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Patient Characteristic for Using Personalized Estimated Glomerular Filtration Rate in Kidney Function Assessment

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In many medical institutions, standardized eGFR, which is based on generalized body surface area, is used for drug dosing evaluations. This can lead to overdosing. This study aimed to investigate the discrepancy between personalized eGFR and standardized eGFR and to identify indicators necessary for pharmacists to perform appropriate pharmacotherapy. From October 2022 to February 2023, the study targeted patients aged 18 years and older who continuously visited the Saera Pharmacy Kurashiki. Among the 347 participants, a significant discrepancy of 6.3 mL/min was observed between personalized eGFR and standardized eGFR ($p < 0.001$). Factors predicting an eGFR discrepancy of 10 mL/min or more were identified as follows: for males, a serum Na level below 140 mEq/L (area under the ROC curve: AUC = 0.656), and for females, a BUN level below 13 mg/dL (AUC = 0.647). Recognizing that patients with these factors are at risk of inaccurate renal function assessment, it is considered beneficial for pharmacists to prioritize obtaining height and weight measurements to ensure appropriate dosing of renally excreted drugs.

Key words pharmacists, renal function assessment, body surface area, receiver operating characteristic curve, chronic kidney disease, renally excreted drugs

INTRODUCTION

As we enter an ultra-aging society, the number of dialysis patients continues to increase.[1)] To prevent the initiation of dialysis, early detection and therapeutic intervention for patients with chronic kidney disease (CKD) are crucial. However, it is challenging for specialized nephrology institutions alone to manage all these patients. There have been instances of overdosage of renally excreted drugs outside of CKD clinical pathways in the past.[2,3)] Therefore, appropriate pharmacotherapy mediated by pharmacists in community pharmacies nationwide is desirable.

To achieve appropriate pharmacotherapy, it is necessary to design dosing regimens based on personal residual renal function. However, in clinical practice, directly measuring renal function is not practical, and most assessments are done using estimation formulas. Recently, the evaluation using the "Japanese GFR formula" created by the Japanese Society of Nephrology Project is recommended. There are two types of estimated glomerular filtration rate (eGFR) used as indicators of renal function: standardized eGFR (mL/min/1.73 m^2), which is based on a standard body size, and personalized eGFR (mL/min), which considers the patient's body size. For elderly patients with low muscle mass, the standardized eGFR corrected for a body surface area of 1.73 m^2 can lead to an overdose of renal function, and therefore it is recommended to use personalized eGFR to evaluate renal function, taking the patient's body size into account.[4)] However, many medical institutions and clinics adopt standardized eGFR, and it is unclear whether appropriate reassessment is conducted in pharmacies.[5)] There have been reports of avoided overdosage of renally excreted drugs and nephrotoxic drugs due to the intervention of pharmacists, however it is unclear whether these assessments were based on standardized or personalized eGFR. Previous reports have evaluated the prescribing practices of renally excreted drugs using personalized eGFR but were limited to patients prescribed six specific drugs or late elderly patients with standardized eGFR above 40,[2,6)] leading to a bias in the study population. To promote the appropriate use of renally excreted drugs, it is necessary to clarify the actual situation of personalized eGFR across a broad range of ages without limiting the drugs being administered. Based on this background, we aimed to investigate the actual discrepancy between personalized eGFR and standardized eGFR and to explore indicators necessary for pharmacists in community pharmacies to perform appropriate pharmacotherapy.

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MATERIALS AND METHODS

Eligible Patients The survey period was set from October 1, 2022, to February 28, 2023, spanning four months. The subjects of this study were patients aged 18 and above who had visited the pharmacy continuously and had their standardized eGFR measured at least once. Patients undergoing peritoneal dialysis or hemodialysis were excluded from the study. Data were obtained from blood test results provided by the patients to the pharmacists, and informed consent was obtained from all patients. Patients who presented a withdrawal of consent during the study were excluded from the research.

Required Sample Size The required sample size, set at 370 patients, was determined using the standard deviation referenced from a study involving measured glomerular filtration rates in humans,[7] with a power of 80% and a significance level of 5%.

Survey Method and Items The collected data included age, sex, height, weight, and clinical laboratory items (hemoglobin A1c [HbA1c], aspartate aminotransferase [AST], alanine aminotransferase [ALT], blood urea nitrogen [BUN], serum creatinine [Scr], standardized eGFR, hemoglobin [Hb], Na, K, and red blood cell count [RBC]). Height and weight were recorded from patient interviews. The personalized eGFR was calculated using the body surface area obtained from the DuBois formula,[8] comparing it to the body surface area of 1.73 m^2 used for standardized eGFR. If the Scr was less than 0.6, the personalized eGFR was calculated using the rounding-up method.[9]

Evaluation Items and Statistical Analysis The primary evaluation item was the difference between personalized eGFR and standardized eGFR. Secondary evaluation items included exploring indicators such as age, sex, and clinical laboratory values that might influence the discrepancy between personalized and standardized eGFR, as well as changes in drug dosages, including discontinuations. Statistical analysis was performed using JMP® Pro 17.0 (SAS Institute Inc.). T-tests was conducted to compare standardized and personalized eGFR, while multiple regression and logistic regression analyses were used for stratified analyses based on patient characteristics and clinical laboratory items. Age, BMI, and Scr values were excluded from explanatory variables in the multiple regression analysis to avoid confounding with eGFR, as they are included in "the Japanese GFR estimation formula"[8]. The relationship of influencing factors for patients with large discrepancies (e.g., ≥10 mL/min/1.73 m^2) in eGFR was represented by Receiver Operating Characteristic (ROC) curves, and cutoff values and area under the ROC curve (AUC) were calculated using the Youden Index method. A significance level of 5% was set, with *p*-values below 0.05 considered statistically significant.

Ethical Considerations The data used in this study included patient age and clinical laboratory items, which were anonymized by numbering to ensure individuals could not be easily identified. Consent was obtained using forms that explained the study's purpose, and only patients who understood and agreed participated. It was also explained that non-participation would not result in any disadvantages. Patients were informed that they could withdraw their consent at any time during the study, and their data would be excluded from the research. The study complied with the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects and was conducted after obtaining approval from the Shujitsu University Education and Research Ethics Committee (Approval No. 259).

RESULTS

Background of the Study Participants A total of 350 individuals consented to participate in this study. Of these, 347 participants were included in the study after excluding three who withdrew their consent. Among the respondents, 49% (170 participants) were male, with a median age of 75 years, and the median standardized eGFR was 59.5 mL/min/1.73 m^2 (Table 1).

Discrepancy Between Standardized and Personalized eGFR The median personalized eGFR was 53.2 mL/min, which was 6.3 mL/min lower than the standardized eGFR ($p < 0.001$, Fig. 1)

Factors Influencing the Discrepancy Between Standardized and Personalized eGFR The factors influencing the difference between standardized and personalized eGFR (Table 2). The influencing factors identified were female ($p < 0.0001$), BUN ($p = 0.003$), and Na ($p = 0.009$). There was no significant influence from RBC ($p = 0.182$) and Hb ($p = 0.536$), which are associated with renal anemia that progresses with CKD.

Further stratified analysis by sex revealed that Na ($p = 0.002$) was a significant factor in male, and BUN ($p = 0.002$) was significant in female (Table 3).

This study revealed that the difference between standardized eGFR and personalized eGFR is 6.3 mL/min. Given that a difference of 15 mL/min/1.73 m^2 can change CKD stage classification, a discrepancy of 10 mL/min or more in eGFR is likely to alter CKD stages and the dosage of renally excreted drugs. Therefore, we focused on these patients and performed further analyses. As a result, 21% (73 / 347) of the patients exhibited an eGFR discrepancy of 10 mL/min or more (data not shown). For these patients, we analyzed the cutoff values

Table 1. Patient Characteristics (units)

Total	n = 347	
Sex		
Male	170 (49%)	
Female	177 (51%)	
Age (years)	75	(24 - 98)
Height (cm)	158	(132 - 182)
Body weight (kg)	58.1	(28 - 127)
BSA (m^2)	1.58	(1.09 - 2.28)
Clinical examination		
HbA1c (%)	6.7	(4.7 - 11.9)
BUN (mg/dL)	16	(7 - 83)
Scr (mg/dL)	0.85	(0.39 - 3.14)
Standardlized eGFR (mL/min/1.73 m^2)	59.5	(12 - 116.8)
Na (mEq/L)	140	(130 - 149)
K (mEq/L)	4.3	(3.1 - 6.2)
AST (IU/L)	23	(8 - 113)
ALT (IU/L)	19	(3 - 110)
RBC (*1,000/μL)	454	(253 - 687)
Hb (g/dL)	13.7	(5 - 20.5)

Expressed as median (min - max)
aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), body surface area (BSA), standardized estimated glomerular filtration rate (eGFR), hemoglobin A1c (HbA1c), hemoglobin (Hb), red blood cell count (RBC), serum creatinine (Scr)

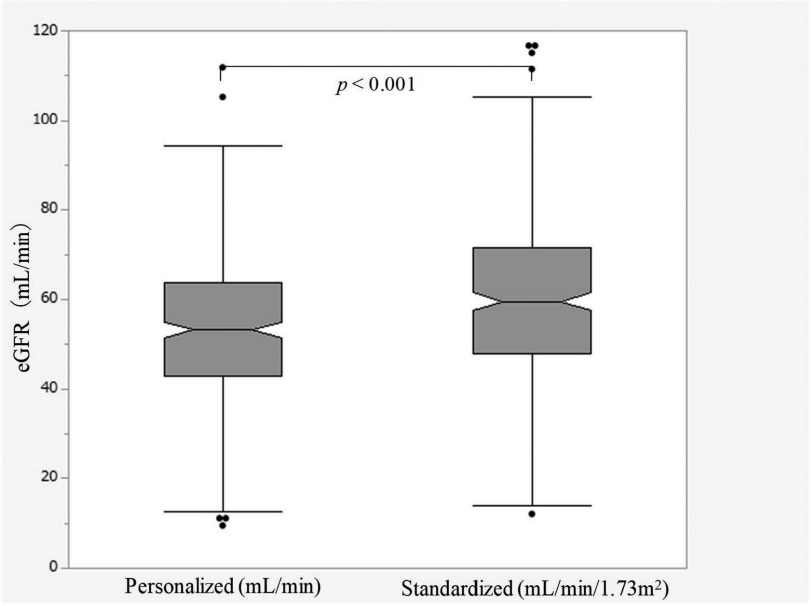

Fig. 1. Comparison of Standardized eGFR and Personalized eGFR (n = 347)

Standardized eGFR was calculated using the "Japanese eGFR formula," while personalized eGFR was calculated based on the ratio of personal body surface area (calculated using the DuBois formula) to the standard body surface area of 1.73 m^2 (n = 347, student's t-test). Japanese eGFR formula: eGFR (mL/min/1.73 m^2) = 194 x Serum creatinine^-1.094 x Age^-0.287 x 0.739 (if female). DuBois formula: BSA = Weight^0.425 x Height^0.725 x 0.007184

Table 2. Factors Influencing eGFR Discrepancy

Clinical examination	Standardization Partial Regression Section	SE	95%CI	*p*-value	
Female	0.51	0.479	2.712 - 4.603	**<.0001**	*
HbA1c (%)	0.104	0.39	-0.172 - 1.368	0.127	
BUN (mg/dL)	-0.195	0.076	-0.385 - -0.083	**0.003**	*
Na (mEq/L)	-0.178	0.187	-0.863 - -0.124	**0.009**	*
K (mEq/L)	0.016	0.955	-1.645 - 2.123	0.803	
AST (IU/L)	0.12	0.05	-0.041 - 0.158	0.247	
ALT (IU/L)	-0.092	0.047	-0.133 - 0.052	0.391	
RBC (*1,000/μL)	-0.146	0.012	-0.04 - 0.008	0.182	
Hb (g/dL)	0.068	0.387	-0.523 - 1.004	0.536	

The difference between standardized and personalized eGFR was used as the dependent variable, and a multiple regression analysis was conducted with patient characteristics and clinical laboratory parameters as independent variables.
aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), hemoglobin A1c (HbA1c), hemoglobin (Hb), red blood cell count (RBC)

of factors influencing the discrepancy (Na for male and BUN for female). The cutoff value was 140 mEq/L for Na in male (AUC = 0.656) and 13 mg/dL for BUN in female (AUC = 0.647) (Fig. 2).

Discontinued and Reduced Dosages of Medications In this study, 36% (126 / 347) had different CKD stages based on personalized eGFR compared to standardized eGFR (data not shown). Incidentally, a total of 30 instances of overdosing medications were identified (Table 4), involving 24 patients (data not shown).

DISCUSSION

In this study, we examined the discrepancy between standardized eGFR and personalized eGFR, the clinical evaluation of medications, and the clinical laboratory items that predict these discrepancies. Although previous studies have reported the clinical evaluation of medications using personalized eGFR, they were limited to specific age groups and medications. Our study is the first to investigate a wide range of ages without restricting the medications being administered. Additionally, in community pharmacies, it can be challenging to obtain patient information such as height and weight when patients do not visit in person. Therefore, identifying factors that may lead to an overdose of kidney function and incorporating them into accurate kidney function assessments is crucial for proper pharmaceutical management in community pharmacies.

It has been reported that eGFRcys, an estimate of glomerular filtration rate using cystatin C (Cys-C), which is neither secreted nor reabsorbed, is a reliable predictive marker for patients with mild to moderate renal impairment.[4] However, insurance coverage is limited to once every three months, and only a limited number of medical institutions can perform the measurement. Thus, using eGFRcys routinely as a kidney function indicator is impractical. Consequently, it is more ver-

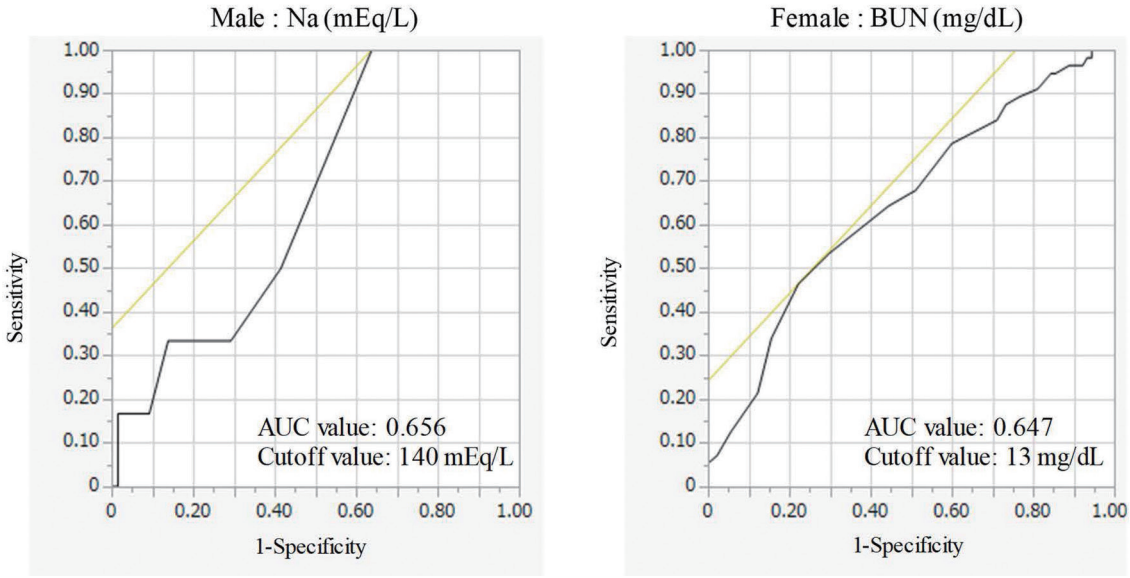

Fig. 2. ROC Curves for Factors That Predict Deviations of eGFR 10 (mL/min) More

Receiver operating curves (ROC), blood urea nitrogen, (BUN), estimated glomerular filtration rate (eGFR)

Table 3. Factors Influencing eGFR Discrepancy: Stratification by Sex

Male (n = 170)

Clinical examination	Standardization Partial Regression Section	SE	95%CI	*p*-value	
HbA1c (%)	-0.08	0.278	-0.777 - 0.328	0.422	
BUN (mg/dL)	-0.027	0.051	-0.116 - 0.087	0.779	
Na (mEq/L)	-0.318	0.125	-0.651 - -0.153	**0.002**	*
K (mEq/L)	-0.057	0.581	-1.521 - 0.787	0.53	
AST (IU/L)	0.104	0.027	-0.034 - 0.073	0.473	
ALT (IU/L)	-0.098	0.024	-0.065 - 0.031	0.492	
RBC (*1,000/μL)	0.001	0.009	-0.018 - 0.019	0.996	
Hb (g/dL)	-0.383	0.318	-1.25 - 0.013	0.055	

Female (n = 177)

Clinical examination	Standardization Partial Regression Section	SE	95%CI	*p*-value	
HbA1c (%)	0.133	0.755	-0.669 - 2.337	0.273	
BUN (mg/dL)	-0.34	0.154	-0.796 - -0.181	**0.002**	*
Na (mEq/L)	-0.167	0.374	-1.291 - 0.197	0.147	
K (mEq/L)	0.089	2.155	-2.541 - 6.04	0.419	
AST (IU/L)	0.033	0.176	-0.326 - 0.376	0.887	
ALT (IU/L)	-0.069	0.173	-0.395 - 0.295	0.774	
RBC (*1,000/μL)	-0.107	0.023	-0.061 - 0.03	0.504	
Hb (g/dL)	0.202	0.683	-0.433 - 2.288	0.179	

Multiple regression analyses were performed for each sex, using the differences between standardized and personalized eGFRs as the objective variables, and the patient's characteristics and clinical laboratory items as explanatory variables.
laboratory parameters as independent variables.
aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), hemoglobin A1c (HbA1c), hemoglobin (Hb), red blood cell count (RBC)

satile in the context of pharmaceutical management to use general blood test items that are commonly measured in clinical practice to assess patients' kidney function. However, it has been reported that in cases with extremely low muscle mass, the assessment of renal function using eGFR based on serum creatinine may lead to overestimation. According to a study by Furukawa *et al*. (2018) involving 226 patients, the correlation coefficient between eGFR and eGFRcys was r = 0.868, indicating a strong correlation.[10] In contrast, 3.5% (8/226) of the cases showed a discrepancy of two or more stages in the GFR classification of CKD severity, and in five cases, the GFR classification based on eGFRcys was lower than that based on eGFR. All these cases involved patients with significant muscle weakness who required assistance with daily activities.

In the current study, all patients were able to walk independently to the pharmacy, and it is unlikely that they had severe muscle weakness or that eGFR based on Scr was overestimated. Nonetheless, in patients with muscle-wasting diseas-

Table 4. Drugs with Observed Overdose

Drug name / Generic name	Number	
Antiarrhythmic	2	
Disopyramide		1
Pilsicainide Hydrochloride Hydrate		1
Antithrombotic	4	
Apixaban		2
Edoxaban		2
Dipeptidyl peptidase 4 inhibitor	10	
Alogliptin Benzoate		4
Vildagliptin		1
Sitagliptin Phosphate Hydrate		3
Saxagliptin Hydrate		2
Biguanide	6	
Metformin Hydrochloride		6
Sodium-glucose transportprotein 2 inhibitor	1	
Empagliflozin		1
Fibrates	3	
Fenofibrate		2
Pemafibrate		1
Nonsteroidal anti-inflammatory drugs (systemic activity)	1	
Esflurbiprofen		1
Mineralocorticoid receptor antagonist	1	
Eplerenone		1
Antihistamine	1	
Cetirizine Hydrochloride		1
Histamine H2-receptor antagonist	1	
Famotidine		1

es, limb amputations, or prolonged bed rest, the use of eGFR based on Scr may lead to overestimation, and an integrated evaluation using eGFRcys should be considered.

In this study, we found that the median personalized eGFR was 53.2 mL/min, significantly lower than the median standardized eGFR of 59.5 mL/min/1.73 m^2 by 6.3 mL/min ($p < 0.001$). Recently, seasonal variations in the eGFR have been reported. According to a study by Masugata *et al*. (2011), regardless of the presence of CKD, eGFR tended to decrease significantly in summer (June 2010 to August 2010) compared to that in spring (March 2010 to May 2010) ($p < 0.05$). In contrast, no significant differences were observed in the other seasons.[11] In our study, the investigation period was from October to February, covering the fall and winter seasons, and we believe that the impact of seasonal variation on the results of this study is minimal.

Using multiple regression analysis, we identified "female," "BUN," and "Na" as predictors of the discrepancy between standardized eGFR and personalized eGFR. Hence, a stratified analysis by sex was performed, revealing that Na ($p = 0.002$) in male and BUN ($p = 0.002$) in female were identified as influencing factors. The standardized partial regression coefficients for these variables were negative. This indicates that in male, for every 0.318 mEq/L decrease in Na levels, the difference between standardized eGFR and personalized eGFR increases by 1 mL/min. In other words, a 1 mEq/L decrease in Na results in a 3 mL/min decrease in personalized eGFR compared to standardized eGFR. Similarly, in female, a 1 mg/dL decrease in BUN results in a 3 mL/min decrease in personalized eGFR compared to standardized eGFR.

For patients with a discrepancy of 10 mL/min or more, cutoff values were 140 mEq/L for Na in male and 13 mg/dL for BUN in female. This suggests that a Na level below 140 mEq/L in male and a BUN level below 13 mg/dL in female are indicators of significant eGFR discrepancies. An additional analysis stratified by age group was performed using the discrepancy in eGFR as the dependent variable. In the 70s age group, an increase in the BUN/Scr ratio, an indicator of dehydration, was identified as a significant factor (standardized partial regression: 0.265, $p = 0.0202$) (data not shown). These results indicate that dehydration accompanied by sodium loss leads to weight loss and a reduction in body surface area, contributing to the discrepancy in eGFR. BUN levels can vary with protein intake and muscle mass, indicating that low BUN levels may reflect low muscle mass and body surface area, which is particularly relevant for female with delicate body structures. Generally, as renal function declines, BUN levels tend to increase, and low BUN levels are often not considered problematic. However, a BUN level below 13 mg/dL suggests that evaluating renal function solely based on standardized eGFR may lead to overdose, and re-evaluation using personalized eGFR is recommended. In this study, we have elucidated for the first time that even in patients who appear to have normal residual kidney function with seemingly low BUN levels, the dosage of renally excreted drugs should be reconsidered using personalized eGFR. We also considered the potential impact of renal anemia on eGFR discrepancies, but RBC and Hb were not significant predictors. Thus, the presence of renal anemia does not seem to significantly affect eGFR discrepancies.

A total of 24 patients were identified with overdosing medications, amounting to 30 medications in total (Table 4). Notably, the majority of these were hypoglycemic agents, followed by antithrombotic agents, and fibrate agents. In recent years, the use of combination drugs that incorporate two or more active ingredients into a single medication has increased to reduce the burden on patients. However, caution is required as there is a concern that overdosing may be overlooked in cases of renal impairment. Additionally, there was one case where a patient with severe renal impairment was administered a transdermal NSAIDs intended for systemic effects. Given that some transdermal formulations are not intended solely for local effects, it is crucial to ensure that such administrations do not result in overdosing.

This study was subject to several limitations. In this study, it was also predicted that in males with Na levels below 140 mEq/L and in female with BUN levels below 13 mg/dL, there would be significant discrepancies in eGFR. However, we were unable to address the clinical implications of these findings. The AUC values were 0.656 (Na) and 0.647 (BUN), indicating that the predictive accuracy was not high. One possible reason for this finding is the insufficient sample size. Although 370 participants were required for the current validation, only 347 were included in this study. This number, 347, represents the limit of the number of cases that can be collected from a single pharmacy over a year. Therefore, increasing the sample size for further re-evaluation is challenging, which represents the limit of validation. We analyzed routine blood test items commonly used by pharmacists in community pharmacies to identify factors predicting eGFR discrepancies, but the impact of other test items such as Cys-C and Cl could not be examined. Additionally, the median age of the patients in this study was 75 years (9.8% were under the age of 60), indi-

cating a predominantly elderly population. As a result, there were instances where the prescribed doses were lower than the standard dosages. The number of potentially overdosed medications listed in Table 4 may vary depending on the prescribing practices of different healthcare institutions. Moreover, patients with severe malnutrition affecting Scr values or muscle mass, as well as those with lower limb amputations, were not included in this investigation, indicating the need for further research.

In conclusion, our study suggests that using standardized eGFR for kidney function assessment may lead to an overdose of renal function. Particularly, in female with low muscle mass, there is a higher likelihood of discrepancies between personalized eGFR and standardized eGFR. Even in female with BUN levels below 13 mg/dL, where there is less concern about decreased renal function, relying solely on standardized eGFR as the evaluation metric may suggest a risk of potential medication overdosage. Factors identified as prone to eGFR discrepancies include female, BUN, and Na. Recognizing the potential for erroneous kidney function assessments in patients with these factors, emphasizing the collection of height and weight information could serve as a critical indicator for community pharmacists in ensuring appropriate dosing of renally excreted medications.

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Conflict of interest The authors declare no conflict of interest.

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