High Versus Low Visit-to-visit Variability in Estimated Glomerular Filtration Rate Predicts Progression to End-stage Renal Disease

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Abstract

Background: It is known that subtle increases in serum creatinine (sCr) levels affect prognosis in patients with acute kidney injury. However, the impact of visit-to-visit variability in estimated glomerular filtration rate (eGFR) on renal prognosis is not understood.

Methods: We studied 215 pre-dialysis patients attending our clinic who had more than 4 serial sCr measurements before 24-hour ABPM between 2005 and 2011. To evaluate eGFR variability, we assessed the difference between observed eGFR value and slope predicted eGFR value and converted it into coefficient of variation value. The primary endpoint was progression to end-stage renal disease (ESRD), the initiation of maintenance dialysis, or uremic death with conservative management.

Results: Among 215 patients with a median follow-up of 4.3 years, there were 39 ESRD events in the high eGFR variability group and 28 ESRD events in the low eGFR variability group (log-rank test, \(p = 0.047\)). Furthermore, high eGFR variability was shown to be a good predictor of progression to ESRD in a sub-analysis of patients with low proteinuria, a less steep eGFR slope, or without hypertension (log-rank test, \(p = 0.039\), \(p = 0.048\), \(p = 0.048\), respectively). In multivariate Cox regression analysis, high proteinuria, low baseline eGFR, and steep eGFR trend but not high eGFR variability were significantly associated with ESRD (\(p = 0.047\), \(p = 0.001\), \(p = 0.016\), \(p = 0.31\), respectively).

Conclusion: High eGFR variability was a good marker of adverse renal prognosis in CKD patients, especially in patients with low proteinuria, slowly progressive CKD, or without hypertension. Further attention is warranted for ambulatory patients with large eGFR fluctuations.

Key words
chronic kidney disease (CKD), renal prognosis, estimated glomerular filtration rate (eGFR) variability

Introduction

There is accumulating evidence that subtle increases in serum creatinine (sCr) levels, even if reversible, are associated with overall mortality or poor renal prognosis\(^{[1-3]}\) in the setting of acute kidney injury (AKI), especially post-surgery\(^{[6,7]}\), in patients with a critical illness\(^{[8-10]}\) and in patients with contrast-induced nephropathy\(^{[11,12]}\).

Ambulatory patients with chronic kidney disease (CKD) often experience visit-to-visit fluctuations in estimated glomerular filtration rate (eGFR). However, to date, the significance of this visit-to-visit variability is largely unknown. A few recent studies have shown an association of eGFR variability with mortality\(^{[13,14]}\), but to the best of our knowledge, there is no report addressing the association of eGFR variability with renal prognosis. We conducted a study in ambulatory patients with CKD to determine whether eGFR variability is associated with renal prognosis.
Materials and methods

Study design, participants, and measurements

This was a single-center, retrospective, observational cohort study. All participants were attending our outpatient clinic for pre-dialysis CKD and were enrolled in the atherosclerosis study conducted in our institute from February 2005. The Committee on Human Research at the St. Marianna University School of Medicine approved the study protocol (No. 1156). All patients provided written, informed consent before inclusion in the study. At first, we studied the patients who had undergone 24-hour ambulatory blood pressure monitoring (ABPM) at our outpatient clinic from February 2005 to October 2011 and defined the day as baseline. Enrolled participants (1) were aged \( \geq 20 \) years, (2) had eGFR measured \( \geq 5 \) times at \( \geq 2 \)-week intervals within 18 months, (3) had baseline eGFR levels < 60 ml/min/1.73m\(^2\), and (4) had never initiated maintenance dialysis. Analysis of sCr was calibrated against an isotope dilution mass spectrometry reference standard. No changes in calibration techniques occurred during the study. The eGFR value was calculated using revised equations from sCr values in Japan\(^{15} \).

Baseline data were collected at the baseline visit that was the fifth eGFR measurement and included urine protein to creatinine ratio (g/gCr), serum albumin, low-density lipoprotein, triglycerides, uric acid, corrected calcium value obtained by albumin value, and inorganic phosphorus (IP) levels. Each sample was collected at our single laboratory with patients in a fasting state. All patients then underwent 24-hour ABPM monitoring with oscillometric A&D Model TM2430 equipment (A&D Medical, Milpitas, CA, USA). We also evaluated the impact of atherosclerosis using brachial-ankle pulse wave velocity (baPWV). The baPWV was measured with the BP203RPEII (Omron-Colin, Tokyo, Japan) according to the manufacturer’s instructions.

End points

The primary end point was end-stage renal disease (ESRD), which was defined by the initiation of maintenance dialysis or uremic death with conservative management. The secondary end point was hospitalization due to the following cardiovascular events: ischemic heart disease, heart failure, stroke, aortic dissection, aortic aneurysm, peripheral artery disease (PAD), or death from any of these causes. We calculated survival time from baseline until occurrence of the first event or end of follow up through October 2013. In addition, we investigated the cumulative probability of the primary end point and performed multiple sub-analyses after classifying patients into the following 5 categories: having urinary protein \( \geq 0.5 \) g/gCr or not, having a steep regression line of eGFR (defined as eGFR slope) or not (see “Variability parameters of eGFR” below), having hypertension or not, having diabetes mellitus or not, and having eGFR higher than median eGFR or not.

Study covariates

Variables considered included smoking status, current medications, comorbid conditions, vital signs, and laboratory data. If a laboratory test value was not available during the observation period, it was considered not ordered. Hypertension was defined as mean systolic blood pressure \( \geq 130 \) mmHg and/or mean diastolic blood pressure \( \geq 80 \) mmHg measured by 24-hr ABPM\(^{16} \). Diabetes mellitus was defined by a self-reported medical history, antidiabetic agent use, a fasting blood glucose level \( \geq 6.99 \) mmol/L, and/or a hemoglobin A1c (HbA1c) \( \geq 6.5\% \) at baseline. The HbA1c was measured using the National Glycohemoglobin Standardization Program.

Variability parameters of eGFR

Several analytical methods have been adopted to evaluate eGFR variability, such as variance or standard deviation (SD). Because eGFR shows large changes by CKD stage, the coefficient of variation (CV), which is the ratio of the SD to the mean, is an efficient analysis method to evaluate eGFR variability. However, because the eGFR-CV is greatly affected by eGFR slope, measurement of eGFR variability that eliminates the effect of the eGFR slope is preferable (Fig. 1). Therefore, we calculated the difference between observed value and slope-predicted eGFR value, which was used in a recent analysis of the association between hemoglobin variability and mortality\(^{17-19} \), and converted it into the CV value (defined as residual eGFR-CV). We divided residual eGFR-CV and the eGFR slope into 2 categories according to each median value. After that, we defined high eGFR variability as any value greater than or equal to the median value of residual eGFR-CV and defined a steep eGFR slope as any slope that was less than or equal to its median value.

Statistical analysis

In bivariate analyses, we examined the associa-
tion of variability status and measures of interest using the chi-square test and Mann-Whitney U-test, as appropriate. We calculated the cumulative probability of study end points using the Kaplan-Meier procedure and log-rank test. We investigated whether baseline covariates were associated with end points using univariate Cox regression analyses. Multivariate Cox regression analysis was used to estimate the hazard ratios (HR) and 95% confidence intervals after adjustment for baseline covariates. For all analyses, we considered a two-tailed p value < 0.05 to be statistically significant. All statistical analyses were performed using SPSS software (version 22.0, SPSS Inc., Chicago, IL, USA).

**Results**

**Patient characteristics**

Between February 2005 and October 2011, 1560 patients were screened, and overall 215 CKD patients were eligible. Participants were followed for a median of 4.3 years (interquartile range [IQR], 2.2 to 5.7). At baseline, median age was 70.0 years (IQR, 60.0 to 76.0), and median eGFR was 31.7 ml/min/1.73m² (IQR, 18.2 to 45.8). Hypertensive nephrosclerosis (47.4%) was the most common primary renal disease, followed by diabetic nephropathy (20.9%) and glomerular disease (18.6%). Median eGFR slope was -2.6 ml/min/1.73m²/year (IQR, -7.5 to 1.9), and median residual eGFR-CV was 0.054 (IQR, 0.037 to 0.072). Table 1 shows baseline characteristics of all study participants and the two groups according to eGFR variability.

**Progression to ESRD or cardiovascular event**

During follow-up, 67 patients developed ESRD (54 hemodialysis, 10 peritoneal dialysis, and 3 uremic deaths with conservative management), and 23 were hospitalized due to a cardiovascular event (7 ischemic heart diseases, 8 strokes, 2 aortic dissections, 2 aortic aneurysms, 3 heart failures, and 1 PAD). There were 23 deaths from any cause, and 7 were due to cardiovascular events (2 from myocardial infarction, 1 from stroke, 2 from aortic aneurysm rapture, 1 from aortic dissection, and 1 from heart failure).

**Primary end point**

There was a significant increase in the primary end point in the high eGFR variability group compared with the low eGFR variability group (log-rank
test, $p = 0.047$) (Fig. 2). Thirty-nine patients in the high variability group and 28 patients in the low variability group reached the primary end point. To examine the utility of eGFR variability as a prognostic indicator in any group of patients, we conducted a sub-analysis stratified by known risk factors including degree of proteinuria, eGFR slope, blood pressure level, diabetes status, and eGFR level. In this sub-analysis, high eGFR variability was significantly associated with the primary end point only in the subgroup of patients with urinary protein < 0.5 g/gCr, a less steep eGFR slope, and without hypertension (log-rank test, $p = 0.039$, $p = 0.048$, $p = 0.048$ respectively) (Fig. 3a-j).

### Table 1. Baseline Characteristics of Patients Overall and 2 Groups Divided by Estimated Glomerular Filtration Rate (eGFR) Variability

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (n=215)</th>
<th>Low eGFR variability* (n=108)</th>
<th>High eGFR variability* (n=107)</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>145 (67.4)</td>
<td>79 (36.7)</td>
<td>66 (30.7)</td>
<td>0.073</td>
</tr>
<tr>
<td>Smoker</td>
<td>122 (56.7)</td>
<td>65 (32.7)</td>
<td>57 (28.2)</td>
<td>0.42</td>
</tr>
<tr>
<td>HTN</td>
<td>146 (67.9)</td>
<td>74 (34.4)</td>
<td>72 (33.5)</td>
<td>0.85</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>67 (31.2)</td>
<td>22 (10.3)</td>
<td>45 (21.1)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>171 (79.5)</td>
<td>87 (40.5)</td>
<td>84 (39.0)</td>
<td>0.74</td>
</tr>
<tr>
<td>CCB</td>
<td>156 (72.6)</td>
<td>73 (34.0)</td>
<td>83 (38.6)</td>
<td>0.13</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>37 (17.2)</td>
<td>15 (7.0)</td>
<td>22 (10.2)</td>
<td>0.21</td>
</tr>
<tr>
<td>HMG CoA reductase inhibitor</td>
<td>60 (27.9)</td>
<td>31 (14.4)</td>
<td>29 (13.5)</td>
<td>0.88</td>
</tr>
<tr>
<td>Age, years</td>
<td>70.0 (60.0 to 76.0)</td>
<td>71.0 (59.0 to 76.0)</td>
<td>70.0 (60.0 to 76.0)</td>
<td>0.94</td>
</tr>
<tr>
<td>BMI, kg/m$^2$</td>
<td>23.3 (21.1 to 25.4)</td>
<td>22.9 (21.1 to 25.1)</td>
<td>23.4 (21.1 to 25.5)</td>
<td>0.29</td>
</tr>
<tr>
<td>Urinary protein, g/gCr</td>
<td>0.57 (0.18 to 1.88)</td>
<td>0.42 (0.15 to 1.56)</td>
<td>0.67 (0.20 to 2.55)</td>
<td>0.061</td>
</tr>
<tr>
<td>LDL, mmol/L</td>
<td>2.92 (1.84 to 3.80)</td>
<td>3.22 (2.68 to 3.77)</td>
<td>2.61 (1.50 to 3.28)</td>
<td>0.15</td>
</tr>
<tr>
<td>TG, mmol/L</td>
<td>1.40 (0.95 to 1.93)</td>
<td>1.53 (1.01 to 2.09)</td>
<td>1.31 (0.89 to 1.78)</td>
<td>0.045</td>
</tr>
<tr>
<td>Uric acid, mmol/L</td>
<td>416 (357 to 506)</td>
<td>416 (345 to 500)</td>
<td>410 (363 to 512)</td>
<td>0.63</td>
</tr>
<tr>
<td>Corrected Ca, mmol/L</td>
<td>2.22 (2.15 to 2.35)</td>
<td>2.25 (2.17 to 2.32)</td>
<td>2.22 (2.12 to 2.37)</td>
<td>0.55</td>
</tr>
<tr>
<td>IP, mmol/L</td>
<td>1.16 (1.0 to 1.29)</td>
<td>1.13 (0.97 to 1.26)</td>
<td>1.19 (1.03 to 1.32)</td>
<td>0.015</td>
</tr>
<tr>
<td>eGFR, mL/s/1.73m$^2$</td>
<td>31.7 (18.2 to 45.8)</td>
<td>36.1 (23.0 to 48.7)</td>
<td>25.0 (16.0 to 43.2)</td>
<td>0.008</td>
</tr>
<tr>
<td>eGFR slope$^c$, mL/s/1.73m$^2$/year</td>
<td>-2.6 (-7.5 to 1.9)</td>
<td>-2.1 (-7.0 to 2.0)</td>
<td>-3.2 (-8.9 to 1.6)</td>
<td>0.29</td>
</tr>
<tr>
<td>Residual eGFR-CV$^d$</td>
<td>0.054 (0.037 to 0.072)</td>
<td>0.037 (0.027 to 0.047)</td>
<td>0.072 (0.062 to 0.103)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>baPWV, cm/sec</td>
<td>1572 (1367 to 1841)</td>
<td>1505 (1296 to 1807)</td>
<td>1652 (1427 to 1890)</td>
<td>0.031</td>
</tr>
</tbody>
</table>

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; baPWV, brachial-ankle Pulse Wave Velocity; BMI, body mass index; CCB, calcium channel blocker; CV, coefficient of variation; eGFR, estimated glomerular filtration rate; HTN, hypertension; HMG CoA reductase, 3-hydroxyl-glutaryl-CoA reductase; IP, inorganic phosphorus; IQR, 25%-75% interquartile range; LDL, low-density lipoprotein; TG, triglyceride.

*Low eGFR variability was defined as less than the median value of residual eGFR-CV.

*High eGFR variability was defined as greater than or equal to median value of residual eGFR-CV.

*eGFR slope was derived from the regression line of eGFR.

*residual eGFR-CV was derived from the difference between observed value and slope-predicted eGFR value and converted into the CV value.
eGFR variability and renal prognosis

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are more likely to develop ESRD. Besides, there is considerable evidence that increased urinary protein level, diabetes, and hypertension are risk factors for adverse renal prognosis\(^{20-22}\). On the other hand, we have seen even in patients with low risk factors, such as low urinary protein, slowly progressive CKD, or normotension, some of them progress to ESRD. Then, we examined the subgroup analysis with these prognostic factors to evaluate the significance of eGFR variability. In the sub-analysis, high eGFR variability was significantly associated with the primary end point in the subgroup of patients with low urinary protein level, slowly progressive CKD, and no hypertension (Fig. 3a, 3c, 3e). Thus, high eGFR variability seems to be a good prognostic marker for ESRD in such low risk patients. Furthermore, concerning the patients with high risk of high proteinuria, rapidly progressive CKD, or hypertension, cumulative event rates were higher in the high eGFR variability group than in the low eGFR variability group, especially in the first half of the observation period (Fig. 3b, 3d, 3f). In the sub-analysis of the category of patients with or without diabetes, although it was not statistically significant, cumulative event rates tended to be higher in the high eGFR variability group than in the low eGFR variability group, both in patients with and without diabetes mellitus,

We then investigated the relationship between different variables and the primary end-point using univariate Cox regression analyses (Table 2). In addition to high eGFR variability, hypertension, diabetes, urinary protein \(\geq 0.5\) g/gCr, baseline eGFR level graded by 10 ml/min/1.73m\(^2\), and steep eGFR slope were significantly associated with the primary end point. However, in multivariate Cox regression analysis, only high proteinuria, low baseline eGFR, and steep eGFR were significantly associated with the primary end point (Table 3).

**Secondary end point**

There were 8 secondary end point events in the low variability group (34.8%) compared with 15 secondary end point events in the high eGFR variability group (65.2%), with no significant differences between groups (log-rank test, \(p = 0.082\)) (Fig. 4).

**Discussion**

In this study, we confirmed that high eGFR variability was associated with adverse renal prognosis. However, high eGFR variability was not significantly associated with ESRD in multivariate analysis with known renal risk factors. It is natural to assume that patients with low baseline eGFR or rapidly progressive CKD recognized by steep negative eGFR slope are more likely to develop ESRD. Besides, there is considerable evidence that increased urinary protein level, diabetes, and hypertension are risk factors for adverse renal prognosis\(^{20-22}\). On the other hand, we have seen even in patients with low risk factors, such as low urinary protein, slowly progressive CKD, or normotension, some of them progress to ESRD. Then, we examined the subgroup analysis with these prognostic factors to evaluate the significance of eGFR variability. In the sub-analysis, high eGFR variability was significantly associated with the primary end point in the subgroup of patients with low urinary protein level, slowly progressive CKD, and no hypertension (Fig. 3a, 3c, 3e). Thus, high eGFR variability seems to be a good prognostic marker for ESRD in such low risk patients. Furthermore, concerning the patients with high risk of high proteinuria, rapidly progressive CKD, or hypertension, cumulative event rates were higher in the high eGFR variability group than in the low eGFR variability group, especially in the first half of the observation period (Fig. 3b, 3d, 3f). In the sub-analysis of the category of patients with or without diabetes, although it was not statistically significant, cumulative event rates tended to be higher in the high eGFR variability group than in the low eGFR variability group, both in patients with and without diabetes mellitus,
(a) Urinary protein < 0.5 g/gCr

(b) Urinary protein ≥ 0.5 g/gCr

(c) Less steep eGFR slope

(d) Steep eGFR slope

(e) No hypertension

(f) Hypertension
(g) Non-diabetes mellitus

Log-rank test, $p = 0.085$

(h) diabetes mellitus

Log-rank test, $p = 0.89$

(i) eGFR $>$ median

Log-rank test, $p = 0.77$

(j) eGFR $\leq$ median

Log-rank test, $p = 0.24$

Fig. 3. Kaplan-Meier analyses of the primary end point and its components.
There were significant differences in the high estimated glomerular filtration rate (eGFR) variability group compared with the low eGFR variability group divided into urinary protein $\geq 0.5$ g/gCr or not, steep eGFR slope or not, hypertension or not, diabetes mellitus or not, and eGFR was higher than median eGFR or not.
Table 2. Univariate Analysis for Primary End Point

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>1.56</td>
<td>0.89-2.74</td>
<td>0.12</td>
</tr>
<tr>
<td>Age</td>
<td>1.00</td>
<td>0.98-1.02</td>
<td>0.75</td>
</tr>
<tr>
<td>BMI</td>
<td>1.01</td>
<td>0.94-1.08</td>
<td>0.86</td>
</tr>
<tr>
<td>Smoker</td>
<td>1.14</td>
<td>0.68-1.90</td>
<td>0.62</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.22</td>
<td>1.21-4.07</td>
<td>0.01</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.99</td>
<td>1.22-3.25</td>
<td>0.006</td>
</tr>
<tr>
<td>Urinary protein ≥ 0.5 g/gCr</td>
<td>4.96</td>
<td>2.70-9.11</td>
<td>0.001</td>
</tr>
<tr>
<td>eGFR^a</td>
<td>3.40</td>
<td>2.57-4.48</td>
<td>0.001</td>
</tr>
<tr>
<td>Steep eGFR slope^b</td>
<td>2.25</td>
<td>1.36-3.73</td>
<td>0.002</td>
</tr>
<tr>
<td>High eGFR variability^c</td>
<td>1.63</td>
<td>1.00-2.65</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate.
^a eGFR was graded by 10 ml/min/1.73m².
^b Steep eGFR slope was defined as less than or equal to the median value of eGFR slope.
^c High eGFR variability was defined as greater than or equal to the median value of residual eGFR-coefficient of variation.

Table 3. Multivariate Cox Regression Model Analysis for Primary End Point

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>1.96</td>
<td>0.99-3.90</td>
<td>0.055</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.05</td>
<td>0.62-1.78</td>
<td>0.86</td>
</tr>
<tr>
<td>Urinary protein ≥ 0.5 g/gCr</td>
<td>1.97</td>
<td>1.01-3.85</td>
<td>0.047</td>
</tr>
<tr>
<td>eGFR^a</td>
<td>3.25</td>
<td>2.42-4.37</td>
<td>0.001</td>
</tr>
<tr>
<td>Steep eGFR slope^b</td>
<td>1.93</td>
<td>1.13-3.30</td>
<td>0.016</td>
</tr>
<tr>
<td>High eGFR variability^c</td>
<td>1.33</td>
<td>0.77-2.27</td>
<td>0.31</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate.
^a eGFR was graded by 10 ml/min/1.73m².
^b Steep eGFR slope was defined as less than or equal to the median value of eGFR slope.
^c High eGFR variability was defined as greater than or equal to the median value of residual eGFR-coefficient of variation.

Fig. 4. Kaplan-Meier plots of the time to the first event of secondary end points.
High estimated glomerular filtration rate (eGFR) variability was defined as values greater than or equal to its median value and low variability was defined as values less than its median value. Cumulative incidence of secondary end point by Kaplan-Meier curves and log-rank test differed significantly by high eGFR variability group (log-rank test, p = 0.082).
and the difference between the curves was especially pronounced in non-diabetic patients (Fig. 3g, 3h). Diabetes mellitus is a well-known cause of ESRD, and the event rate in patients with diabetes mellitus was quite high in this study. It seems likely that the high incidence of ESRD masked the significance of eGFR variability in patients with diabetes mellitus. Sub-analysis in patients with a different baseline eGFR level showed different patterns of Kaplan-Meier curves between two groups. In the high baseline eGFR group, cumulative event rates became higher only at the end of the observation period in the high eGFR variability group (Fig. 3i). Since it takes time to ESRD in patients with a high baseline eGFR, the effect of eGFR variability would only be apparent after a period of time. On the other hand, cumulative event rates were higher in the high eGFR variability group than in the low eGFR variability group among patients with a low baseline eGFR, especially in the first half of the observation period (Fig. 3j). Although the effect of eGFR variability on renal prognosis became obscure in high-risk patients as described above, high eGFR variability still seems to be a good prognostic marker for the progression to ESRD, especially in low-risk patients.

The purpose of this study is not to elucidate the pathogenesis or cause of ESRD. However, we at least need to speculate why high eGFR variability was associated with bad prognosis. As baseline characteristics showed the relations between high eGFR variability and high values of IP and baPWV (Table 1), it is likely that high eGFR variability is a marker of more severe systemic atherosclerosis, which is apparently associated with bad cardiovascular risk, including ESRD. It is possible to speculate that increases in eGFR variability might be derived from poor adaptation to renal hemodynamic changes augmented by intra-renal arteriosclerosis. It is known that one of the main pathogeneses of diabetic nephropathy is arteriosclerosis (20). In this study, significantly higher incidence of high eGFR variability compared with low eGFR variability in patients with diabetes at baseline also supports this inference. The relationship of atherosclerosis with high eGFR variability may account for current reports regarding high eGFR variability and mortality (13). Although we could not find an association between high eGFR variability and cardiovascular events (Fig. 4), there was a trend towards this association. Although the Japanese population generally exhibits a lower incidence of cardiovascular disease compared with Western countries (23), we cannot exclude the possibility that, had the sample size been bigger or follow-up longer, differences between eGFR variability and cardiovascular event variability might have reached significance.

In the setting of AKI, there is evidence that subtle increases in sCr levels, even if reversible, are associated with poor renal prognosis (11–21). In this respect, AKI is similar to eGFR variability, and it is possible that eGFR variability could represent a condition of repeated mild AKI. However, it is not clear whether eGFR variability indicates a process of repeated mild AKI or a result of renal auto-regulation dysfunction or another indeterminate condition; in any case, even a subtle decrease in renal function could predict a worse renal prognosis.

Decreases in eGFR values are generally regarded as a bad sign; however, if these findings are followed by an increase in eGFR, it may be good. In fact, the Kidney Disease Improving Global Outcomes guidelines (25) state “small fluctuations in GFR are allowed by an increase in eGFR, it may be good. In fact, the Kidney Disease Improving Global Outcomes guidelines (25) state “small fluctuations in GFR are common and do not necessarily indicate progression.” On the other hand, based on the present study, fluctuations in eGFR may not be favorable. It seems likely that patients with large fluctuations in eGFR values at a certain time will show worse renal prognosis. Therefore, rather than viewing an increase in eGFR simply as a positive sign, we should pay more attention in daily clinical practice to its variations; that is, in addition to eGFR slope, eGFR variability also seems to be a useful predictor of renal prognosis, especially in patients with low proteinuria, slowly progressive CKD, and without hypertension.

This study has several limitations. First, it was performed in a single medical facility and included a small number of patients. Multi-center trials with more participants are needed. Second, because we cannot predict eGFR variability, only observational studies can be conducted. We can only conduct a prospective clinical trial if we can identify factors that affect eGFR variability. Third, considering that the high eGFR variability group tended to be higher in diabetes and lower in baseline eGFR, and that high eGFR variability was not significantly associated with ESRD in multivariate analysis, eGFR variability could only be a marker of poor renal prognosis.

**Conclusion**

High eGFR variability was a good marker for predicting adverse renal prognosis, especially in patients with low proteinuria, slowly progressive CKD, and without hypertension in whom good prognostic
markers were not previously identified. In daily clinical practice, we should pay more attention to large eGFR fluctuations, as well as proteinuria, high blood pressure, and steep slope of sCr to identify patients at greater risk of progressing to ESRD.

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Conflict of interest: The authors have declared that no conflict of interest exists.

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