【 ORIGINAL ARTICLE 】

A Long-term Estimated Glomerular Filtration Rate Plot Analysis Permits the Accurate Assessment of a Decline in the Renal Function by Minimizing the Influence of Estimated Glomerular Filtration Rate Fluctuations

Jun Nakazawa [1,2], Satoru Yamanaka [3], Shohei Yoshida [1], Mamoru Yoshibayashi [1], Miho Yoshioka [1], Takamasa Ito [4], Shin-ichi Araki [2], Shinji Kume [2] and Hiroshi Maegawa [2]

Abstract:
Objective   Evaluating the rate of decline in the estimated glomerular filtration rate (eGFR) may help identify patients with occult chronic kidney disease (CKD). We herein report that eGFR fluctuation complicates the assessment of the rate of decline and propose a long-term eGFR plot analysis as a solution.
Methods   In 142 patients with persistent eGFR decline in a single hospital, we evaluated the factors influencing the rate of eGFR decline, calculated over the long term (≥3 years) and short term (<3 years) using eGFR plots, taking into account eGFR fluctuation between visits.
Results   The difference between the rate of eGFR decline calculated using short- and long-term plots increased as the time period considered in the short-term plots became shorter. A regression analysis revealed that eGFR fluctuation was the only factor that explained the difference and that the fluctuation exceeded the annual eGFR decline in all participants. Furthermore, the larger the eGFR fluctuation, the more difficult it became to detect eGFR decline using a short-term eGFR analysis. Obesity, a high eGFR at baseline, and faster eGFR decline were associated with larger eGFR fluctuations. To circumvent the issue of eGFR fluctuation in the assessment of the rate of eGFR decline, we developed a system that generates a long-term eGFR plot using all eGFR values for a participant, which enabled the detection of occult CKD, facilitating early therapeutic intervention.
Conclusion   The construction of long-term eGFR plots is useful for identifying patients with progressive eGFR decline, as it minimizes the effect of eGFR fluctuation.

Key words: chronic kidney disease, eGFR, long-term eGFR plot, eGFR fluctuation, occult CKD

Introduction

The increasing prevalence of chronic kidney disease (CKD) is a major health issue in many countries and is the result of the increasing incidence of diabetes and the aging of the population (1-3). The early identification of patients with a poor renal prognosis is now being attempted in many countries using the definition of CKD generated by Kidney Disease: Improving Global Outcomes (KDIGO) (4). However, the incidences of CKD and subsequent end-stage renal disease (ESRD) continue to rise. Therefore, the identification of limiting factors and the development of novel strategies is required to further improve renal prognosis.

Although the creatinine-based estimated glomerular filtration rate (eGFR) is useful for evaluating the renal function in clinical practice (5), the difference between the actual GFR measured using inulin and the eGFR increases along

with the actual GFR value (6-9). Therefore, assessing the renal function using eGFR at a single time point is often inadequate for the identification of CKD (10). The rate of eGFR decline has recently received much attention as an outcome in clinical research and may be useful for predicting progression to ESRD (11-13). Thus, a strategy that involves assessing the eGFR decline may contribute to the more efficient identification of occult CKD.

To facilitate the evaluation of eGFR decline as a means of identifying patients with occult CKD, limiting factors must be identified and addressed. The creatinine-based eGFR is known to fluctuate with the seasons. Therefore, the eGFR varies considerably between hospital visits by a patient. In many hospitals, the time period displayed in electronic medical records is typically approximately one to two years. Thus, if the eGFR fluctuation is greater than the annual eGFR decline, it may be masked during such a short-term evaluation, implying that short-term observations may be insufficient to identify patients with persistent eGFR decline.

In the present study, we investigated the problems associated with assessing the rate of eGFR decline using data collected over a short period of time by comparing the eGFR trends over periods of ≥3 years (long-term) and <3 years (short-term), focusing on eGFR fluctuation.

Materials and Methods

Ethics

We performed a cross-sectional study at Otsu City Hospital that was approved by the Ethics Committee of the Hospital. This study was conducted in accordance with the Declaration of Helsinki and its amendments and complied with appropriate institutional guidelines.

Definition of long-term and short-term eGFR plot analysis

The eGFR was calculated using the Japanese GFR equation (7).

eGFR (mL/min/1.73 m^2)=194×Cr$^{-1.094}$ × Age$^{-0.287}$ (×0.739 for women)

A "long-term eGFR plot" was defined as a lumped plot of the long-term eGFR trend, which incorporated all available eGFR data, and was generated using the Excel software program (Microsoft, Redmond, USA), with the eGFR on the vertical axis and time on the horizontal axis. It was designed to show all values over the entire period as a scatter plot, with the most recent data located near the center of the graph, enabling the detection of a sustained decline in the eGFR, which is likely to lead to ESRD. In addition, eGFR plots created using values obtained in the preceding one to three years were designated as "short-term eGFR plots".

Participants

Patient information, including the results of blood and urine tests, sex, age, height, body weight, primary disease,

medical history, and drug administration history, was collected from the electronic medical records of Otsu City Hospital. Long-term eGFR plots were prepared for all 388 outpatients in October 2016 using data collected between January 1, 1991, and October 31, 2016, during their regular visits to the Division of Nephrology. Of these patients, 142 were included in the study after excluding 68 who were seen in the hospital for less than 3 years, 1 under 20 years old, 17 whose eGFR had been measured fewer than 5 times in the last 3 years, 95 whose eGFR trend had changed significantly in the last 3 years (29 hospitalized, 23 with acute kidney injury, 1 with nephrectomy, 1 with steroid pulse therapy, and 41 for other reasons), 11 whose eGFR trend had remained unchanged, and 54 whose eGFR trend had increased.

In each of these 142 patients, the period during which the eGFR trend was almost linear was defined as the respective observation period. The duration of the linearity was determined by agreement between two nephrologists using a long-term eGFR plot. The characteristics of the participants are listed in Table 1.

Definition and analyses of eGFR fluctuations

In the long-term eGFR plot for each participant, the regression residual over the entire period of relatively constant decline in the renal function during the preceding ≥3 years was defined as r. The mean of the square root of the square of r ($\sqrt{r^2}$) was defined as (mean$\sqrt{r^2}$), the standard deviation of mean$\sqrt{r^2}$ was defined as sd, and the eGFR fluctuation was defined as 2× (mean$\sqrt{r^2}$ + 2sd) the upper and lower squares of the regression line of mean$\sqrt{r^2}$ + 2sd. Thus,

eGFR fluctuation = 2(mean$\sqrt{r^2}$ + 2sd).

We evaluated the distribution of eGFR fluctuation in the participants. The gradient of the regression line of the eGFR plot over the entire observation period was defined as the long-term ΔeGFR, and this was compared with the eGFR fluctuation. The ΔeGFRs obtained from the gradients of the regression lines of the eGFR plots of the preceding three, two, and one years were defined as the short-term ΔeGFRs (ΔeGRF3y, ΔeGFR2y, and ΔeGFR1y, respectively), and the long- and short-term ΔeGFRs were compared. When calculating the ΔeGFR and eGFR fluctuation, we excluded the eGFRs calculated at the time of hospitalization and after acute kidney injury.

Effect of the introduction of long-term eGFR plots on renal care

The number of consultations with nephrologists, CKD education admissions, and the nutritional guidance for the purpose of improving the renal prognosis were counted in the hospital between 2015 and 2019, with long-term eGFR plots being introduced in 2016.

Statistical analyses

Wilcoxon's rank sum test was used to identify significant differences in median values between multiple groups.

Table 1. Baseline Characteristics of the Patients Enrolled in the Study.

Baseline Characteristics	Mean (SD) or Median [IQR] or n (%)
Age	69.0 (SD, 14.1)
Men	97 (68.3)
Body weight (kg)	64.2 (SD, 14.6)
Height (cm)[a]	1.62 (0.88)
Body mass index (kg/m^2)[b]	24.2 (SD, 4.7)
Observation period (years)	6.4 [4.7-9.5]
Diabetes	67 (47.2)
Hypertension	122 (85.9)
Dyslipidemia	83 (58.5)
Hyperuricemia	99 (69.7)
The underlying disease of CKD	
Diabetic kidney disease	67 (47.2)
Nephrosclerosis	38 (26.8)
CGN	29 (20.4)
ADPKD	6 (4.2)
others	2 (1.4)
Median number of eGFR measurements in the last 3 years (times/year)	7.0 [5.1-10.9]
Median creatinine levels (mg/dL)	1.5 [1.1-2.7]
Median eGFR (mL/min/1.73m^2)	33.6 [16.6-50.5]
Median HbA1c (%)[c]	6.6 [6.0-7.3]
Median non-HDL-C levels (mg/dL)[d]	128 [106.3-150.1]
Median uric acid levels (mg/dL)[e]	6.5 [5.6-7.5]
Median proteinuria (g/g creatinine)	0.5 [0.1-1.4]
Insulin use	16 (11.3)
ACE inhibitor or ARB use	106 (74.6)
HMG-CoA reductase inhibitor use	59 (41.5)
Xanthine oxidase inhibitor use	66 (46.5)
Diuretic use	39 (27.5)
Number in each stage of CKD[f] at baseline	
Stage 1	1
Stage 2	24
Stage 3a	22
Stage 3b	31
Stage 4	33
Stage 5	31

CKD: Chronic kidney disease, CGN: chronic glomerulonephritis, ADPKD: autosomal dominant polycystic kidney disease, eGFR: estimated glomerular filtration rate, HbA1c: glycated hemoglobin, HDL-C: high-density lipoprotein cholesterol, ACE: angiotensin-converting enzyme, ARB: angiotensin receptor blocker, HMG-CoA: 3-Hydroxy-3-Methylglutaryl-Coenzym-A, IQR: interquartile range

[a]Missing in n=5, [b]Missing in n=5, [c]Missing in n=75, [d]Missing in n=78, [e]Missing in n=1, [f]Stage 1: eGFR ≥90 mL/min/1.73 m^2, stage 2: eGFR =60-89.9 mL/min/1.73 m^2, stage 3a: eGFR =45-59.9 mL/min/1.73 m^2, stage 3b: eGFR =30-44.5 mL/min/1.73 m^2; stage 4: eGFR =15-29.9 mL/min/1.73 m^2, stage 5: eGFR <15 mL/min/1.73 m^2

Spearman's rank correlation coefficient was used to evaluate the relationships between two parameters. In the multivariate analysis of the association of the difference between long-term ΔeGFR and ΔeGFR1y with potential determinants, four parameters that were significant in the univariate analysis were used as explanatory variables in Model 1, and six parameters that were identified using the stepwise (variable increase or decrease) method were used as explanatory variables in Model 2. In the multivariate analysis of the association between GFR fluctuation and potential determinants, six parameters that were significant in the univariate analysis were used as explanatory variables in Model 1, and six items that were identified using the stepwise (variable increase or decrease) method were used as explanatory variables in Model 2.

Results

Evaluating the eGFR decline is difficult using the short-term trend in the eGFR

First, the short-term (1 year) and long-term eGFR plots of two patients with persistent eGFR decline with and without macroalbuminuria are presented to illustrate the difficulty as-
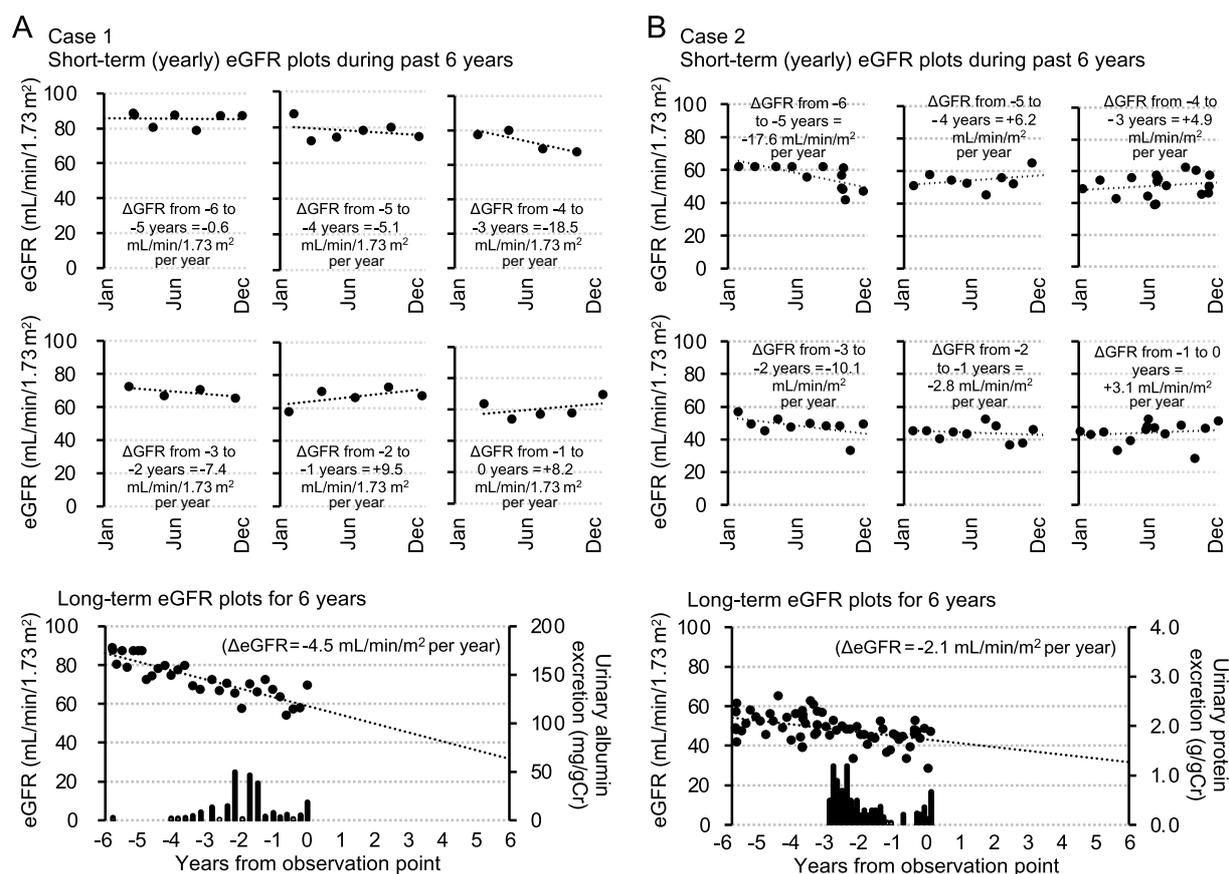
Figure 1. Annual short-term eGFR plots and long-term eGFR plots in specific patients with a sustained decline in the eGFR. (A) Case 1: Annual short-term trends in the eGFR and urinary albumin excretion during the preceding six years in patients who did not meet the current criteria for the diagnosis of CKD over most of the period but did show a decrease in the eGFR over time, and the long-term eGFR plots for the same patients. (B) Case 2: Annual short-term trends in the eGFR and urinary protein excretion over the preceding six years in patients with overt proteinuria, and the long-term eGFR plots for the same patients.

sociated with the assessment of the decline in the renal function using one-year eGFR trends (Fig. 1). The clinical characteristics of the two patients at the start of long-term eGFR plot utilization are shown in Supplementary material.

Case 1

(Fig. 1A) shows the short- and long-term eGFR plots of a 53-year-old man with diabetes who had not had macroalbuminuria during the preceding 6 years. The eGFR decline, based on annual observations, ranged from -18.5 to +9.5 mL/min/1.73 m^2 per year. Thus, there was substantial annual variation. Furthermore, at a glance, there appeared to be no significant eGFR decline at any point, and when all of the eGFR values for the entire 6 years were plotted in a single figure, the eGFR decline appeared relatively constant, at -4.5 mL/min/1.73 m^2 per year, and at the end of the period, it was <60 mL/min/1.73 m^2, which is a criterion of CKD.

Case 2

Fig. 1 B shows the short- and long-term eGFR plots for a 58-year-old man with diabetes who had overt proteinuria. In this patient, the reduction in the eGFR obtained using an-

nual observations was also inconsistent, and a marked decrease in the eGFR was difficult to recognize. Indeed, in 5 out of 8 years, the eGFR appeared to improve (ΔeGFR was positive), but the eGFR decline was -2.1 mL/min/1.73 m^2 per year when assessed using the long-term eGFR plot of the entire 6-year period.

Thus, eGFR plots covering approximately one year, which are likely to be widely used in clinical practice, may not be suitable for detecting persistent eGFR decline. Specifically, patients who have a declining renal function but do not meet the standard criteria for the diagnosis of CKD, as in Case 1, or who have progressive CKD but appear to have no eGFR decline, as in Case 2, tend not to visit a nephrologist in a timely fashion, resulting in a delay in starting or intensifying therapy.

Usefulness of long-term eGFR plots for detecting persistent decreases in the eGFR

To determine whether or not short-term eGFR assessments led to an underestimation of the eGFR decline in patients with a persistent eGFR decline, we compared the utility of long-term (≥3 years) and short-term eGFR plots in the
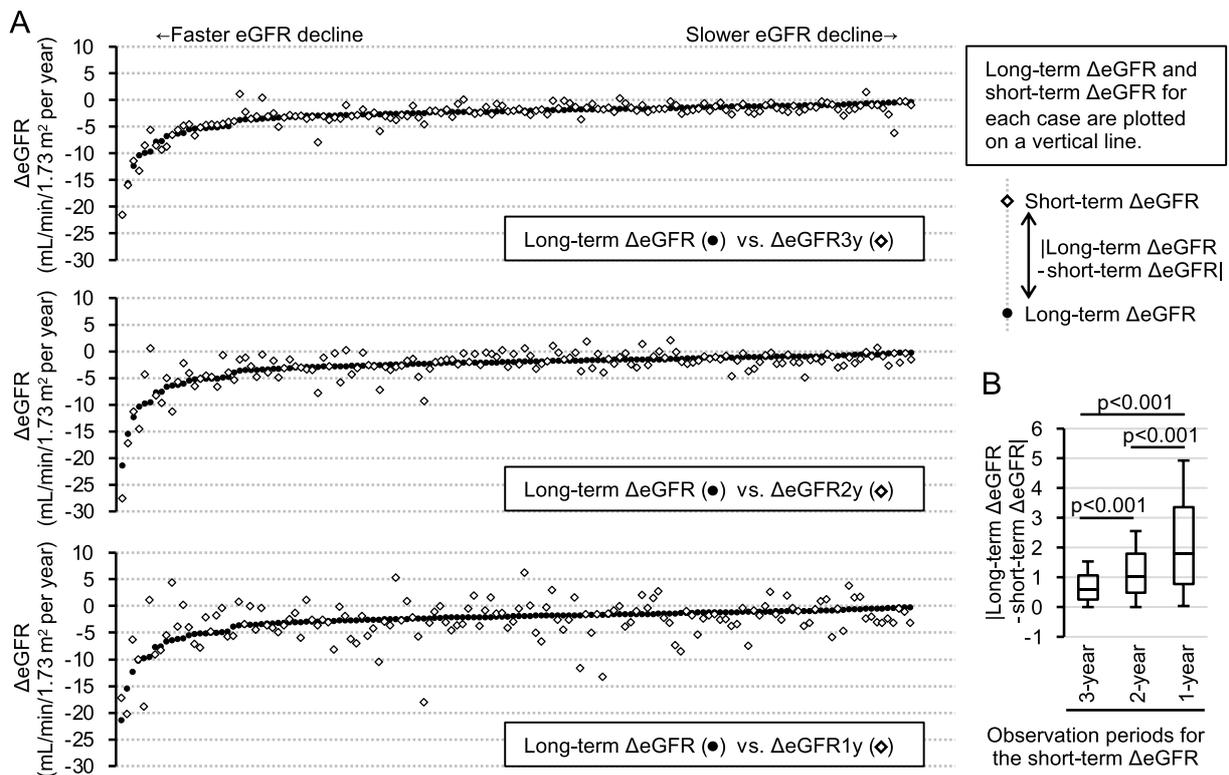
Figure 2. Usefulness of long-term eGFR plots for the identification of persistent decreases in the eGFR. (A) Long-term ΔeGFR values (●) are displayed in order, from the most rapid decline (left side) to the least rapid (right side), versus the short-term ΔeGFR (◇) for the same patient. The long-term ΔeGFR calculated from the eGFR plots over 3 years and 3-year (upper), 2-year (middle), or 1-year (lower) ΔeGFR for the same patient are vertically aligned. (B) The median difference between the long-term ΔeGFR and ΔeGFR, using 3, 2, and 1 year of data. Graphs show the median, lower and upper quartile values (boxes), and ranges (whiskers) of the differences. *$p<0.05$.

142 participants who showed relatively constant decreases in eGFR over at least the preceding 3 years. Table 1 shows the clinical characteristics of the participants. The median observation period was 6.4 years. The median number of eGFR measurements in the preceding 3 years was 7.0 times/year.

In Fig. 2A, the long-term ΔeGFRs of all the participants were plotted in order of the rate of eGFR decline, from fastest to slowest, and then for each participant, the short-term ΔeGFR values were plotted versus the long-term ΔeGFR values. This allowed for the visualization of differences between long- and short-term ΔeGFRs for each participant. The differences between the long- and short-term ΔeGFRs (ΔeGFR3y, ΔeGFR2y, and ΔeGFR1y) became extremely larger as the observation period shortened (Fig. 2), implying that short-term eGFR trends are unsuitable for identifying patients with sustained decreases in the eGFR.

eGFR fluctuation masks sustained decreases in the eGFR

As shown in Cases 1 and 2, the eGFR varies considerably among visits. Therefore, we hypothesized that the fluctuation in the eGFR might cause an eGFR decline to be missed if only relatively short periods of time are considered. Therefore, we assessed the effect of eGFR fluctuation on the

evaluation of the eGFR decline. The eGFR fluctuation was calculated as shown in Fig. 3A. The median eGFR fluctuation was 13.5 mL/min/1.73 m² (Fig. 3B). In all participants, the eGFR fluctuation was greater than the absolute value of the long-term ΔeGFR calculated using the regression line on the eGFR plot (Fig. 3C). Thus, an eGFR decline may be masked by such fluctuations.

We next aimed to identify the factors associated with the difference between long-term ΔeGFR and ΔeGFR1y, considering a number of clinical indices and eGFR fluctuation (Table 2). Although a univariate analysis identified some clinical parameters as such factors, a multivariate analysis revealed that eGFR fluctuation was the only factor that was associated with a marked difference. The evaluation of the relationships between eGFR fluctuation and the differences between long-term ΔeGFR and ΔeGFR3y, ΔeGFR2y, and ΔeGFR1y showed that the difference became extremely large as the eGFR fluctuation increased, regardless of whether three-, two-, or one-year observation periods were considered (Fig. 4A-C). The fluctuation in the eGFR being greater than the annual decrease in the eGFR likely hampers the recognition of a persistent decrease in eGFR decline in many patients, but long-term observation can reduce this risk.
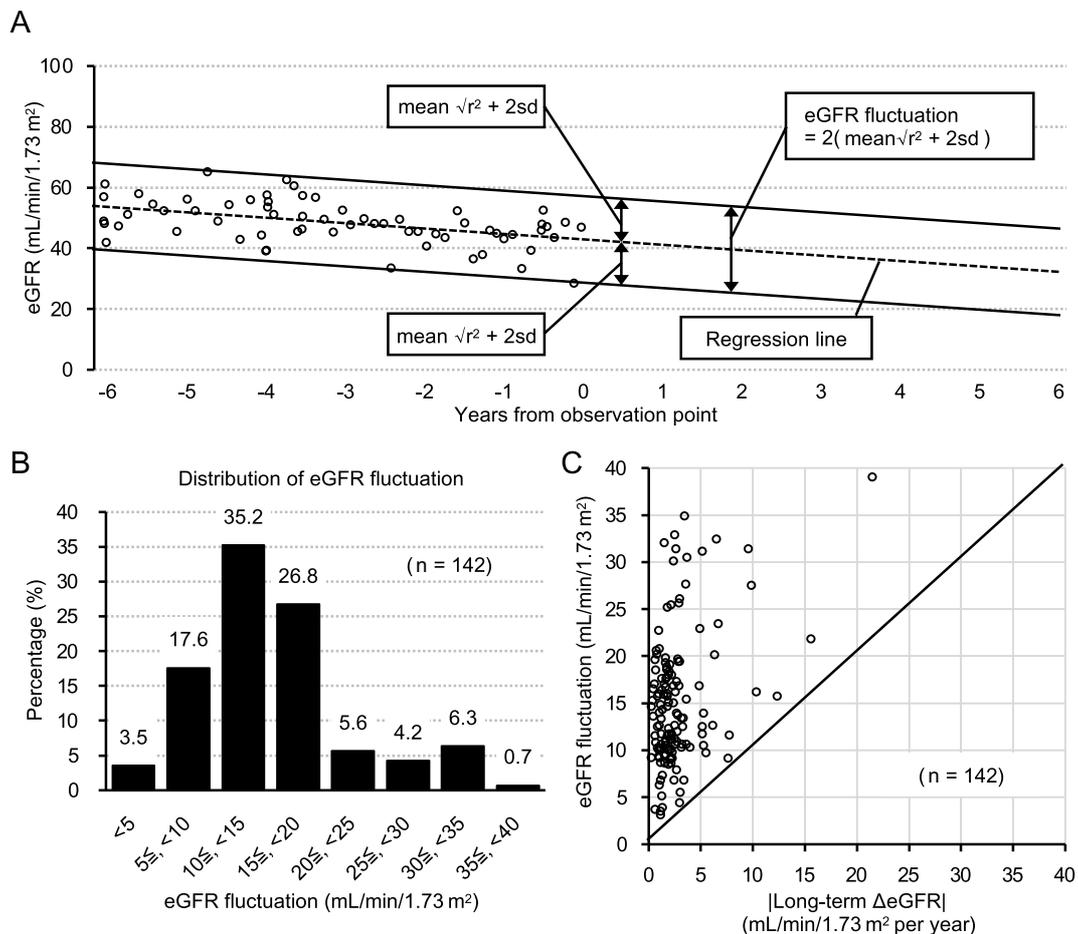
Figure 3. Relationships between the eGFR fluctuation and annual decline in the eGFR. (A) The definition of eGFR fluctuation using the long-term eGFR plot, as in Fig. 1B. eGFR fluctuation was defined as 2 (mean$\sqrt{r^2}$+2sd) (mL/min/1.73 m^2). r: the regression residual between the regression line of the eGFR plot and each eGFR plot, sd: the standard deviation of $\sqrt{r^2}$ (B) Distribution of the eGFR fluctuation, calculated using the definition in (A), in 142 eligible patients. (C) Correlation between the fluctuation in eGFR and |ΔeGFR|, calculated using the long-term eGFR plot for the 142 participants.

Fig. 3C shows that even over the median observation period of 6.4 years that was used in the present study, the fluctuation in eGFR was larger than the absolute value of long-term ΔeGFR in all participants. Therefore, we estimated how the number of participants in which the absolute value of the ΔeGFR exceeded the fluctuation in the eGFR would change as the observation period increased (Fig. 4D). We found that the absolute value of the ΔeGFR exceeded the fluctuation in the eGFR in none of the participants during the 1-year observation period and in only 15% of the participants during the 3-year period. Furthermore, we found that it would take over 10 years of observation before the percentage of participants in whom the absolute value of the ΔeGFR exceeded the eGFR fluctuation reached >80% of the total. Therefore, if the number of years required for the absolute value of the ΔeGFR to exceed the fluctuation in the eGFR is the required observation period for the identification of a decline in the renal function, it follows that a very long period of observation would be required for many patients.

We next aimed to identify parameters associated with the fluctuation in eGFR, and found that it was associated with age, body weight, hypertension, long-term ΔeGFR, eGFR, and glycated hemoglobin (HbA1c) in univariate analysis. In addition, the fluctuation in the eGFR was associated with the body weight, eGFR, and long-term ΔeGFR in a multivariate analysis that included six parameters found to be associated in a univariate analysis as explanatory variables (Table 3). Furthermore, the fluctuation in the eGFR was associated with the body weight and eGFR in a multivariate analysis that included six explanatory variables identified using the stepwise method (Table 3). Thus, obese patients and patients with a preserved eGFR but a relatively rapid eGFR decline may experience larger fluctuations in eGFR than others, and clinicians should be careful not to miss occult but persistent declines in the renal function in such patients.

Effect of using long-term eGFR plots in clinical practice

These results indicate that eGFR fluctuation is a misleading factor when observing short-term eGFR plots and that long-term eGFR plots are useful for eliminating the effects

Table 2. Univariate and Multivariate Analyses to Identify Factors Associated with the Difference between Long- and Short-term ΔeGFR.

Variables	Univariate analyses				Multivariate analyses							
					Model 1				Model 2			
	β	SE	95%CI	p	β	SE	95%CI	p	β	SE	95%CI	p
Age (years)	-0.049	0.015	-0.079 to -0.020	0.0012	-0.016	0.017	-0.049 to 0.018	0.3619				
Men	0.083	0.23	-0.38 to 0.55	0.7243								
Body weight (kg)	0.023	0.015	-0.0062 to 0.053	0.1213					-0.03	0.021	-0.072 to 0.011	0.1504
Diabetes	-0.074	0.22	-0.51 to 0.36	0.7333								
Hypertension	0.36	0.31	-0.26 to 0.97	0.2548								
Dyslipidemia	0.2	0.22	-0.24 to 0.64	0.3639								
Hyperuricemia	0.14	0.24	-0.33 to 0.61	0.5639								
Long-term ΔeGFR (mL/min/1.73 m² per year)	-0.2	0.077	-0.35 to -0.047	0.0106	-0.55	0.083	-0.22 to 0.11	0.5093	-0.11	0.088	-0.29 to 0.062	0.1989
eGFR fluctuation (mL/min/1.73 m²)	0.16	0.028	0.10 to 0.21	<0.0001	0.12	0.038	0.05 to 0.2	0.0012	0.17	0.049	0.067 to 0.26	0.0013
Median number of eGFR measurements in the last 3 years (times/year)	0.01	0.048	-0.086 to 0.11	0.8293								
eGFR (mL/min/1.73 m²)	0.033	0.0095	0.014 to 0.052	0.0007	0.0069	0.012	-0.017 to 0.03	0.5634	0.014	0.017	-0.02 to 0.049	0.4015
HbA1c (%)	0.032	0.29	-0.54 to 0.61	0.9108					-0.48	0.28	-1.05 to 0.084	0.0935
Non-HDL-C levels (mg/dL)	0.005	0.009	-0.013 to 0.023	0.579								
Uric acid levels (mg/dL)	0.12	0.13	-0.14 to 0.38	0.3719								
Proteinuria (g/g creatinine)	0.035	0.15	-0.26 to 0.32	0.8143								
Insulin use	0.3	0.34	-0.38 to 0.98	0.3895								
ACE inhibitor or ARB use	0.19	0.25	-0.3 to 0.68	0.4483								
HMG-CoA reductase inhibitor use	0.32	0.22	-0.11 to 0.76	0.1415								
Xanthine oxidase inhibitor use	0.16	0.22	-0.27 to 0.6	0.4534								
Diuretic use	-0.41	0.24	-0.89 to 0.069	0.093					-0.37	0.31	-0.98 to 0.25	0.2367

Model 1 of the multivariate analysis included age, long-term ΔeGFR, eGFR fluctuation, and eGFR.

Model 2 of the multivariate analysis included body weight, long-term ΔeGFR, eGFR fluctuation, eGFR, HbA1c, and diuretic use.

eGFR: estimated glomerular filtration rate, HbA1c: glycated hemoglobin, HDL-C: high-density lipoprotein cholesterol, HMG-CoA: 3-Hydroxy-3-Methylglutaryl-Coenzym-A, ACE: angiotensin-converting enzyme, ARB: angiotensin receptor blocker

of eGFR fluctuation and painting a more accurate picture of eGFR changes. We therefore next explored how to easily create a long-term eGFR plot in clinical practice. To address this issue, we introduced a clinical application to generate long-term eGFR plots and discussed its impact. In 2016, we began using an Excel-based long-term eGFR plot, and then in 2018, we implemented a system that automatically collected data from the electronic medical records and other data storage locations to construct long-term eGFR plots. In addition, from 2019, we introduced a system that simultane-ously used not only the eGFR but also the cystatin C-based eGFR (eGFRcys), HbA1c, urine protein/creatinine ratio, and urine albumin/creatinine ratio (Research Institute of Systems Planning, Tokyo, Japan) (Fig. 5A).

Fig. 5A shows a patient with diabetes mellitus referred to a nephrologist from a diabetologist in our hospital. In this case, during poor glycemic control, albuminuria and protein-uria began to increase. Subsequently, with treatment by a diabetologist, the HbA1c levels improved, but the protein-uria did not decrease, and the renal function continued to
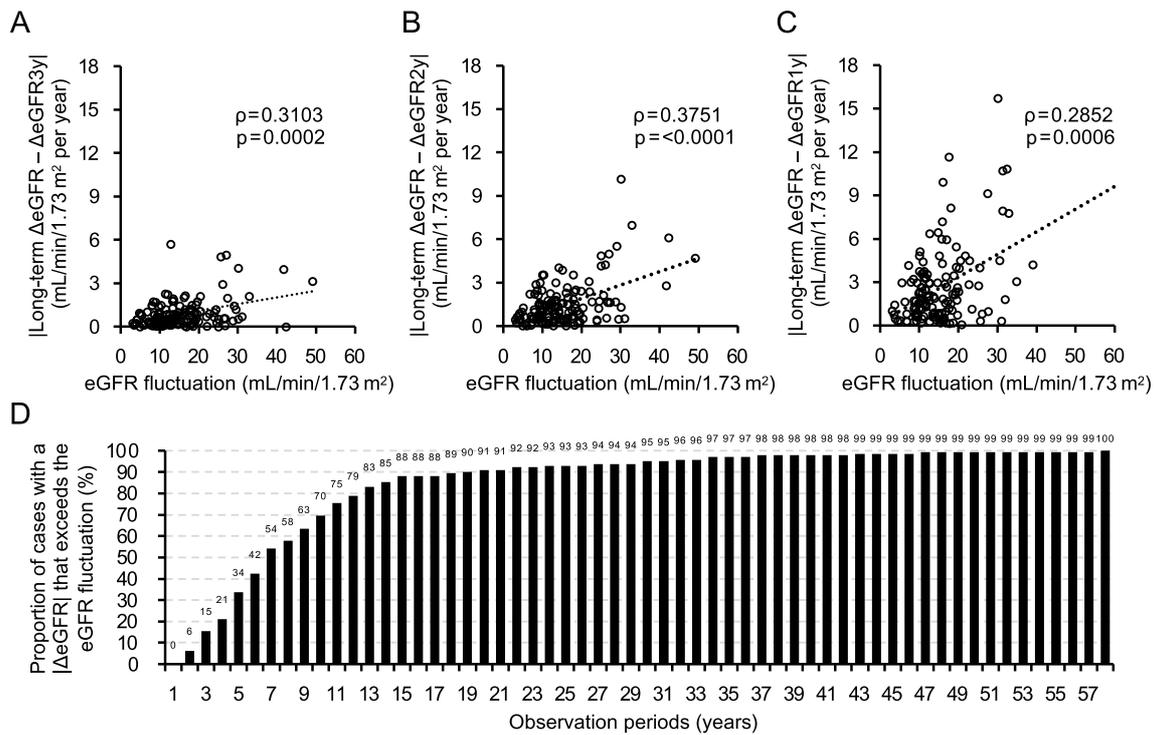
Figure 4. Relationships between eGFR fluctuation and the difference between the long- and short-term ΔeGFR. (A-C) Correlations between the fluctuation in the eGFR and the difference between long-term ΔeGFR, calculated using the eGFR plots over 3 years, and the 3- (A), 2- (B), and 1-year (C) ΔeGFR. ρ: Spearman's rank correlation coefficient. (D) Expected proportion of cases with a |ΔeGFR| that exceeds the eGFR fluctuation per year of observation.

decline, so the patient was referred to us. The same situation persisted for some time after treatment was initiated by the nephrologist. However, after that, we introduced the long-term eGFR plot system into daily practice, explained the decline in the renal function to patients using this system, and indicated the predicted date of renal replacement therapy. As a result, the proteinuria decreased remarkably, and the eGFR rate of decline began to slow. Although the HbA1c did not change, the blood pressure decreased significantly before and after the introduction of the long-term eGFR plot viewer without any change in anti-hypertensive agents, suggesting that a medical explanation with the system may have improved adherence to medication and dietary therapy.

In addition, the red line shows the range of eGFR fluctuation in this case. Even with such a relatively large range of fluctuation, the long-term eGFR plot allows us to grasp at a glance the timing of the change in the eGFR rate of decline and to infer the factors associated with it. In the case presented here, the timing of improvement in the eGFR decline was the start of the use of a long-term eGFR plot.

After introducing the program in 2016, the numbers of consultations with nephrologists (Fig. 5B), CKD education admissions (Fig. 5C), and nutritional counseling sessions for preventing CKD progression (Fig. 5D) increased year by year. These results suggest that a large number of patients with a declining eGFR may be hidden in other departments and that long-term eGFR plots may be able to identify occult CKD, thereby facilitating early referral to nephrologists

and the initiation of appropriate care.

Discussion

To provide better care for patients with CKD, the eGFR should be evaluated in terms of its rate of decline rather than at a single point in time (11, 12). The present study demonstrated the importance of the eGFR rate of decline in clinical practice, highlighted a limitation of using this measure, and proposed a means of circumventing this limitation. Specifically, we found that the fluctuation in the eGFR between hospital visits represents a challenge in the assessment of the eGFR decline, and we proposed the use of a long-term eGFR plot analysis as a solution to this problem.

Under the current CKD criteria (4), if the eGFR is not <60 mL/min/1.73 m[2] and/or proteinuria is absent, the progression to fulfillment of the CKD criteria is not considered abnormal. In addition, even if the eGFR is <60 mL/min/1.73 m[2], but the eGFR decline is relatively slow, the patient may not be referred to a nephrologist until they develop ESRD. However, if the eGFR rate of decline is assessed, it should be possible to identify patients with occult CKD of these types. Given that the goal of CKD treatment is to maintain rather than improve the renal function, the initiation of treatment of CKD based on the eGFR rate of decline may become more important in the future.

We found that fluctuation in the eGFR makes the evaluation of short-term trends in the eGFR difficult. eGFR fluc-

Table 3. **Univariate and Multivariate Analyses to Identify Factors Associated with eGFR Fluctuation.**

| Variables	Univariate analyses				Multivariate analyses							
					Model 1				Model 2			
	β	SE	95%CI	p	β	SE	95%CI	p	β	SE	95%CI	p
Age (years)	-0.2	0.038	-0.28 to -0.13	<0.0001	0.059	0.077	-0.094 to 0.21	0.4449				
Men	-0.47	0.63	-1.72 to 0.79	0.4622								
Body weight (kg)	0.16	0.038	0.083 to 0.23	<0.0001	0.12	0.057	0.009 to 0.24	0.035	0.12	0.053	0.017 to 0.23	0.0232
Diabetes	-0.51	0.59	-1.67 to 0.66	0.3933					-1.78	2.05	-5.89 to 2.32	0.3881
Hypertension	1.78	0.84	0.12 to 3.43	0.0352	-1.55	1.34	-4.22 to 1.13	0.2527				
Dyslipidemia	-0.56	0.6	-1.74 to 0.63	0.3543								
Hyperuricemia	0.65	0.64	-0.62 to 1.91	0.3145								
Long-term ΔeGFR (mL/min/1.73 m^2 per year)	-0.94	0.2	-1.33 to -0.56	<0.0001	-0.55	0.23	-1.01 to -0.83	0.0216	-0.45	0.23	-0.91 to 0.014	0.057
Median number of eGFR measurements in the last 3 years (times/year)	-0.18	0.13	-0.44 to 0.076	0.1634								
eGFR (mL/min/1.73 m^2)	0.17	0.022	0.13 to 0.22	<0.0001	0.18	0.036	0.10 to 0.25	<0.0001	0.16	0.038	0.086 to 0.24	<0.0001
HbA1c (%)	2.92	0.83	1.26 to 4.59	0.0008	0.64	0.75	-0.86 to 2.15	0.3974	0.46	0.87	-1.28 to 2.2	0.6025
Non-HDL-C levels (mg/dL)	0.029	0.027	-0.025 to 0.084	0.2842								
Uric acid levels (mg/dL)	0.0094	0.36	-0.70 to 0.71	0.979								
Proteinuria (g/g creatinine)	-0.6	0.39	-1.38 to 0.18	0.1276								
Insulin use	-0.7	0.93	-2.54 to 1.15	0.4572					0.00073	0.97	-1.95 to 1.95	0.9994
ACE inhibitor or ARB use	0.19	0.68	-1.15 to 1.54	0.7759								
HMG-CoA reductase inhibitor use	0.14	0.6	-1.04 to 1.33	0.811								
Xanthine oxidase inhibitor use	0.47	0.59	-0.69 to 1.64	0.4244								
Diuretic use	-0.37	0.66	-1.68 to 0.94	0.5748								

Model 1 of the multivariate analysis included age, body weight, hypertension, long-term ΔeGFR, eGFR, and HbA1c.

Model 2 of the multivariate analysis included body weight, diabetes, long-term ΔeGFR, eGFR, HbA1c, and insulin use.

eGFR: estimated glomerular filtration rate, HbA1c: glycated hemoglobin, HDL-C: high-density lipoprotein cholesterol, ACE: angiotensin-converting enzyme, ARB: angiotensin receptor blocker, HMG-CoA: 3-Hydroxy-3-Methylglutaryl-Coenzym-A

tuation occurred in all patients, and the magnitude of the fluctuation exceeded the eGFR decline when the eGFR1y was considered. Furthermore, the larger the eGFR fluctuation, the more difficult it was to assess the rate of decline in the renal function using short-term eGFR plots. A preserved residual renal function, more rapid decreases in the eGFR, and higher body weight were associated with larger eGFR fluctuations, implying that it would be difficult to accurately assess the rate of eGFR decline in such patients, which are at a high risk of CKD progression. To reduce the risk of missing this progression, a long-term eGFR plot should be used.

Based on the present findings, a system that automatically constructed a long-term eGFR plot and included all eGFR data from 1991 to the day of consultation was established at the Otsu City Hospital. With this approach, the number of consultations with nephrologists increased rapidly, as many patients were found to have shown decreases in the renal function over a long period of time but were not under current treatment by a nephrologist. In addition, the patients were able to better understand their renal function by seeing a clear representation of their eGFR decline, which increased their motivation to undergo treatment. This resulted in an increase in the number of in-hospital CKD education
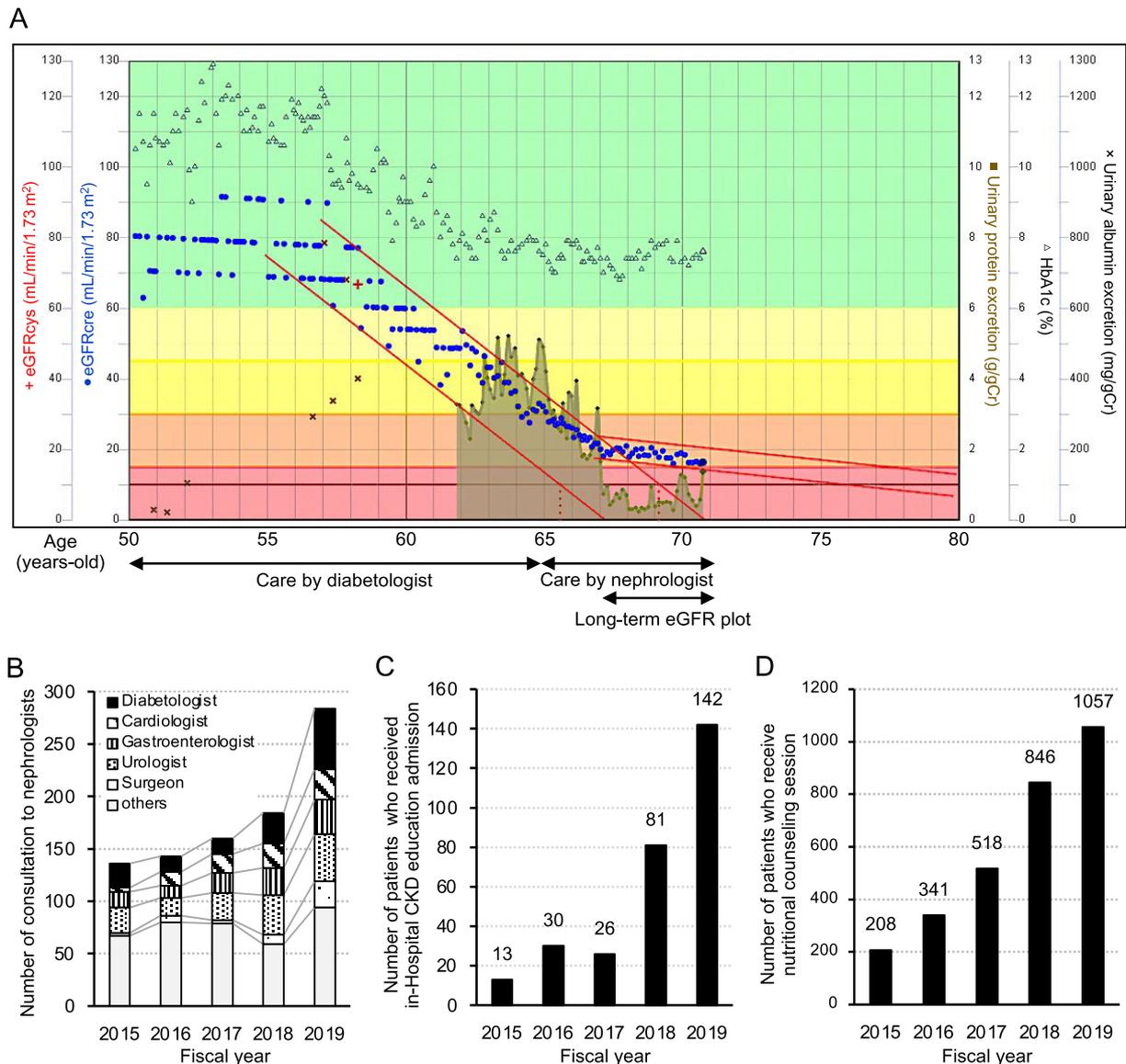
Figure 5.   **Effect of the introduction of long-term eGFR plots on CKD care. (A) An automated long-term eGFR plot system was introduced to the Otsu City Hospital. Historical data accumulated at the hospital could be immediately displayed on a single screen. Creatinine-based eGFR, cystatin C-based eGFR (eGFRcys), HbA1c, urinary protein excretion, and urinary albumin excretion could be depicted simultaneously, and changes in the eGFR decline over time could be easily recognized. Under the long-term eGFR plot, the time period during which the patient was treated by the diabetologist and nephrologist and the time period during which the long-term eGFR plot was used were added. (B) Number of patients consulting nephrologists from the indicated departments between 2015 and 2019. The use of long-term eGFR plots was introduced in 2016. (C) Number of patients who were admitted for in-hospital CKD education between 2015 and 2019. (D) Number of patients who attended a nutritional counseling session to prevent the progression of kidney disease between 2015 and 2019.**

admissions and nutritional counseling sessions. Thus, the introduction of long-term eGFR plots has the potential to increase the quality of CKD practice.

The fact that clinicians often judge that the eGFR is not declining as a result of only considering the short-term trend in the eGFR may be a common problem in nephrology practice. Therefore, we believe that the identification of patients with progressive decreases in the renal function who

are not under treatment by a nephrologist is important to improve CKD care. In a region with a limited number of nephrologists, the challenge is to build a community-based system that integrates all eGFR data obtained during health checks, including data collected by family doctors and in hospitals. If such a system could be established, it might be possible to diagnose CKD at an earlier stage.

Although reciprocal creatinine (1/Cr) plots have been used

to predict the decline in the renal function, it is not widely used in daily practice, as it requires generating 1/Cr plots. However, calculated eGFR values have usually been available in most cases, making these values easier to use than 1/Cr plots for not only nephrologists but also non-nephrologists. Unlike 1/Cr, the eGFR is a measure of the renal function itself. Therefore, it is easier for physicians and patients to understand the renal function when using the eGFR rather than 1/Cr. In addition, 1/Cr has been used mainly for predicting the timing of dialysis induction, but with the eGFR, which represents renal function itself, it can be used for not only predicting the timing of dialysis induction but also predicting the timing of drug changes and CKD referral due to a decreased renal function. It is expected that physicians in all departments will have more opportunities to treat patients with CKD as a comorbidity in the future. This expectation is supported by the fact that the number of consultations to nephrologists has increased rapidly in our hospital since we established a system that allows the use of long-term eGFR plots, regardless of the department, as shown in Fig. 5. A system that allows for the easy use of the long-term eGFR plot across many institutions would be extremely useful.

Several limitations associated with the present study warrant mention. Data from a relatively small number of patients from a single institution were analyzed, and all of these patients were eventually referred to a nephrologist; therefore, there was some selection bias. Further studies are required to determine whether or not the conclusions are valid for other populations. Furthermore, although the present analysis used the Japanese creatinine-based eGFR (6), whether or not the results would be similar for the cystatin C-based eGFR or other eGFR formulas, such as the CKD-Epidemiology Collaboration (EPI) equation, is unclear (14). Finally, although we suggest the importance of being aware of eGFR fluctuation, the method we used to evaluate eGFR fluctuation in this paper needs further validation.

Conclusion

The "long-term eGFR plot", which displays the trend in the eGFR over as long a period of time as possible, minimizes the effect of eGFR fluctuation on the detection of a decline in the renal function. In addition to its utility for the diagnosis of CKD using the current CKD criteria, the use of the "long-term eGFR plot" in a hospital or community is an effective means of identifying patients with occult CKD, and we expect it to contribute to an improvement in CKD care in the future.

The authors state that they have no Conflict of Interest (COI).

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