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# Comparing the accuracy of creatinine – and cystatin C based equations in diagnosing and staging pediatric chronic kidney disease in clinical practice

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Estimated glomerular filtration rate (eGFR) plays a crucial role in management of pediatric patients; however, there is still a paucity of data regarding benefits of tailored use of eGFR equations in different subgroups of pediatric patients.

**Aim** – to compare the eGFR of children using creatinine and cystatin C based equations, to evaluate clinical accuracy in diagnosing and staging pediatric chronic kidney disease (CKD).

**Materials and methods.** The retrospective controlled study of 33 pediatric patients aged from 2 to 18 years was carried out over the period from 2023 to 2025. All patients underwent comprehensive clinical examination and work up to evaluate eGFR.

**Results.** CKD in children under 25 equation (CKiD U25) creatinine or cystatin has shown moderate-to-strong positive correlation with CKiD U25 cystatin C-creatinine ( $r_s=0.6791$ ;  $r_s=0.9334$ ). Patients whose eGFR was estimated using CKiD U25 creatinine have 3,6 times the odds of being misdiagnosed than those estimated with CKiD U25 cystatin C. The proportion of females misdiagnosed with CKiD creatinine was significantly higher in comparison to CKiD cystatin C (37.5% (6/16); 6.2% (1/16), respectively,  $p=0.0322$ ).

**Conclusions.** The tailored approach of eGFR measurement should be utilized in pediatric practice using available validated eGFR equations. Female pediatric patients may significantly benefit from evaluating eGFR based on cystatin C or creatinine/cystatin C (Cre/Cys) combined equations. Utilizing the same CKiD U25 equation during the follow-up of pediatric patients in low-resource settings may prevent bias in CKD staging in the long-term management of pediatric patients with CKD.

The research was carried out in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Local Ethics Committee of participating institution. The informed consent of the patient was obtained for conducting the studies.

No conflict of interest was declared by the authors.

**Keywords:** chronic kidney disease in children under 25 equation, creatinine, cystatin C, estimated glomerular filtration rate, chronic kidney disease, children.

## Порівняння точності використання рівнянь на основі цистатину С / креатиніну при діагностиці та стадіюванні хронічної хвороби нирок у дітей у клінічній практиці

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Розрахована швидкість клубочкової фільтрації (рШКФ) відіграє вирішальну роль у діагностично-лікувальному процесі в пацієнтів дитячого віку; однак, досі бракує даних щодо переваг індивідуалізованого використання рівнянь для розрахунку рШКФ у різних підгрупах дітей.

**Мета** – порівняти рШКФ у дітей за допомогою рівнянь на основі креатиніну та цистатину С, щоб оцінити клінічну точність діагностики та стадіювання хронічної хвороби нирок (ХХН) у дітей.

**Матеріали та методи.** Протягом 2023–2025 рр. було проведено ретроспективне контрольоване дослідження 33 пацієнтів дитячого віку від 2 до 18 років. Усім пацієнтам здійснено комплексне клінічне та лабораторне обстеження для оцінки рШКФ.

**Результати.** Рівень креатиніну або цистатину за формулою CKiD U25 (chronic kidney disease in children under 25) показав помірну або сильну позитивну кореляцію з рівнем цистатину С-креатиніну CKiD U25 ( $rs=0,6791$ ;  $rs=0,9334$ ). Пацієнти, в яких ШКФ оцінювали за допомогою креатиніну CKiD U25, мають у 3,6 раза вищу ймовірність неправильного діагнозу, ніж ті, в кого оцінювали за допомогою цистатину С CKiD U25. Частка дівчат, в яких неправильно діагностували креатинін CKiD, була значно вищою порівняно з цистатином С CKiD (37,5% (6/16); 6,2% (1/16) відповідно,  $p = 0,0322$ ).

**Висновки.** У педіатричній практиці слід використовувати індивідуальний підхід до вимірювання ШКФ із використанням доступних валідованих рівнянь. Пацієнти дитячого віку можуть отримати значну користь від оцінки ШКФ на основі цистатину С або комбінованих рівнянь creatinine/cystatin C (Cre/Cys). Використання того самого рівняння CKiD U25 під час спостереження за пацієнтами дитячого віку в умовах обмежених ресурсів може запобігти систематичній помилці у стадіюванні ХХН при довгостроковому лікуванні пацієнтів із ХХН.

Дослідження проведено відповідно до принципів Гельсінської декларації. Протокол дослідження схвалено місцевим етичним комітетом установи-учасника. Інформовану згоду пацієнта отримано для проведення досліджень.

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**Ключові слова:** хронічна хвороба нирок у дітей віком до 25 років, креатинін, цистатин С, розрахункова швидкість клубочкової фільтрації, хронічна хвороба нирок, діти.

Estimated glomerular filtration rate (eGFR) in children plays a crucial role in the management of these patients and their transition to the adult specialist when switching from the height-dependent chronic kidney disease (CKD) in children under 25 (CKiD U25) in pediatric care to the age-dependent Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation in adult settings [1]. Furthermore, utilizing different equations may potentially mislead the physician managing the disease over a period of time. Recent studies have shown the significance of a tailored approach to genetics and comorbidities in children with CKD as an ultimate goal of precision nephrology [5]. However, there is still a paucity of data regarding the benefits of tailored use of eGFR equations in different subgroups of pediatric patients.

Validated and age-appropriate equations have been updated and introduced recently, replacing the methods used before. A set of calculators by C.B. Pierce (2021) is now suggested to be used in the pediatric population (Kidney Disease: Improving Global Outcomes (KDIGO), 2024). CKiD U25 was found to better detect initial eGFR decline in healthy adolescents. Thus, it may be considered a promising tool for CKD screening in this population [3]. The U25 equations can monitor kidney function and disease progression longitudinally, without the «jumps» in eGFR that may occur when transitioning from pediatric-specific equations to adult equations at age 18 [11,12].

Routine panel of renal function tests includes measurement of creatinine; however, cystatin C has recently been assumed to be more accurate for children with mild-to-moderate CKD with some limitations in end-stage kidney disease (ESKD) and healthy cohort. Serum cystatin C is a sensitive biomarker for detecting changes

in eGFR and identifying preclinical renal disease, particularly in diabetic patients with a normal serum creatinine concentration [15]. Compared with creatinine, it is less affected by non-renal factor influences such as gender, age, muscle mass, and analytical interfering substances during its measurement [13,15]. Thus, the CKiD U25 creatinine-cystatin C (Cre/Cys) equation provides a more accurate estimate than using either serum creatinine or cystatin C alone in CKD [11,12].

Due to the lack of availability of cystatin C in low-resource health care facilities [13], there is a necessity to develop an efficient approach to estimate eGFR of a pediatric patient with CKD, and define subgroups benefiting from particular equations in clinical practice.

**Aim** – to compare the eGFR of children using creatinine and cystatin C-based equations, to evaluate clinical accuracy in diagnosing and staging pediatric CKD.

## Materials and methods of the study

We retrieved retrospective data of 33 pediatric patients with CKD treated in CNE «Vinnytsia Regional Children's Clinical Hospital of Vinnytsia Regional Council» from 2023 to 2025, as shown in Table 1.

Inclusion criteria were as follows: age from 2 to 18 years, previous admission and diagnosis of CKD; availability of laboratory values of cystatin C and serum creatinine.

eGFR was estimated using online calculators of the validated equations (CKiD U25) [10,12], which assessed the sex, age, height, laboratory values of serum creatinine and cystatin C, namely CKiD U25 creatinine, CKiD U25 cystatin C, CKiD U25 creatinine-cystatin C. We compared creatinine and cystatin-only equations with CKiD U25 Cre/Cys (as a relative clinical standard) based on the following criteria: sex, prior surgical/endoscopic

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**Table 1**

Baseline characteristics of the cohort

Characteristics		Absolute values (n=33)	%
Sex	male	17	51.5
	female	16	48.5
Age (yo)		14.1±3.39	n/a
Height (cm)		159.42±19.42	n/a
Cause of CKD	CAKUT*	26	78.8
	Miscellaneous	7	
Surgery and/or endoscopic correction		18	54,5
Pharmacological renoprotection		12	36.4

Note: CAKUT – Congenital Anomalies of the Kidney and Urinary Tract.

**Table 2**

Estimation of eGFR and CKD staging

Renal function tests/GFR equations	Absolute values	P-value	CKD stage*		
			G1	G2	G3a
Creatinine (ummol/l)	75.15±19.26	<0.0001	-	-	-
Cystatin C (mg/l)	1.03±0.41	<0.0001	-	-	-
CKiD U25 creatinine	81.02±17.67	>0.05	9	21	3
CKiD U25 Cystatin C	88.79±36.82		12	16	5
CKiD U25 Cre/Cys	84.90±22.87		11	17	4

Note: \* – CKD stages in the table refer to: G1 – ≥90 ml/min/1.73 m<sup>2</sup>; G2 – 60-89 ml/min/1.73 m<sup>2</sup>; G3a – 45-59 ml/min/1.73 m<sup>2</sup>.

correction, presence of CAKUT syndrome, use of reno-protective therapy angiotensin-converting enzyme (ACE) inhibitors – Enalapril.

Conventional CKD staging system according to eGFR was used: G1 – ≥90 ml/min/1.73 m<sup>2</sup>; G2 – 60–89 ml/min/1.73 m<sup>2</sup>; G3a – 45–59 ml/min/1.73 m<sup>2</sup>; G3b – 30–44 ml/min/1.73 m<sup>2</sup>; G4 – 15–29 ml/min/1.73 m<sup>2</sup>; G5 – <15 ml/min/1.73 m<sup>2</sup> [4].

Statistical analysis was performed using the software package Statistica v.10.0 (StatSoft, USA). Data has been displayed as the mean and standard deviation (m±SD) and/or proportion (%). Normality of the data was assessed using the Kolmogorov–Smirnov test. A two-tailed t-test for dependent variables was used to evaluate intergroup differences for continuous variables with normal distribution; Fisher’s exact test was used for the evaluation of non-parametric data. Correlations of eGFR measured with different equations were evaluated using Spearman’s rank correlation. P-value <0.05 was considered statistically significant. Odd ratios (OR) with 95% confidence intervals (CI) were calculated using the online calculator MdCalc (<https://www.medcalc.org>).

The research was carried out in accordance with the principles of the Declaration of Helsinki (1964) and its later amendments. The study protocol was approved by the Local Bioethics Committee of Vinnytsia National Pirogov Memorial Medical University (protocol No. 1, 09.01.25).

## Results of the study and discussion

The vast majority of patients enrolled in the study had CAKUT syndrome as the main cause of CKD (78.0%; 26/33). The spectrum of congenital anomalies included: uni- and bilateral vesicoureteral reflux (VUR) – 65.3% (17/26), unilateral renal agenesis – 15.3% (4/26), obstructive uropathy – 7.6% (2/26), congenital simple cysts – 7.6% (2/26), multicystic dysplastic kidney – 3.8% (1/26). Eighteen (54.5%) out of thirty-three patients gave a history of either surgical or endoscopic correction of CAKUT. Upon enrollment in the study, 12 (36.4%) patients were receiving renoprotective therapy – Enalapril. All of the patients received vitamin D supplements and/or were on continuous antibiotic prophylaxis (CAP).

Mean GFR estimated by different equations and corresponding CKD stages are shown in Table 2.

CKiD U25 creatinine or cystatin has shown moderate-to-strong positive correlation with CKiD U25 Cre/Cys ( $r_s=0.6791$ ;  $r_s=0.9334$ ). However, eGFR calculated with different formulas has shown discrepancies in CKD staging (Fig.).

Based on CKiD U25 creatinine, 11 (33.3%) patients had a different stage of CKD compared with CKiD U25 Cre/Cys, while only 4 (12.1%) patients were misdiagnosed based on the CKiD U25 cystatin C equation (OR=3.6; 95% CI: 1.0165–12.9275; P=0.0471). Thus, patients whose eGFR was estimated using CKiD U25 creatinine have 3.6 times the odds of being misdi-

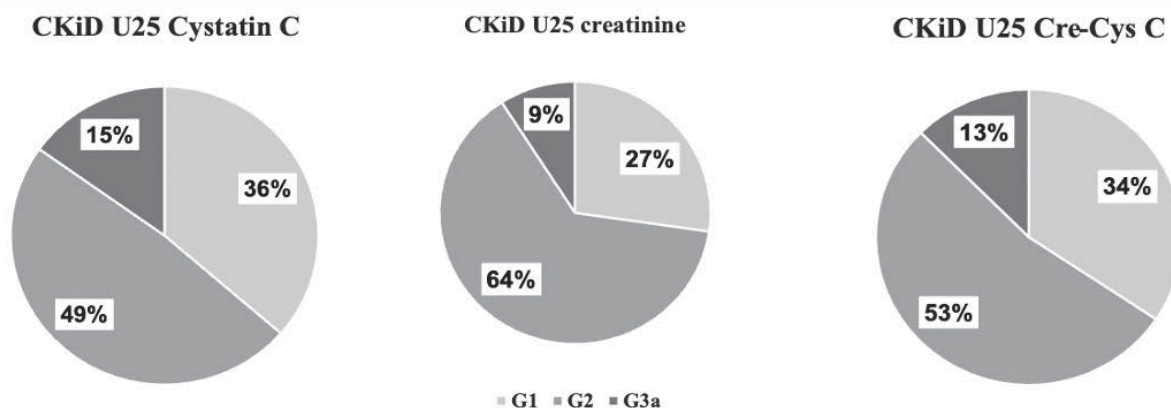


Fig. Distribution of CKD stages measured with different equations

agnosed than those estimated with CKiD U25 cystatin C (Table 3).

We obtained results from five subgroups created based on the presence of CAKUT, history of surgery, renoprotective therapy, and sex (Table 4).

There were 34.6% (9/26) patients with CAKUT misdiagnosed using CKiD U25 creatinine and 15.3% (4/26) using CKiD U25 cystatin C, respectively ( $p=0.1078$ ).

No significant difference was found based on receiving surgical treatment ( $p=0.7458$ ) or renoprotective therapy ( $p=0.3445$ ). The proportion of females misdiagnosed with CKiD creatinine was significantly higher in comparison to CKiD cystatin C (37.5% (6/16); 6.2% (1/16), respectively,  $p=0.0322$ ). It may reflect the variety of non-renal factors, including thyroid dysfunction, low body mass index (BMI), C-reactive protein, etc. [8].

According to KDIGO (2024) guidelines, CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health [9]. eGFR remains one of the crucial parameters to evaluate, along with albumin-to-creatinine ratio (ACR) and protein-to-creatinine ratio (PCR), so as to stage CKD and provide effective management of the patients. Recent studies confirm that CAKUT, steroid-resistant nephrotic syndrome, chronic glomerulonephritis, and ciliopathies account for > 70% of cases of CKD [2,3]. CAKUT itself affects approximately 30% of children with CKD [9].

Based on CKD etiology, we grouped our patients into two main groups: CAKUT and miscellaneous, reflecting a similar approach of D.K. Ng et al. (2021), who created three groups: non-glomerular disease, hemolytic uremic syndrome (HUS), and other glomerular, non-HUS dis-

Table 3

Discrepancy in CKD staging based on different eGFR equations (n=33)

Stage of CKD	eGFR equation			
	CKiD U25 creatinine		CKiD U25 cystatin C	
	cases	%	cases	%
Overestimated*	8	24	3	9
Underestimated*	3	9	1	3
Total number of misdiagnosed cases*	11	33	4	12

Note: \* - in comparison to the result measured with CKiD U 25 Cre/Cys.

Table 4

Relative estimation of CKD staging discrepancy measured with CKiD U25 creatinine or cystatin C

Parameter	Patients misdiagnosed using CKiD U 25 creatinine*	Patients misdiagnosed using CKiD U 25 cystatin C*	p value
Total patients with CAKUT (n=26)	9 (34.6%)	4 (15.3%)	0.1078
Total patients with surgery (n=8)	5 (27.7%)	3 (23%)	0.7458
Total patients taking renoprotective therapy (n=12)	4 (33.3%)	2 (16.6%)	0.3445
Total males (n=17)	5 (29.4%)	3 (17.6%)	0.4171
Total females (n=16)	6 (37.5%)	1 (6.2%)	0.0322**

Notes: \* – in comparison to the result measured with CKiD U 25 Cre/Cys; \*\* – statistically significant intergroup difference ( $p<0.05$ ).

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ease [11]. Incidence of CAKUT-originated CKD was similar in both studies (78% and 71%, respectively). It complies with the current etiological structure of CKD in children and young adults (i.e., younger than 25 years old).

As eGFR is a crucial tool to assess renal function in patients with CKD, the customized approach to measure it in clinical and experimental settings may be beneficial for particular groups of pediatric patients. Use of exogenous tracers (inulin) is considered the gold standard to measure eGFR (mGFR); however, it is not widely available, costly, and time-intensive. Therefore, renally excreted endogenous analytes are preferred in clinical settings (eGFR) [17]. Recent studies on eGFR equations have shown that CKiD U25 equations are internally validated and the most up-to-date tools for clinical use [7,9].

In our study, we estimated GFR using three equations: CKiD U25 creatinine-based, CKiD U25 Cystatin C-based, and CKiD U25 Cre-Cys C – combined equation. The absolute values obtained did not depend on the equation used, and no significant difference was found ( $p>0.05$ ).

However, according to Ng et al. (2021), the combined equation (CKiD U25 Cre/Cys) to estimate GFR has been more accurate and precise than CKiD U25 creatinine or cystatin C alone [11]. Thus, we further evaluated and compared the incidence of CKD stages estimated using these three formulas separately. Interestingly, despite moderate-to-strong positive correlation between creatinine-based equation, cystatin C-based equation, and the combined equation, respectively, stages of CKD estimated with CKiD U25 creatinine had 3,6 times the odds of misdiagnosing stage of CKD than GFR estimated with CKiD U25 cystatin C compared to the combined equation ( $p=0.0471$ ).

In our study, several factors were considered to affect eGFR estimated by CKiD U25 creatinine, cystatin C, or their combination, namely etiology of CKD, surgical and/or endoscopic treatment, sex, and use of renoprotection strategy. Current renoprotective strategy relies on ACE inhibitors and angiotensin blockers (ARBs), which are used to reduce albuminuria and improve blood pressure control [15,16]. L.I. Vakulenko (2021) suggests this choice of ACE inhibitor improves dynamics in 75.2% of pediatric patients [16].

In our study, the criteria to begin the renoprotective therapy (Enalapril) depended on the stage of CKD ( $\geq 2$ ), presence of hypertension, and impaired ACR values. Despite differences in the severity of CKD between ACE inhibitor-takers and those who did not receive renoprotective therapy, eGFR measured with different equations was not statistically significant. Therefore, the equation

to estimate eGFR should not be chosen based on a renoprotective strategy as a factor of possible bias.

We evaluated risks of misstaging bias using two single-marker estimates alone compared to a combination of the two markers in each group. However, the analysis showed no significant difference in misstaging CKD between these groups based on creatinine or cystatin equations alone. We found that regardless of the cause of CKD in children, all three CKiD U25 equations will show insignificant discrepancies. Furthermore, the equation to estimate eGFR should not be chosen based on a renoprotective strategy as a factor of possible bias.

A single-center study, published by H. Pizzo et al. (2024), has shown that the cys C-based equation alone or the combined formula may have better bias, precision, and accuracy in predicting eGFR in a cohort of pediatric kidney transplant recipients [13]. However, the degree of difference may not be clinically significant and does not demonstratively show superiority of one biomarker over the other in this particular population. Hence, the utilization of cys C-based equations could be tailored to the individual pediatric patient [13]. While comparing differences in eGFR based on sex, we found that 37.5 % of females had either over- or underestimated eGFR compared with the combined equation ( $p=0.0322$ ). It may reflect the variety of non-renal factors, including thyroid dysfunction, low BMI, C-reactive protein, etc. [8] Thus, this cohort of patients may benefit from using a cystatin C-based equation.

This study has several limitations. Firstly, we did not measure eGFR using inulin or other agents; instead, we used a validated eGFR formula, which is available in clinical settings. Thus, participants may benefit from this approach. However, we are going to address this limitation in our further studies as well as increase the sample size in the cohort based on receiving surgical, endoscopic, and conservative treatment (renoprotection) to identify the cohort that will ultimately benefit from using the creatinine or cystatin C approach.

## Conclusions

A quarter of pediatric patients with CAKUT who underwent surgical/endoscopic correction may be misstaged using creatinine-based equations only. Thus, the tailored approach of eGFR measurement should be used in pediatric practice. While the presence of CAKUT, history of surgery, and intake of renoprotective therapy are not significantly affected by the CKiD equation that we routinely use to estimate eGFR, female pediatric patients may significantly benefit from evaluating eGFR based on cystatin C or Cre/Cys combined equations. As CKiD U25 creatinine levels are

three times more likely to affect the staging of CKD in pediatric patients, which can impact the management of these patients, we consider utilizing the same CKiD equation during the follow-up of pediatric patients in low-resource settings to prevent bias, which may affect the staging of CKD.

**Perspectives of further research.** We are going to further conduct this study in a longitudinal fashion to evaluate the significance of continuous use of different equations and possible bias.

*The authors declare no conflict of interests.*

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