lack the specificity typical of a pure linear correlation.

CONCLUSION

According to this study, the constant that allows to estimate GFR when measuring plasma creatinine with the CKC method is 0.499. ■

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