

Prediction of renal function improvement in azotemic patients using glomerular filtration rate from ^{99m}Tc -DTPA renal scan

An observational study

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Abstract

This study aimed to evaluate the ratio of glomerular filtration rate (GFR) from ^{99m}Tc -diethylenetriamine-pentaacetic acid dynamic renal scan (GFR_{SCAN}) to estimated GFR (eGFR) as a predictor of renal function improvement in patients with azotemia.

A retrospective review of medical records was conducted to identify consecutive patients with newly discovered or aggravated azotemia who underwent ^{99m}Tc -diethylenetriamine-pentaacetic acid renal scan. Significant renal function improvement was defined as $\geq 100\%$ and $\geq 10\text{ mL/min}$ improvement of eGFR at 12 weeks compared to eGFR on the day of renal scan (eGFR_0). The $\text{GFR}_{\text{SCAN}}/\text{eGFR}_0$ ratio was evaluated as a predictor of significant renal function improvement using logistic regression and receiver operating characteristic (ROC) curve analyses. Added value of the $\text{GFR}_{\text{SCAN}}/\text{eGFR}_0$ ratio in the prediction of significant renal function improvement were demonstrated by adjusting for best clinical predictor variables.

The eligibility criteria were met by 224 patients, among whom 22 patients (9.8%) showed significant renal function improvement. The odds ratios of the $\text{GFR}_{\text{SCAN}}/\text{eGFR}_0$ ratio for predicting significant renal function improvement were 1.76 (95% confidence interval [CI]: 1.26–2.45, $P < .001$) in the univariable analysis and 1.70 (95% CI: 1.19–2.42, $P = .003$) after adjusting for clinical variables. The area under the ROC curve of the $\text{GFR}_{\text{SCAN}}/\text{eGFR}_0$ ratio for predicting significant renal function improvement was 0.762 (95% CI: 0.648–0.871). The addition of the $\text{GFR}_{\text{SCAN}}/\text{eGFR}_0$ ratio to the best clinical prediction model raised the area under the ROC curve from 0.726 to 0.794, and this increment was statistically significant ($P = .02$).

The $\text{GFR}_{\text{SCAN}}/\text{eGFR}$ ratio can predict renal function improvement in patients with azotemia. Future prospective studies are necessary to validate its potential clinical utilities.

Abbreviations: AKI = acute kidney injury, AUC = area under the receiver-operating characteristic curve, CI = confidence interval, CKD = chronic kidney disease, DM = diabetes mellitus, DTPA = diethylenetriamine-pentaacetic acid, eGFR = estimated glomerular filtration rate, eGFR_0 = estimated glomerular filtration rate on the day of ^{99m}Tc -DTPA renal scan, $\text{eGFR}_{12\text{wk}}$ = estimated glomerular filtration rate at 12 weeks after ^{99m}Tc -DTPA renal scan, GFR = glomerular filtration rate, GFR_{SCAN} = glomerular filtration rate calculated on ^{99m}Tc -DTPA renal scan, ROC = receiver-operating characteristic.

Keywords: azotemia, diethylenetriamine-pentaacetic acid, glomerular filtration rate, renal function improvement

Editor: Ismaheel Lawal.

This research was supported by Medical Research Promotion Program through the GangNeung Asan Hospital funded by the Asan Foundation (2018S002, 2021I001).

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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How to cite this article: Yu H, Kim H, Shin HS, Lee HS. Prediction of renal function improvement in azotemic patients using glomerular filtration rate from ^{99m}Tc -DTPA renal scan: an observational study. *Medicine* 2021;100:51(e28332).

Received: 29 June 2021 / Received in final form: 2 November 2021 / Accepted: 30 November 2021

<http://dx.doi.org/10.1097/MD.00000000000028332>

1. Introduction

In the clinical setting, glomerular filtration rate (GFR), the single most important measure of global renal function, is usually assessed using estimated GFR (eGFR) calculated from serum creatinine and other relevant clinical variables. Despite its convenience and extensive validation, eGFR has some limitations. The serum level of endogenous filtration agents such as creatinine is a cumulative result of the balance between its production and glomerular filtration; thus, an acute change in the GFR is reflected, with a time delay, in the serum creatinine level and thereby in the eGFR.^[1] Consequently, eGFR overestimates underlying true GFR while it is decreasing, and underestimates the true GFR while it is increasing. This tendency can be problematic for the management of acutely changing renal function because the creatinine can continue to increase even after the onset of renal function recovery.^[2] Even experienced physicians may find it difficult to interpret this continued rise correctly.^[3]

^{99m}Tc-diethylenetriamine-pentaacetic acid (DTPA) renal scintigraphy is a safe and widely available nuclear medicine imaging test. It provides information on the kidney morphology and function under various conditions including renal failure.^[4] It also permits image-based quantification of GFR.^[5] However, GFR calculated on ^{99m}Tc-DTPA renal scans (GFR_{SCAN}) was reported to be less accurate than eGFR in patients with chronic kidney disease (CKD).^[6] Nevertheless, GFR_{SCAN} does not suffer from the over- or underestimation caused by acute changes in renal function because it uses an exogenous filtration agent. This suggests that GFR_{SCAN} might be less biased than eGFR while renal function is acutely changing. However, few studies have been conducted regarding this potential advantage of GFR_{SCAN}.

Correct prediction of renal function improvement in patients with azotemia is important because it impacts on subsequent management and prognostication of the patients. In routine clinical practice, we observed that azotemic patients whose eGFR was lower than their GFR_{SCAN} tended to show renal function improvement during follow-up. We hypothesized that a high ratio of the GFR_{SCAN} to eGFR might indicate ongoing renal function improvement because, in patients who have already begun to recover, eGFR underestimates true GFR and therefore would be lower than GFR_{SCAN}. This study aimed to evaluate the performance of the GFR_{SCAN}/eGFR ratio in predicting renal function improvement in patients with azotemia.

2. Materials and methods

2.1. Study design and participants

A single-center, retrospective cohort study was conducted to evaluate the performance of the GFR_{SCAN}/eGFR ratio in predicting renal function improvement. The institutional review board approved the study, and the requirement to obtain informed consent was waived due to the retrospective nature of the study. Medical records from November 2013 to December 2018 were reviewed to identify consecutive patients with newly discovered or aggravated azotemia who underwent ^{99m}Tc-DTPA renal scan. The eligibility criteria for inclusion were azotemic patients with an eGFR of <60 mL/(min 1.73 m²) who underwent ^{99m}Tc-DTPA renal scan within 1 day from the creatinine measurement. We aimed to select patients whose renal dysfunction had potential to recover. Patients with stable CKD, confirmed by creatinine measurements within the previous

3 months, were excluded because their renal function was unlikely to improve. In addition, we excluded patients with postrenal azotemia, genitourinary cancers and/or single kidney, renal replacement therapy on the day of renal scan (day 0), and end-stage renal disease with or without kidney transplantation evaluation. Patients for whom 12-week eGFR was unavailable were excluded. The initial eGFR (eGFR₀) was calculated from a creatinine value measured on day 0. If the eGFR was measured 1 day before or after day 0, eGFR₀ was calculated by interpolating 2 eGFR values measured within 2 days from day 0. If there was only 1 eGFR measurement within the ±2-day time window, the case was excluded.

2.2. GFR_{SCAN}/eGFR₀ ratio

The predictor variable was the ratio of GFR_{SCAN} to eGFR (GFR_{SCAN}/eGFR₀ ratio), in which the eGFR was obtained on day 0 (eGFR₀). The eGFR values were calculated according to the chronic kidney disease epidemiology collaboration formula.^[7]

^{99m}Tc-DTPA renal scan was performed in patients with new or aggravated azotemia to evaluate kidney function and morphology, and to rule out the possibility of obstructive nephropathy. Patients underwent intravenous bolus injection of ^{99m}Tc-DTPA at 300 MBq/70 kg body weight after sufficient hydration. Dynamic renal images (3 s/frame for 1 minute followed by 1 min/frame for 20 minutes) were obtained in the supine position by using an E. CAM gamma camera (Siemens, Erlangen, Germany) equipped with a low-energy high-resolution collimator (matrix size, 128 × 128 pixels). The image-derived GFR was calculated using Gates method^[5] and normalized to a body surface area of 1.73 m² to obtain the GFR_{SCAN}. Kidney sizes were also measured from the scans.

2.3. Renal function improvement

A binary outcome variable to be predicted was significant renal function improvement. Because many patients did not have appropriate baseline creatinine measurement, we could not define significant renal function improvement in terms of recovery to baseline. Instead, we defined significant renal function improvement as an increase of the patient's eGFR at 12 weeks (eGFR_{12wk}) by ≥100% and ≥10 mL/(min 1.73 m²) from the eGFR₀ (ie, eGFR_{12wk} ≥ 2 × eGFR₀ and eGFR_{12wk} ≥ eGFR₀ + 10 mL/[min 1.73 m²]) or up to normal range (eGFR_{12wk} ≥ 90 mL/[min 1.73 m²]). The first eGFR measurement after the 12-week time point was defined as eGFR_{12wk}. If no creatinine measurement was performed after 12 weeks, a 10- to 12-week interval was alternatively searched. Failure to wean from renal replacement therapy at the time of eGFR_{12wk} measurement was regarded as no significant improvement. A period of 12 weeks was selected as the time for assessing renal function improvement because non-recovery until 3 months is regarded as CKD.^[8] Additionally, eGFR data were collected approximately at 1 week (4 days–2 weeks).

The analyzed clinical predictor variables were the patients' age and sex, whether they had comorbid diabetes mellitus (DM), hypertension or CKD, suspected cause of azotemia, average kidney size, and hemoglobin level measured within 3 days from day 0.

2.4. Statistical analysis

The co-primary measures of predictive performance were the area under the receiver operating characteristic curve (AUC) and

the odds ratio for significant renal function improvement. The secondary measures were the sensitivity and specificity of the $GFR_{SCAN}/eGFR_0$ ratio dichotomized at the optimal cutoff value for the prediction of significant renal function improvement. To determine the optimal cutoff value, the patients were divided in a 1:1 ratio into the derivation set (earlier half) and validation set (later half). A cutoff value that maximized the Youden index in the derivation set was determined as the optimal cutoff value, which was subsequently applied to the validation set to calculate the secondary performance measures.

Univariable and multivariable logistic regression were performed to calculate odds ratios of the $GFR_{SCAN}/eGFR_0$ ratio and clinical variables for predicting significant renal function improvement. In the multivariable analysis, clinical variables with $P < .3$ in the univariable analysis were included in the initial model and the variables underwent stepwise variable selection to obtain a set of best clinical variables that minimized the Akaike information criterion. Subsequently, the $GFR_{SCAN}/eGFR_0$ ratio was added in this clinical prediction model to evaluate whether the GFR had predictive ability independent of the best clinical variables.

To demonstrate the incremental predictive value of the $GFR_{SCAN}/eGFR_0$ ratio over the clinical predictors, the following steps were performed. First, the AUC of the best clinical predictor was calculated using the linear predictor from the multivariable logistic regression model of the best clinical variables. Next, the AUC of the combined predictor of the clinical variables and the $GFR_{SCAN}/eGFR_0$ ratio was calculated using the linear predictor from the multivariable logistic regression model of the best clinical variables and the $GFR_{SCAN}/eGFR_0$ ratio. The AUC of the best clinical variables was compared with that of the best clinical variables plus the $GFR_{SCAN}/eGFR_0$ ratio to test whether there was a significant increase in AUC by adding the $GFR_{SCAN}/eGFR_0$ ratio to the clinical variables. Comparison between the AUCs was performed using the bootstrap method ($B=2000$).

We performed sensitivity analyses to test the robustness of our results against variation of some definitions and assumptions made in this study. First, since the 100% threshold for defining significant renal functional improvement was arbitrary, we tested the performance under a different threshold, that is, 50%. Next, we assessed the renal functional improvement at a different time point (1 week) and again tested the predictive performance.

Independent-samples *t* test or paired-samples *t* test were used to compare the means of 2 continuous variables. Two-tailed $P < .05$ was regarded as an indicator of statistical significance. The R statistical software (version 4.0.2; <https://www.r-project.org>) was used for all the statistical analyses. The reporting was performed following the STROBE statement.^[9]

3. Results

3.1. Patient characteristics

Two hundred twenty-four patients who met the eligibility criteria were analyzed in the study (Fig. 1, Table 1). Among the 224 patients, 181 (80.8%) were admitted to the hospital and 43 (19.2%) were treated in the outpatient clinic. Causes of hospital admission were renal failure in 34 (18.8%), infection or inflammation in 32 (14.3%), cardiopulmonary disorders in 45 (20.1%), gastrointestinal disorders in 13 (7.2%), trauma or other musculoskeletal disorders in 8 (4.4%), malignancy in 6 (3.3%), poor general condition in 10 (5.5%), and others in 33 (18.2%)

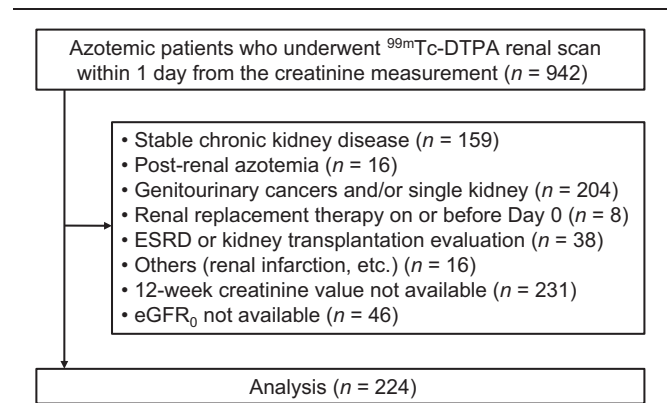


Figure 1. Flow diagram. DTPA = diethylenetriamine-pentaacetic acid, eGFR₀ = estimated glomerular filtration rate on the day of 99mTc-DTPA renal scan.

Table 1

Patient characteristics.

Characteristic	Patient number (%) or mean ± standard deviation
Age (yr)	67.2 ± 13.8 (range: 23–96)
Sex	
Female	76 (33.9)
Male	148 (66.1)
Diabetes mellitus	
No	93 (41.5)
Yes	131 (58.5)
Hypertension	
No	46 (20.5)
Yes	178 (79.5)
Underlying chronic kidney disease	
No	9 (4.0)
Yes	153 (68.3)
Uncertain	62 (27.7)
Cause of azotemia	
Unknown	160 (71.5)
Known	64 (28.6)
Renal replacement therapy ^a	
Not performed	212 (94.6)
Transient	8 (3.6)
Permanent	4 (1.8)
Hospital admission	
No admission (outpatient care)	43 (21.5)
Hospital stay ≤ 7 d	126 (63.0)
Hospital stay > 7 d	55 (27.5)
Average kidney size (cm)	9.6 ± 1.2 (range: 6.1–14.8)
Creatinine on day 0 (mg/dL)	3.6 ± 2.3 (range: 1.0–15.0)
BUN on day 0 (mg/dL)	47.9 ± 28.6 (range: 6.3–174.4)
Hemoglobin (mg/dL) ^c	10.2 ± 1.8 (range: 6.0–17.2)
eGFR ₀ (mL/min/m ²)	23.3 ± 13.7 (range: 3.1–58.5)
GFR _{SCAN} (mL/min/m ²)	28.6 ± 14.8 (range: 1.0–70.2)
GFR _{SCAN} /eGFR ₀ ratio	1.58 ± 1.72 (range: 0.18–18.6)
Total	224 (100)

patients. Suspected causes of the development or exacerbation of azotemia were infection in 26 (11.6%), iodinated contrast agent in 7 (3.1%), medication in 10 (4.5%), prerenal condition in 12 (5.4%), and others in 9 (4.0%) patients. The cause was uncertain for the other 160 patients (71.4%). Twelve patients (5.4%) received renal replacement therapy during the treatment course. There were no mortality cases.

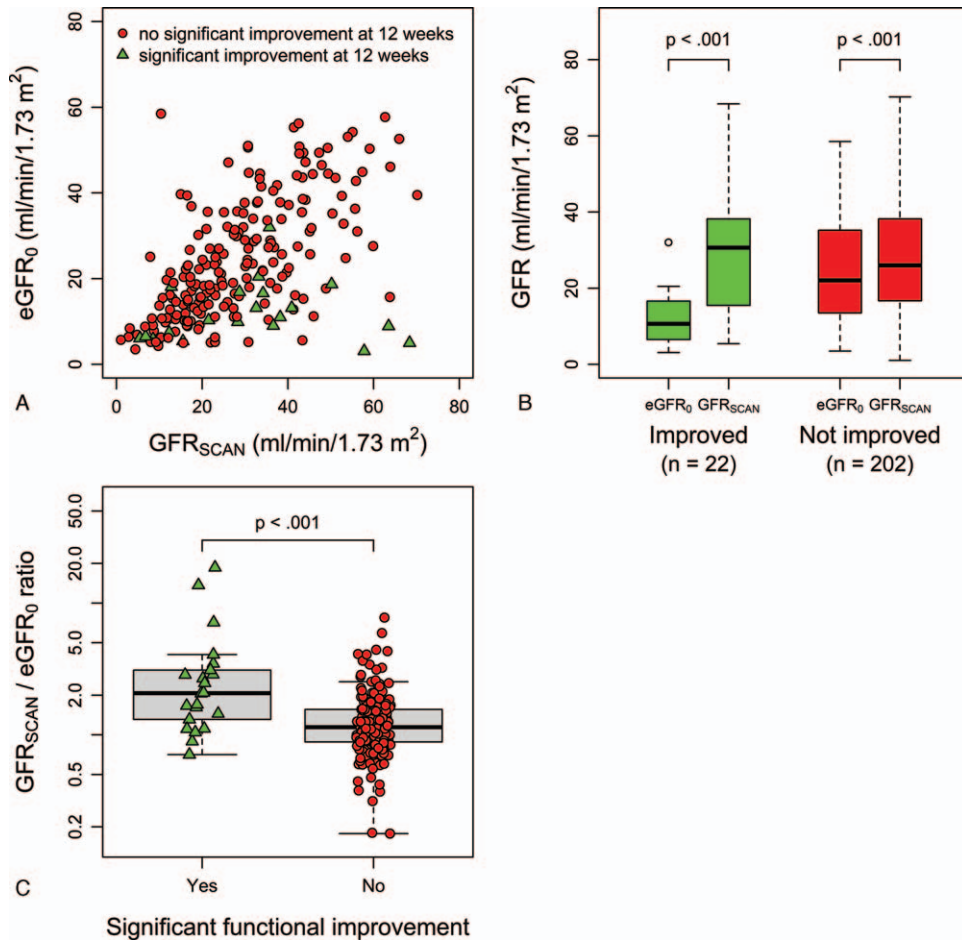


Figure 2. (A) A scatter plot between the ^{99m}Tc-DTPA scan GFR (GFR_{SCAN}) and eGFR on Day 0 (eGFR₀). (B) A boxplot of GFR_{SCAN} and eGFR₀ according to whether the renal function improved significantly at 12 weeks. (C) A boxplot showing the ratio of GFR_{SCAN} to eGFR₀ according to whether the renal function improved significantly at 12 weeks. The y-axis is in log scale. DTPA = diethylenetriamine-pentaacetic acid.

3.2. Renal function improvement and glomerular filtration rates

Twenty-two patients (9.8%) showed significant renal function improvement. In the improvement group, there was a significant discrepancy between eGFR₀ and GFR_{SCAN}, and eGFR₀ tended to be lower than GFR_{SCAN} (Fig. 2A and B). Conversely, in the nonimprovement group, the discrepancy between the eGFR₀ and GFR_{SCAN} was less pronounced than that in the improvement group, although the difference was still statistically significant (Fig. 2A and B). The ratio of GFR_{SCAN} to eGFR₀ was significantly higher in the improvement group than in the nonimprovement group (median: 2.07 [interquartile range: 1.34–3.04] vs median: 1.15 [interquartile range: 0.88–1.56]; $P < .001$; Fig. 2C).

3.3. Predictive performance

In the ROC curve analysis, the AUC of the GFR_{SCAN}/eGFR₀ ratio was 0.762 (95% confidence interval [CI]: 0.648–0.871; Fig. 3A). To calculate the optimal cutoff value of the GFR_{SCAN}/eGFR₀ ratio and the corresponding sensitivity and specificity, the patients were divided into a derivation set (n=112) and a validation set (n=112) in a 1:1 ratio. From the derivation set, the optimal cutoff value of the GFR_{SCAN}/eGFR₀ ratio was determined to be 1.643. When the GFR_{SCAN}/eGFR₀ ratio > 1.643 was

applied to the validation set, the sensitivity and specificity for predicting renal function improvement were 0.73 (95% CI: 0.43–0.90) and 0.76 (95% CI: 0.67–0.84), respectively.

The AUC of the best clinical predictor was 0.726 (95% CI: 0.617–0.826), which increased to 0.794 (95% CI: 0.683–0.892) when the best clinical variables and the GFR_{SCAN}/eGFR₀ ratio were used in combination to predict renal function improvement (Fig. 3B). The increase in AUC was statistically significant ($P = .02$), suggesting an incremental value of the GFR_{SCAN}/eGFR₀ ratio over the clinical variables in predicting renal function improvement.

In the univariable logistic regression analysis, the GFR_{SCAN}/eGFR₀ ratio was significantly associated with increased odds of renal function improvement (odds ratio=1.76 [95% CI: 1.26–2.45], $P < .001$; Table 2). Among the clinical variables, comorbidity with DM was significantly associated with decreased odds of renal function improvement. The presence of the suspected cause of azotemia was associated with increased odds of renal function improvement, which may be explained by the fact that patients who received cause-specific managements were more likely to be improved.

In the multivariable analysis using clinical variables, DM and the presence of a suspected cause of azotemia were selected as the best clinical predictor variables of renal function improvement

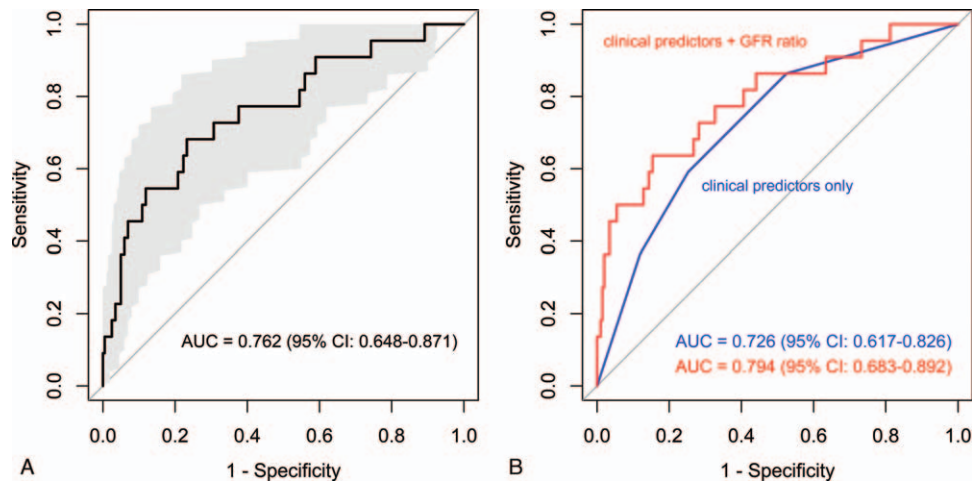


Figure 3. (A) The receiver operating characteristic curve of the $GFR_{SCAN}/eGFR_0$ ratio. The gray band represents 95% confidence interval. (B) The receiver operating characteristic curves of the best clinical predictor (blue line) and the best clinical predictor combined with the $GFR_{SCAN}/eGFR_0$ ratio (red line). AUC=area under the curve, CI=confidence interval, GFR = glomerular filtration rate.

Variable	Odds ratio	95% CI	P
$GFR_{SCAN}/eGFR_0$ ratio	1.76	1.26–2.45	<.001
Age (>55 yr)	1.71	0.48–6.06	.40
Sex (male)	1.11	0.43–2.85	.83
Diabetes mellitus (yes)	0.37	0.15–0.92	.03
Hypertension (yes)	0.51	0.20–1.34	.17
CKD (yes)	0.33	0.06–1.73	.19
CKD (uncertain)	0.45	0.08–2.58	.37
Cause of azotemia (known)	4.28	1.73–10.6	.002
Kidney size (cm)	1.22	0.86–1.73	.26
Hemoglobin (mg/dL)	1.01	0.79–1.29	.91

CI=confidence interval, CKD=chronic kidney disease, GFR=glomerular filtration rate.

(Table 3). When the $GFR_{SCAN}/eGFR_0$ ratio was added to the best clinical prediction model, the $GFR_{SCAN}/eGFR_0$ ratio remained as a significant predictor of renal function improvement independent of the clinical predictor variables (odds ratio=1.70 [95% CI: 1.19–2.42], $P=.003$; Table 3).

Figure 4 shows representative cases that demonstrate the ability of the $GFR_{SCAN}/eGFR_0$ ratio to predict significant renal function improvement.

3.4. Sensitivity analyses

When the threshold for defining significant renal functional improvement was set to 50%, 48 patients (21.4%) improved at

12 weeks. In the univariable analysis, the GFR ratio significantly predicted renal functional improvement (odds ratio=1.52 [95% CI: 1.14–2.03], $P=.004$; Table 4). In the multivariable analysis, the GFR ratio remained as a significant predictor after adjusting for the best clinical variable (odds ratio=1.44 [95% CI: 1.09–1.90], $P=.01$; Table 5).

When the improvement was assessed at 1 week, 99 out of the 224 patients were removed from the analysis because of the absence of estimated glomerular filtration rate at 1 week after ^{99m}Tc -DTPA renal scan measurement. Among the remaining 125, 8 (6.4%) improved at 1 week. In the univariable analysis, the GFR ratio significantly predicted renal functional improvement (odds ratio=1.53 [95% CI: 1.10–2.13], $P=.01$; Table 6). In the multivariable analysis, the GFR ratio remained as a significant predictor after adjusting for the best clinical variables (odds ratio=1.48 [95% CI: 1.05–2.09], $P=.02$; Table 7).

4. Discussion

In this study, we analyzed the ability of the ratio of GFR_{SCAN} to eGFR for predicting significant renal function improvement in patients with azotemia. A high $GFR_{SCAN}/eGFR$ ratio predicted significant renal function improvement, and this predictive ability was independent of the clinical predictor variables. The addition of the $GFR_{SCAN}/eGFR$ ratio to the best clinical prediction model significantly enhanced the predictive ability, which suggests that the $GFR_{SCAN}/eGFR$ ratio possesses an added value over the clinical variables for the prediction of significant renal function improvement. The predictive ability was robust under the

Variable	Best clinical predictor variables			Best clinical variables + GFR ratio		
	Odds ratio	95% CI	P	Odds ratio	95% CI	P
DM (yes)	0.41	0.16–1.05	.06	0.39	0.14–1.07	.07
Cause of azotemia (known)	3.95	1.58–9.90	.003	3.46	1.27–9.42	.02
GFR ratio				1.70	1.19–2.42	.003

CI=confidence interval, DM=diabetes mellitus, GFR ratio= $GFR_{SCAN}/eGFR_0$ ratio, GFR=glomerular filtration rate.

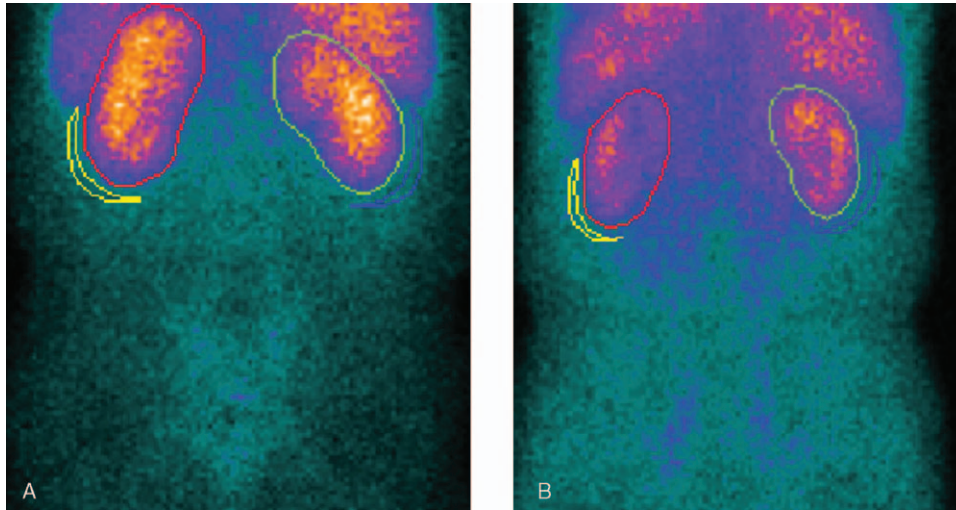


Figure 4. Representative cases. ^{99m}Tc-DTPA renal scan images of 2–3 min interval with kidney and background regions of interest are shown. (A) A 57-year-old male patient was admitted to the hospital for anuria. The cause of kidney injury was uncertain. The eGFR on Day 0 was 3.5 mL/(min 1.73 m²), whereas the GFR_{SCAN} was 57.8 mL/(min 1.73 m²). The GFR_{SCAN}/eGFR ratio was 16.5. The patient’s eGFR was improved to 83.2 mL/(min 1.73 m²) on follow-up. (B) An 81-year-old male patient with diabetes mellitus who had been admitted to the hospital for endoscopic sphincterotomy was referred to a nephrologist for azotemia. Due to the lack of previous medical data, the patient was uncertain about the cause of azotemia and about whether he had underlying chronic kidney disease. The eGFR on Day 0 was 18.5 mL/(min 1.73 m²) and the GFR_{SCAN} was 21.7 mL/(min 1.73 m²), thereby producing the GFR_{SCAN}/eGFR ratio of 1.17. The patient’s eGFR did not improve significantly on follow up; it was 21.2 mL/(min 1.73 m²) at 12 weeks.

Table 4
Univariable analysis under the 50% threshold for significant renal functional improvement at 12 weeks.

Variable	Odds ratio	95% CI	P
GFR ratio	1.52	1.14–2.03	.004
Age (>55 yr)	1.67	0.69–4.01	.25
Sex (male)	0.82	0.42–1.59	.56
Diabetes mellitus (yes)	0.58	0.30–1.10	.10
Hypertension (yes)	0.62	0.30–1.30	.21
CKD (yes)	0.22	0.06–0.87	.03
CKD (uncertain)	0.15	0.04–0.68	.01
Suspected cause of azotemia (known)	3.40	1.75–6.62	<.001
Kidney size (cm)	0.93	0.72–1.22	.62
Hemoglobin (mg/dL)	0.94	0.78–1.13	.53

CI = confidence interval, CKD = chronic kidney disease, GFR ratio = GFR_{SCAN}/eGFR₀ ratio, GFR = glomerular filtration rate.

sensitivity analyses. Given that ^{99m}Tc-DTPA renal scan requires little patient preparation, is widely available, and can be performed in a short time, it may serve as a useful adjunct tool for prompt clinical assessment of the azotemic patients for tailoring therapy.

The derivation of all eGFR equations (Cockcroft-Gault, Modification of Diet in Renal Disease, chronic kidney disease epidemiology collaboration, etc) requires a steady-state assumption, the violation of which may result in significant discrepancy

with the underlying true GFR. In the nonsteady state of underlying renal function, the calculated eGFR lags behind the actual change in the underlying true GFR; that is, eGFR underestimates the underlying true GFR while the underlying true GFR is increasing, and overestimates it while it is decreasing. In contrast, the GFR measured on ^{99m}Tc-DTPA renal scan (GFR_{SCAN}) does not require a steady-state assumption; therefore, the change in the underlying true GFR is reflected instantaneously on the GFR_{SCAN}. If the underlying true GFR is improving, the eGFR may underestimate its value, while the GFR_{SCAN} should not suffer from such underestimation. This resulted in an increased GFR_{SCAN}/eGFR ratio. Therefore, the increased GFR_{SCAN}/eGFR ratio may be regarded as an indicator of ongoing renal function improvement. This reasoning informed the hypothesis and rationale of this study, and may explain why a single-point measurement of the GFR_{SCAN} could be associated with the renal function improvement in the future.

The GFR_{SCAN}/eGFR ratio provides information about the underlying process of renal function improvement in azotemic patients, and therefore would be able to forecast the future evolution of eGFR. Some of its potential utilities in the management of azotemia would be as follows. First, a high GFR_{SCAN}/eGFR ratio suggests that underlying renal function has already been improved significantly and hence that eGFR would be increased shortly. Therefore, in severely azotemic patients (eg, eGFR < 10 mL/(min 1.73 m²)), it might be helpful for therapeutic

Table 5
Multivariable analysis under the 50% threshold for significant renal functional improvement at 12 weeks.

Variable	Best clinical predictors			Best clinical predictors + GFR ratio		
	Odds ratio	95% CI	P	Odds ratio	95% CI	P
Suspected cause of azotemia (known)	3.40	1.75–6.62	<.001	3.07	1.54–6.12	.001
GFR ratio				1.44	1.09–1.90	.01

CI = confidence interval, GFR ratio = GFR_{SCAN}/eGFR₀ ratio, GFR = glomerular filtration rate.

Table 6**Univariable analysis under the 100% threshold for significant renal functional improvement at 1 week.**

Variable	Odds ratio	95% CI	P
GFR ratio	1.53	1.10–2.13	.01
Age (>55 yr)	2.97	0.37–23.9	.31
Sex (male)	1.33	0.43–4.09	.62
Diabetes mellitus (yes)	0.32	0.11–0.95	.04
Hypertension (yes)	0.46	0.14–1.49	.20
CKD (yes)	0.35	0.06–2.06	.25
CKD (uncertain)	0.30	0.04–2.11	.23
Suspected cause of azotemia (known)	4.19	1.40–12.53	.01
Kidney size (cm)	1.02	0.66–1.57	.94
Hemoglobin (mg/dL)	0.99	0.73–1.34	.97

CI = confidence interval, CKD = chronic kidney disease, GFR ratio = $GFR_{SCAN}/eGFR_0$ ratio, GFR = glomerular filtration rate.

decision making such as averting the initiation of dialysis. This point is demonstrated in the representative case shown in Fig. 4A. Second, the $GFR_{SCAN}/eGFR$ ratio might be utilized for differential diagnosis between acute kidney injury (AKI) and CKD in newly discovered azotemic patients whose previous medical records are lacking. This kind of patients are common in emergency departments and at hospitals located in areas of poor medical accessibility.^[10,11] The differentiation between AKI and CKD is important because it influences management, prognosis, and disposition of the patients.^[11] A $GFR_{SCAN}/eGFR$ ratio near 1 suggests that the process of renal function improvement is not ongoing. Therefore, in combination with chronicity indicators such as small kidney size and/or long-lasting DM, treating physicians might be able to pose the diagnosis of CKD more confidently. This point is demonstrated in the representative case shown in Fig. 4B. Each of these utilities need to be validated in larger prospective studies.

As stated above, a significant proportion of the patients included in this study did not have appropriate baseline creatinine measurement. Several methods of estimating a missing baseline creatinine value have been proposed in previous studies, such as the imputation of previous creatinine values or back-calculation of a serum creatinine from an eGFR of 75 mL/(min 1.73 m²).^[12,13] Among them, the creatinine back-calculation is one of the most widely used technique for baseline creatinine estimation.^[14] However, the back-calculation technique tends to misdiagnose CKD as AKI and hence to underestimate the rate of renal function improvement in AKI, especially if the population contains a large number of CKD cases. In our study population, about 70% or more of the patients had comorbid CKD, which is far higher than the CKD prevalence of 9.1% in the general population.^[15] Therefore, in this study, we used an alternative method for defining significant renal function improvement that does not need baseline creatinine measure-

ment, that is, more than 100% and 10 mL/(min 1.73 m²) improvement of eGFR on follow up. We are curious to know if this method might help mitigate a bias of current AKI research that results from excluding cases without baseline creatinine measurement.^[14,16]

In the calculation of the $GFR_{SCAN}/eGFR$ ratio, GFR_{SCAN} could be substituted in principle by any GFR measured using exogenous filtration agents such as inulin, ⁵¹Cr-EDTA, or iohexol. However, the quantification of these agents is laborious and time-consuming, which limits their routine use in clinical practice.^[17] ^{99m}Tc-DTPA renal scan takes only 20 min and therefore is a quick method for determining GFR. Moreover, ^{99m}Tc-DTPA renal scan can provide data on split renal function, kidney morphology, and urinary obstruction, which are not obtainable from laboratory methods.

This study has some limitations. First, the number of included patients was relatively small; however, this number was sufficient to show a significant association between the $GFR_{SCAN}/eGFR_0$ ratio and renal function improvement. This study is an exploratory study and future validation studies in a larger patient cohort may be necessary. Second, a threshold of 100% for defining significant renal function improvement is somewhat arbitrary and therefore needs to be validated in subsequent studies. However, as experienced nephrologists, we authors think that the 100% improvement makes sense as an exploratory cutoff value for defining clinically meaningful improvement of renal function. Third, due to the retrospective nature of the study, important variables such as urine output could not be obtained, and serum creatinine and other laboratory values such as calcium and phosphorus could not be measured on a regular basis. Future prospective studies should analyze these variables appropriately.

5. Conclusion

The $GFR_{SCAN}/eGFR$ ratio can predict renal function improvement in patients with azotemia. The $GFR_{SCAN}/eGFR$ ratio might be useful for tailoring therapy in patients with AKI and for differentiating AKI from CKD in patients whose previous medical records are lacking. Future prospective studies are necessary to validate its potential clinical utilities.

Author contributions

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Table 7**Multivariable analysis under the 100% threshold for significant renal functional improvement at 1 week.**

Variable	Best clinical predictors			Best clinical predictors + GFR ratio		
	Odds ratio	95% CI	P	Odds ratio	95% CI	P
DM (yes)	0.36	0.12–1.09	.07	0.31	0.10–1.02	.06
Suspected cause of azotemia (known)	3.87	1.27–11.76	.02	3.13	0.97–10.12	.06
GFR ratio				1.48	1.05–2.09	.02

CI = confidence interval, DM = diabetes mellitus, GFR ratio = $GFR_{SCAN}/eGFR_0$ ratio, GFR = glomerular filtration rate.

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