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ORIGINAL ARTICLE

# Variability in estimated glomerular filtration rate and patients' outcomes in a real-world heart failure population

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## Abstract

**Aims** The prognostic significance of renal function variability has not been fully elucidated in heart failure (HF). This multicentre, prospective cohort study aimed to evaluate the usefulness of visit-to-visit variability in estimated glomerular filtration rate (eGFR) for predicting patients' outcomes in a real-world HF population.

**Methods** A total of 564 patients who had survived HF hospitalization were randomly assigned with a 2:1 ratio to derivation and validation cohorts, and they were then followed after discharge. Using the data for 6 months after discharge, each patient's visit-to-visit eGFR variability (EGV) was estimated. In the derivation cohort, Cox regression analyses were performed to assess the association of EGV with a subsequent composite event (death and HF hospitalization). In the validation cohort, the predictive performance was compared among Cox regression models with EGV, those with B-type natriuretic peptide (BNP) and those with eGFR.

**Results** In the derivation cohort (376 patients), median age, left ventricular ejection fraction (LVEF), BNP and eGFR at discharge were 72 years, 53.3%, 134.8 pg/mL and 58.7 mL/min/1.73 $m^2$, respectively. During a median follow-up of 2.2 years, higher EGV was associated with an increased risk of the composite event (adjusted hazard ratio [per standard deviation increase in log-transformed EGV], 1.5; 95% confidence interval, 1.1–2.0). A similar finding was observed in a stratified analysis by LVEF. In the validation cohort (188 patients), better model fit, discrimination, reclassification and calibration were observed for EGV than for 6-month averaged BNP or eGFR for predicting the composite event when added to HF risk prediction models. Adding EGV to models with BNP or eGFR improved model discrimination and reclassification.

**Conclusions** EGV predicts HF outcomes regardless of LVEF. Risk prediction models with EGV have good performance in real-world HF patients. The study findings highlight the clinical importance of observing visit-to-visit fluctuations in renal function in this population.

**Keywords** Heart failure (HF); Risk prediction; eGFR variability; B-type natriuretic peptide (BNP); Estimated glomerular filtration rate (eGFR)

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## Introduction

Heart failure (HF) is a growing public health problem worldwide. Despite remarkable advances in diagnosis and treatment over the last several decades, HF remains a major cause of mortality, morbidity and hospitalization.[1–4] To make matters worse, the number of patients with HF has been increasing worldwide, recently reaching 38 million.[5] Therefore,

the medical costs associated with HF are expected to increase, with projected costs of $70 billion in the United States by 2030.[2] Given these circumstances, accurate and economical risk classifications are needed in order to optimize therapies for patients based on their own specific risks.

The use of the natriuretic peptides (NPs) for HF risk classifications is associated with several limitations. Admittedly, NPs themselves predict cardiac outcomes in both acute decompensated heart failure (ADHF) and stable HF. In addition, B-type natriuretic peptide (BNP) at discharge was reported to improve the performance of the MAGGIC prediction model,[6] an established HF risk prediction model.[7] However, frequent measurements of NPs would be a substantial economic burden on patients and healthcare systems because of their high measurement costs. In addition, the high prevalence (40–50%) of chronic kidney disease (CKD) in HF patients[8] raises a concern that NP levels are strongly affected by renal function in patients with an estimated glomerular filtration rate (eGFR) $<$ 60 mL/min/1.73 m$^2$.[9–12]

Renal function variability may be a novel biomarker for HF risk classification regardless of left ventricular ejection fraction (LVEF). In CKD, visit-to-visit eGFR variability (EGV) predicts mortality[13,14] and end-stage renal disease.[15] In HF, a cross-sectional eGFR predicts cardiac outcomes regardless of LVEF.[16,17] Based on eGFR longitudinal data, EGV may provide additional prognostic information beyond a single eGFR, probably reflecting variability in renal haemodynamics in HF. From the viewpoint of medical economics, EGV can be a useful biomarker because measuring serum creatinine, from which EGV is derived, costs much less than measuring NPs.

The present study aimed to (1) investigate whether EGV predicts cardiac outcomes in a real-world HF population, including a substantial number of patients with HF with reduced ejection fraction (HFrEF) or renal dysfunction, and (2) compare the usefulness of EGV with BNP and eGFR for predicting cardiac outcomes in this population.

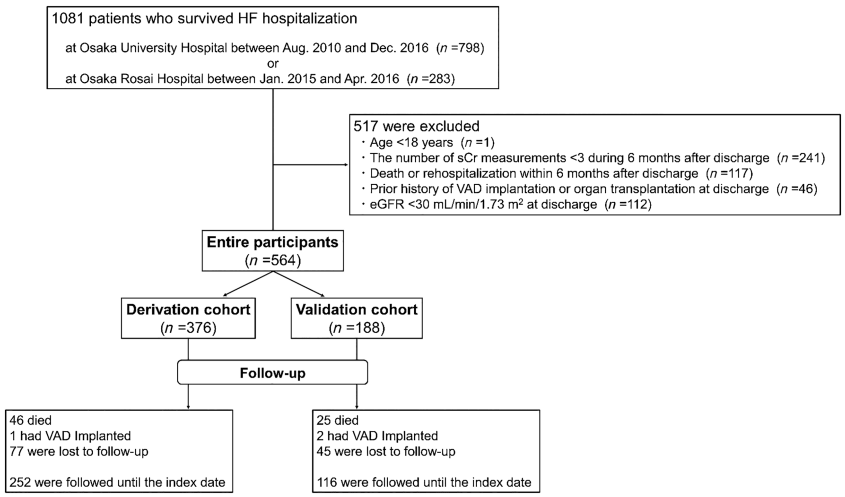
# Methods

## Study design and population

In this multicentre, prospective cohort study, consecutive patients who had survived hospitalization with ADHF in Osaka University Hospital between August 2010 and December 2016 or Osaka Rosai Hospital between January 2015 and April 2016 were enrolled (*Figure 1*). The diagnosis of ADHF was based on the Framingham criteria.[18] Patients who met at least one of the following criteria were excluded: (1) age $<$18 years; (2) the number of serum creatinine measurements (eGFR measurements) $<$ 3 during the 6 months just after discharge; (3) death or rehospitalization within 6 months after discharge; (4) a prior history of ventricular assist device (VAD) implantation or solid organ transplantation at discharge; or (5) eGFR $<$ 30 mL/min/1.73 m$^2$ at discharge (*Figure 1* and *Table S1*). Each patient's EGV was estimated using the data for 6 months after discharge ('EGV definition period'). The follow-up period was from 6 months after discharge to the date of death, VAD implantation, heart transplantation or the last visit before the index date (31 May 2017 in Osaka University Hospital or 31 December 2018 in Osaka Rosai Hospital).

This study was conducted in accordance with the Declaration of Helsinki. All patients provided written, informed consent. The Ethics Committees in the facilities approved the study (approval number: 18155).

**Figure 1** Flow diagram of the study.



## Baseline characteristics and laboratory measurements

Patients' characteristics were collected at enrolment. Data at discharge were used as baseline laboratory data. Transthoracic echocardiography was performed just before discharge by experienced sonographers blinded to the clinical details. The eGFRs were calculated using the following Japanese standard formula: $194 \times \text{creatinine}^{-1.094} \times \text{age}^{-0.287}$ (if female, ×0.739).[19] CKD was defined as baseline eGFR $<$ 60 mL/min/1.73 m$^2$. HFrEF was defined as baseline LVEF $<$ 40%, and HF with preserved ejection fraction (HFpEF) was defined as LVEF $\geq$ 40%. Patients with missing data for these variables were excluded from each multivariable analysis.

## Exposure of interest and study outcomes

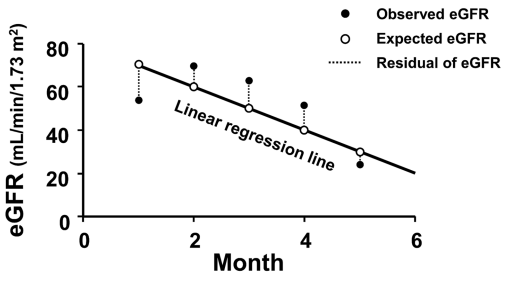
As an exposure of interest, EGV was estimated in each patient. Using the data for 6 months after discharge (EGV definition period), each patient's eGFR was linearly regressed against time, and EGV was calculated as '(mean sqrt [residual of eGFR]$^2$)/(mean observed eGFR) × 100 (%)' (*Figure 2*).

The outcomes of interest were time to death or HF hospitalization, whichever occurred first, and the number of HF hospitalizations and death during the follow-up period.

## Derivation and validation cohorts

Patients were randomly assigned with a 2:1 ratio to derivation and validation cohorts (*Figure 1*). The derivation cohort was used to examine the association of EGV with the composite event (death and HF hospitalization) and develop Cox regression models with covariates, including EGV, BNP or eGFR. Then, the regression coefficients from these models were fixed. By applying the fitted models to the validation cohort, the usefulness of these biomarkers for predicting study outcomes was compared.

**Figure 2** Estimation of eGFR variability in each patient.Observed eGFRs for 6 months just after discharge were linearly regressed against time. A residual of eGFR was defined as the difference between the observed eGFR and the expected eGFR by the linear regression.




**eGFR variability**
**= (mean sqrt [residual of eGFR]$^2$) / (mean observed eGFR) ×100 (%)**

## Statistical analyses

### *Descriptive statistics*

Data are presented as means (standard deviation [SD]), medians (interquartile range [IQR]) or percentages. Between-group differences were evaluated by Student's *t*-test, the Mann–Whitney test, ANOVA, the Kruskal–Wallis test, Pearson $\chi^2$ test or Fisher's exact test, as appropriate. Statistical tests were two-tailed with $P < 0.05$ considered significant. All statistical analyses were performed using Stata/IC 14.0 software (StataCorp, College Station, TX, USA).

### *Analyses in the derivation cohort*

Factors associated with EGV were identified using the baseline data. A multivariable logistic regression analysis was performed to estimate the odds ratio (OR) of the highest quartile of EGV for each variable.

On time-to-event analyses, Kaplan–Meier curves stratified by quartiles of EGV were estimated. Hazard ratios (HRs) of the composite event (death and HF hospitalization) were calculated by EGV, both as categorical (quartiles) and continuous (SD of log-transformed EGV) variables, using Cox regression models stratified by facility. The stratified approach was used, considering the potential difference in clinical practice patterns between facilities. The multivariable models were adjusted for age, sex, systolic blood pressure (BP), history of HF hospitalization other than the preceding one, LVEF, baseline laboratory data (eGFR, haemoglobin levels, serum albumin levels and log-transformed plasma BNP levels), medications (angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, β-blockers, loop diuretics, aldosterone antagonists and statins) and the number of eGFR measurements over the EGV definition period. For the validation analyses, a further Cox regression model was developed with EGV and clinically important factors, the MAGGIC score or the EMPHASIS-HF score[20] as covariates. These clinically important factors were selected from the covariates in the fully adjusted Cox regression model by using a backward stepwise method with a significance level of 0.05 for variable retention. Schoenfeld residuals were used to assess the proportional hazard assumption.

Incidence rate ratios (IRRs) of HF hospitalizations and death were also estimated by EGV. The distribution and zero inflation of the number of events were checked. When overdispersion was observed in the number, facility-clustered negative binomial regression models were employed.

We performed some sensitivity analyses, repeating facility-stratified Cox regression analyses. First, to exclude potential confounding by the number of eGFR measurements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during the EGV definition period, the analysis was restricted to patients who had their eGFRs measured at 0, 2, 4 and 6 months after discharge, and EGV was recalculated using eGFR data at these four time points only. Second, to address potential confounding by in-hospital treatments, EGV was recalculated using data from 1 to 7 months after discharge. Third, the analysis was restricted to patients without acute kidney injury (AKI) during the EGV definition period. Fourth, EGV was recalculated using eGFR estimated by the CKD-EPI formula,[21] which is a global standard, not by the Japanese standard formula. Finally, EGV was redefined as the 'averaged percent change in eGFR from the nearest preceding visit'. In addition, we performed exploratory subgroup analyses to evaluate the interaction between EGV and various factors including baseline LVEF using Cox regression models.

#### *Analyses in the validation cohort*

In the validation analyses, both BNP and eGFR levels were redefined as the average values of 6 months after discharge because EGV was derived from data during this period. We compared model fitting (the overall goodness of fit [GOF]), discrimination (Harrell's C statistic, integrated discrimination improvements [IDIs] and non-categorical net reclassification improvements [NRIs]) and calibration among the Cox regression models, adding EGV, BNP or eGFR to a model of the clinically important factors, the MAGGIC model or the EMPHASIS-HF model. The GOF was compared based on the likelihood ratio tests and Akaike information criterion (AIC). IDIs and NRIs in logistic regression models for the 1-year composite event were also calculated to compare the ability of models to reclassify patients. Expected and observed 1-year event risks were compared across quintiles of expected risks using the Hosmer–Lemeshow test for each model.

# Results

## Study population and patients' characteristics

A total of 564 participants were analysed (376 and 188 in the derivation cohort and validation cohort, respectively). Patients in the two cohorts showed similar characteristics (*Table S2*). In the derivation cohort, median age, LVEF, eGFR, BNP at discharge, and EGV were 72 years, 53.3%, 58.7 mL/min/1.73 $m^2$, 134.8 pg/mL and 4.7%, respectively (*Table 1*). Of the 376 patients, 112 (29.8%) had HFrEF, and 194 (51.6%) had CKD. Patients with higher EGV had lower LVEF, eGFR, serum sodium levels and higher plasma BNP levels ($P$ for trend $< 0.05$). The median (IQR) personal cost of serum creatinine measurements for 6 months after discharge was ¥550 (440–770) [almost equivalent to $5.00 (4.00–7.00)], whereas that of BNP measurements was ¥4080 (2720–6800) [$37.09 (24.73–61.82)] ($P < 0.001$). During this period, 50 patients developed AKI, of whom 42 developed HF-related AKI and 8 developed HF-unrelated AKI (4, infection; 1, malignancy; 1, fever of unknown origin; 1, dehydration; and 1, macrohaematuria).

## Factors associated with EGV in the derivation cohort

On a multivariable logistic regression analysis, four variables were identified as factors associated with the highest EGV quartile: loop diuretic use (OR, 3.2; 95% confidence interval [CI], 2.5–4.1), lower serum albumin levels (OR, 0.8 [per 1 g/dL increase]; 95% CI, 0.7–0.8), lower serum sodium levels (OR, 0.95 [per 1 mEq/L increase]; 95% CI, 0.92–0.99) and the number of eGFR measurements ≥5 during the EGV definition period (OR, 2.9; 95% CI, 2.0–4.0) (*Table 2*). The negative association of serum albumin levels with the highest EGV quartile was pronounced in loop diuretic users (OR, 0.7; 95% CI, 0.5–0.8), but it was attenuated in non-users (OR, 1.0; 95% CI, 0.9–1.1) ($P$ for interaction $< 0.001$).

## HF outcomes in association with EGV in the derivation cohort

During a median (IQR) follow-up period of 2.2 (1.0–3.3) years, 46 subjects died (incidence rate, 4.9 per 100 person-years), and only one subject had a VAD implanted. There were no cases of heart transplantation. The total number of subsequent HF hospitalizations was 140 (incidence rate, 14.8 per 100 person-years). Higher incidence rates of the composite event (death and HF hospitalization) were observed in patients with a higher quartile of EGV ($P$ for trend $< 0.001$) (*Figure S1A*).

Kaplan–Meier curves showed that higher EGV was associated with a higher cumulative incidence of the composite event (log-rank, $P < 0.001$) (*Figure 3A*). On a facility-stratified Cox regression analysis, a higher quartile of EGV was significantly associated with an increased risk of the composite event, even after adjustment for established risk factors of HF outcomes ($P$ for trend = 0.003) (*Figure 3B*). Treating EGV as a continuous variable yielded similar results (HR [per SD increase in log-transformed EGV], 1.45; 95% CI, 1.07–1.96) (*Table S3*). Similar relationships between EGV quartiles and the number of events (death and HF hospitalizations) were observed in negative binomial regression models (*Table S3* and *Figure S1B*). In sensitivity analyses, significant associations were confirmed between EGV and cardiac outcomes (*Table S4* and *Figures S2* and *S3*), supporting the robustness of the main results. The association was somewhat stronger when EGV was recalculated using eGFRs at the four specific time points than in the primary analysis (*Table S4*).

**Table 1** Baseline patients' characteristics stratified by quartiles of eGFR variability in the derivation cohort

| | Total ($N$ = 376) | Q1 ($N$ = 94) | Q2 ($N$ = 94) | Q3 ($N$ = 94) | Q4 ($N$ = 94) | Missing | $P$-value |
|---|---|---|---|---|---|---|---|
| eGFR variability (%) | 4.7 (2.9, 6.6) | 1.7 (0.7, 2.4) | 3.8 (3.4, 4.3) | 5.8 (5.2, 6.0) | 8.6 (7.8, 11.2) | 0 | <0.001 |
| Age (years) | 72 (62, 80) | 72 (61, 78) | 76 (66, 81) | 66 (56, 76) | 74 (63, 80) | 0 | 0.60 |
| Male gender | 226 (60.1%) | 56 (59.6%) | 54 (57.5%) | 59 (62.8%) | 57 (60.6%) | 0 | 0.90 |
| Body mass index (kg/m$^2$) | 21.6 (19.0, 24.2) | 21.9 (19.9, 24.6) | 21.9 (18.9, 23.8) | 21.4 (19.2, 24.3) | 21.1 (18.2, 24.0) | 0 | 0.10 |
| Systolic blood pressure (mmHg) | 112 (100, 124) | 116 (104, 132) | 111 (102, 122) | 107 (98, 120) | 112 (100, 123) | 0 | 0.06 |
| Heart rate (bpm) | 70 (62, 80) | 70 (61, 76) | 70 (62, 78) | 72 (63, 81) | 70 (62, 78) | 0 | 0.61 |
| Current smoking | 46 (12.2%) | 14 (14.9%) | 9 (9.6%) | 12 (12.8%) | 11 (11.7%) | 0 | 0.93 |
| Comorbidities | | | | | | | |
| DM | 109 (29.1%) | 24 (25.5%) | 31 (33.3%) | 24 (25.5%) | 30 (31.9%) | 0 | 0.51 |
| COPD | 35 (9.3%) | 10 (10.6%) | 8 (8.5%) | 9 (9.6%) | 8 (8.5%) | 0 | 0.95 |
| CKD | 194 (51.6%) | 38 (40.4%) | 48 (51.1%) | 50 (53.2%) | 58 (61.7%) | 0 | 0.03 |
| CHD | 170 (45.2%) | 49 (52.1%) | 50 (53.2%) | 32 (34.0%) | 39 (41.5%) | 0 | 0.02 |
| DCM | 47 (12.5%) | 10 (10.6%) | 5 (5.3%) | 17 (18.1%) | 15 (16.0%) | 0 | 0.04 |
| HCM | 12 (3.2%) | 2 (2.1%) | 5 (5.3%) | 4 (4.3%) | 1 (1.1%) | 0 | 0.39 |
| Advanced malignancy | 17 (4.5%) | 3 (3.2%) | 3 (3.2%) | 6 (6.4%) | 5 (5.3%) | 0 | 0.72 |
| Histories of HF | | | | | | | |
| Duration of HF (months) | 14.1 (1.7, 86.0) | 6.2 (1.4, 48.7) | 10.0 (1.7, 81.0) | 20.0 (1.8, 101.7) | 51.6 (2.9, 171.4) | 0 | 0.01 |
| Past HF hospitalization | 205 (54.5%) | 48 (51.1%) | 53 (56.4%) | 48 (51.1%) | 56 (59.6%) | 0 | 0.57 |
| NYHA classification | | | | | | 0 | 0.33 |
| I or II | 323 (85.9%) | 79 (84.0%) | 86 (91.5%) | 78 (83.0%) | 80 (85.1%) | | |
| III or IV | 53 (14.1%) | 15 (16.0%) | 8 (8.5%) | 16 (17.0%) | 14 (14.9%) | | |
| LVEF (%) | 53.3 (36.0, 67.0) | 54.0 (38.0, 67.5) | 58.0 (38.5, 69.0) | 54.5 (35.0, 67.0) | 45.0 (31.0, 64.0) | 0 | 0.047 |
| The MAGGIC Score | 21 (17, 25) | 20 (16, 25) | 23 (19, 25) | 21 (15, 24) | 22 (18, 26) | 1 | 0.13 |
| Medical devices | | | | | | 0 | 0.41 |
| Pacemaker | 45 (12.0%) | 9 (9.6%) | 11 (11.8%) | 17 (18.1%) | 8 (8.5%) | | |
| ICD | 8 (2.1%) | 1 (1.1%) | 3 (3.2%) | 3 (3.2%) | 1 (1.1%) | | |
| CRT devices | 20 (5.3%) | 4 (4.3%) | 5 (5.4%) | 3 (3.2%) | 8 (8.5%) | | |
| Medications | | | | | | | |
| ACEI/ARB | 243 (64.6%) | 54 (57.5%) | 63 (67.0%) | 62 (66.0%) | 64 (68.1%) | 0 | 0.40 |
| β-Blocker | 249 (66.2%) | 59 (62.8%) | 62 (66.0%) | 59 (62.8%) | 69 (73.4%) | 0 | 0.37 |
| Aldosterone antagonist | 193 (51.3%) | 42 (44.7%) | 46 (48.9%) | 48 (51.1%) | 57 (60.6%) | 0 | 0.16 |
| Loop diuretics | 250 (66.5%) | 47 (50.0%) | 58 (61.7%) | 65 (69.2%) | 80 (85.1%) | 0 | <0.001 |
| Thiazide diuretics | 41 (10.9%) | 5 (5.3%) | 8 (8.5%) | 13 (13.8%) | 15 (16.0%) | 0 | 0.07 |
| Tolvaptan | 23 (6.1%) | 2 (2.1%) | 4 (4.3%) | 9 (9.6%) | 8 (8.5%) | 0 | 0.11 |
| Statin | 170 (45.3%) | 50 (53.2%) | 51 (54.8%) | 34 (36.2%) | 35 (37.2%) | 0 | 0.01 |
| Laboratory data | | | | | | | |
| Haemoglobin (g/dL) | 12.3 (11.0, 13.6) | 12.4 (11.3, 13.9) | 12.4 (11.2, 13.7) | 12.7 (11.3, 13.6) | 11.4 (10.5, 12.9) | 2 | 0.049 |
| Albumin (g/dL) | 3.7 (3.4, 3.9) | 3.7 (3.4, 3.9) | 3.6 (3.3, 3.9) | 3.8 (3.4, 4.1) | 3.6 (3.3, 3.9) | 29 | 0.41 |
| Total cholesterol (mg/dL) | 165 (142, 197) | 172 (151, 204) | 159 (140, 187) | 169 (138, 194) | 161 (139, 194) | 2 | 0.45 |
| Blood urea nitrogen (mg/dL) | 19 (14, 26) | 16 (13, 20) | 18 (14, 23) | 18 (13, 25) | 23 (17, 30) | 5 | <0.001 |
| Creatinine (mg/dL) | 0.9 (0.7, 1.1) | 0.8 (0.7, 1.0) | 0.9 (0.7, 1.0) | 0.9 (0.7, 1.1) | 1.0 (0.8, 1.2) | 0 | 0.01 |
| eGFR (mL/min/1.73 m$^2$) | 58.7 (45.9, 74.1) | 66.1 (50.3, 77.9) | 58.9 (46.8, 72.9) | 58.5 (45.2, 75.0) | 53.8 (39.4, 68.1) | 0 | 0.02 |
| Sodium (mEq/L) | 139 (136, 140) | 140 (138, 141) | 139 (137, 140) | 138 (136, 140) | 138 (136, 140) | 0 | <0.001 |
| BNP (pg/mL) | 134.8 (58.6, 299.5) | 114.3 (53.6, 211.8) | 125.7 (64.9, 333.5) | 107.7 (40.8, 315.4) | 197.5 (112.2, 353.3) | 7 | 0.004 |
| hsCRP (mg/L) | 2.0 (0.7, 7.1) | 2.8 (0.9, 8.1) | 1.9 (0.8, 7.2) | 2.3 (0.6, 5.2) | 1.6 (0.7, 7.7) | 11 | 0.36 |

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BNP, B-type natriuretic peptide; CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT-devices, cardiac resynchronization therapy devices; DCM, dilated cardiomyopathy; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HCM, hypertrophic cardiomyopathy; HF, heart failure; hsCRP, high sensitivity C-reactive protein; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.
Data are presented as median (interquartile range) or number (%).

**Table 2** Logistic regression analyses with the highest quartile of eGFR variability as a dependent variable

| | Univariable | | | Multivariable ($N$ = 362) | | |
|---|---|---|---|---|---|---|
| Variables | OR | 95% CI | *P*-value | OR | 95% CI | P-value |
| Age (per 5 years) | 1.06 | 1.02, 1.10 | 0.003 | 1.06 | 0.92, 1.21 | 0.41 |
| Male gender | 1.03 | 0.82, 1.29 | 0.80 | 1.12 | 0.84, 1.50 | 0.45 |
| Diabetes mellitus | 1.20 | 0.95, 1.51 | 0.12 | 0.99 | 0.93, 1.06 | 0.77 |
| Systolic BP (per 5 mmHg) | 0.99 | 0.97, 1.00 | 0.10 | 1.00 | 0.98, 1.02 | 0.94 |
| Heart rate (per 5 bpm) | 0.98 | 0.96, 0.99 | 0.02 | 0.96 | 0.91, 1.01 | 0.08 |
| ACEI/ARB | 1.23 | 0.54, 2.77 | 0.62 | 1.15 | 0.51, 2.63 | 0.74 |
| Aldosterone antagonists | 1.65 | 0.81, 3.36 | 0.16 | 0.86 | 0.48, 1.54 | 0.62 |
| Loop diuretics | 3.76 | 2.73, 5.19 | <0.001 | 3.20 | 2.53, 4.06 | **<0.001** |
| Thiazide diuretics | 1.87 | 1.86, 1.87 | <0.001 | 1.23 | 0.99, 1.53 | 0.07 |
| Serum albumin (g/dL) | 0.60 | 0.55, 0.65 | <0.001 | 0.76 | 0.71, 0.80 | **<0.001** |
| eGFR (per 5.0 mL/min per 1.73 $m^2$) | 0.93 | 0.92, 0.93 | <0.001 | 0.99 | 0.91, 1.07 | 0.82 |
| Serum sodium (mEq/L) | 0.92 | 0.90, 0.95 | <0.001 | 0.95 | 0.92, 0.99 | **0.01** |
| Log-transformed BNP (per 1 SD) | 1.46 | 1.46, 1.47 | <0.001 | 1.17 | 0.98, 1.38 | 0.08 |
| Creatinine measurement ≥5 times | 2.62 | 2.61, 2.64 | <0.001 | 2.86 | 2.03, 4.03 | **<0.001** |
| Summer season | 1.09 | 0.88, 1.34 | 0.42 | 0.93 | 0.78, 1.10 | 0.41 |

95%CI, 95% confidence interval; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BNP, B-type natriuretic peptide; BP, blood pressure; eGFR, estimated glomerular filtration rate; OR, odds ratio; SD, standard deviation. Significant *P*-values in the multivariable analysis are shown in bold.

In addition, it was confirmed that both the higher MAGGIC and EMPHASIS-HF[20] scores were significantly associated with increased risks of the composite event (HR, 1.1; 95% CI, 1.0–1.1, and HR, 1.3; 95% CI, 1.2–1.4, respectively).

## Exploratory subgroup analyses in the derivation cohort

Similar significant associations of EGV with the composite event were found both in patients with HFrEF and those with HFpEF (*P* for interaction = 0.44) (*Figure 4*). Most factors including sex, worsening or improving renal function (eGFR slope $< 0$ or $\geq 0$), the number of creatinine (eGFR) measurements and diuretic dose changes during the EGV definition period did not modify this association. However, in patients aged <75 years and those without CKD, event risks associated with EGV were higher than in the other patients (*P* for interaction = 0.02 and 0.048, respectively). The effect of EGV on the events was pronounced in patients with percent body weight changes during hospitalization $\geq -4.3\%$ (median) compared with the rest of the patients (*P* for interaction = 0.047). This indicates that event risks associated with EGV were higher among patients who experienced less fluid loss during hospitalization.

## Comparison of prediction models in the validation cohort

By the backward stepwise method, six factors (age, past HF hospitalization, LVEF, haemoglobin levels, loop diuretics and aldosterone antagonists) were identified as covariates in a baseline Cox regression model (Six factor model). Adding EGV to this baseline model (EGV-Six factor model) yielded a higher log-likelihood chi-squared statistic (3.8, *P* = 0.04) than adding BNP or eGFR to the model (BNP-Six factor model or eGFR-Six factor model) (*Table S5*). Of the four models (the EGV-Six factor, BNP-Six factor, eGFR-Six factor, and Six factor models), the EGV-Six factor model had the lowest AIC. These indicate a better model fit when EGV was added to the baseline model than when 6-month averaged BNP or eGFR was added.

Regarding discrimination, the EGV-Six factor model had the highest Harrell's C-statistic of 0.70 (*Table S5*). Even in patients with CKD, this model had the highest C-statistic of 0.68. The non-categorical NRI and IDI favoured the EGV-Six factor model, indicating a significant improvement in risk classification of patients for the 1-year composite event when EGV was added to the Six factor model (*Table 3*, Model 4). The non-categorical NRI and IDI were still significant when EGV was added to the BNP-Six factor model (*Table 3*, Model 6 [vs. Model 3]) or eGFR-Six factor model (*Table 3*, Model 5 [vs. Model 2]). Restricting the analyses to patients with CKD did not change the results substantially (*Table S6*).

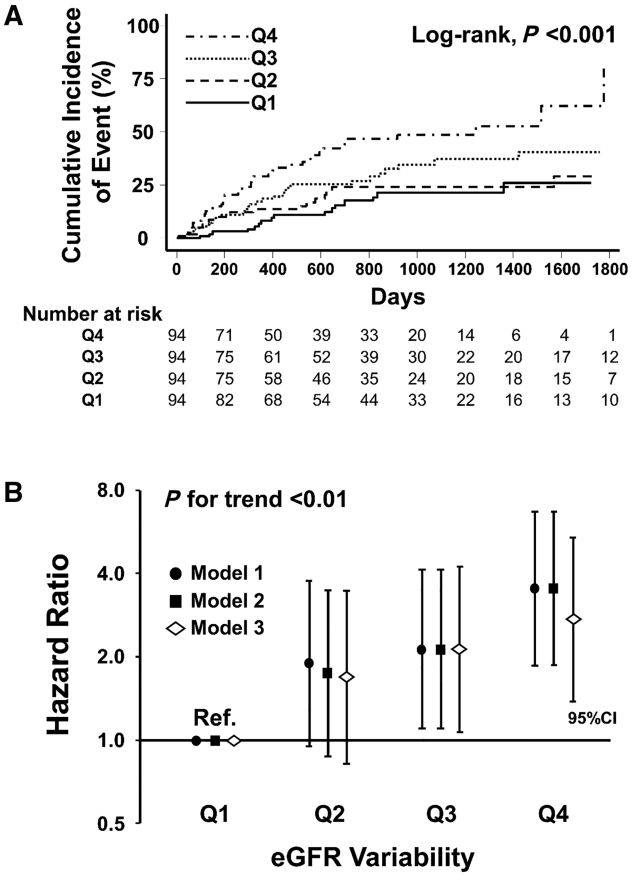
Calibration was compared among the EGV-Six factor, BNP-Six factor, eGFR-Six factor and Six factor models. Of these four models, the EGV-Six factor model was best calibrated, as shown by the highest *P*-value on the Hosmer–Lemeshow test (*Figure 5*).

The best model fit, discrimination, reclassification and calibration were still observed when EGV was added to a different baseline model (the MAGGIC or EMPHASIS-HF prediction model) (*Tables S5*, *S7* and *S8*; *Figures S4* and *S5*).

# Discussion

In this multicentre, prospective cohort study enrolling patients who had survived HF hospitalization, higher EGV during 6 months after discharge was significantly associated with an

**Figure 3** Associations between eGFR variability stratified by quartiles and cardiac events.(A) Unadjusted Kaplan–Meier curves and (B) hazard ratios by Cox regression analyses. The outcome was time to HF hospitalization or death, whichever occurred first.Model 1 was unadjusted.Model 2 was adjusted for the MAGGIC score.Model 3 was adjusted for age, sex, systolic blood pressure, history of HF hospitalization other than the preceding one, LVEF, baseline laboratory data (eGFR, haemoglobin levels, serum albumin levels and log-transformed plasma BNP levels), medications (angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, β-blockers, loop diuretics, aldosterone antagonists and statins) and the number of serum creatinine measurements over the 6 months after discharge.




increased risk of subsequent death and HF hospitalization, even after adjustment for established HF risk factors. The stratified analysis by LVEF yielded similar results. Better model fit, discrimination, reclassification and calibration were observed when EGV was added to several risk prediction models for predicting death or HF hospitalization than when 6-month averaged BNP or eGFR was added.

The present data highlight the clinical importance of observing visit-to-visit fluctuations in renal function in HF. The observed relationship between EGV and HF outcomes was consistent with a recent post hoc analysis of a randomized controlled trial (the TOPCAT trial) enrolling patients with HFpEF.[22] Analysing the data for a real-world HF population, the present study extended the finding to patients with HFrEF (*Figure 4*). To the best of our knowledge, the present study is the first to evaluate the usefulness of HF risk predictions using EGV. EGV outperformed BNP when added to risk prediction models. This finding allowed us to speculate that EGV could act as an inexpensive substitute for BNP for predicting HF outcomes. Indeed, serum creatinine can be measured at a much lower cost than BNP (e.g. ¥110 [$1.00] vs. ¥1360 [$12.36] in Japan). Interestingly, EGV still outperformed BNP in patients with CKD. Given that BNP concentrations are markedly influenced by renal function in patients with an eGFR $<$ 60 mL/min/1.73 $m^2$ and that this may be an obstacle to the accurate interpretation of HF states,[9–12] EGV can be more useful than BNP, particularly in this subpopulation. Importantly, adding EGV to the model with BNP or eGFR improved model discrimination (IDI) and reclassification (NRI) (*Tables 3* and *S6-S8*). This suggests that observing visit-to-visit fluctuations in renal function is clinically relevant even in patients with BNP or eGFR already measured.

Because eGFR data during the EGV definition period were obtained at the discretion of the attending physicians, potential confounding by the number of measurements, which might be a proxy of HF severity, should be noted for the observed association between EGV and HF outcomes. However, in the sensitivity analysis where EGV was recalculated using eGFR data at four time points (0, 2, 4, and 6 months after discharge) only, the somewhat stronger association was found than in the primary analysis (*Table S4* and *Figure S2*). This indicates that potential confounding by the number of eGFR measurements was, at most, modest. In addition, this relationship was robust even after adjustment for this number in the regression models (*Figure 3B*; *Table S3*; *Figure S1B*).

The relationship between EGV and cardiac outcomes may be explained by renal plasma flow (RPF) fluctuations due to intravascular volume depletion or fluctuating cardiac output. In the present study, EGV was associated with serum levels of albumin, sodium and loop diuretic therapy at baseline. The present association between lower albumin levels and higher EGV was more pronounced in patients receiving loop diuretics. Hypoalbuminaemic or hyponatraemic patients are susceptible to RPF decreases when they receive loop diuretics or are in conditions such as low dietary intake, diarrhoea, sweating and low BP.[23] In most cases, this RPF decrease is reversible, resulting in RPF fluctuations. Consistently, previous literature showed significant associations between diuretic therapies and changes in renal function, regardless of the direction, in patients with ADHF.[24] RPF fluctuations, in other words, frequent temporary RPF decreases, may activate the renin–angiotensin–aldosterone and sympathetic nervous systems, causing adverse cardiac outcomes.[25] In addition, HF states were likely to be more severe in patients with higher EGV (*Table 1*). In these patients, cardiac output would vary greatly in parallel with renal fraction. For example, high EGV can be attributed to temporary

**Figure 4** Hazard ratios of the composite of death and HF hospitalization by the increase in the standard deviation of log-transformed eGFR variability in different subgroups of patients.The percent body weight (BW) change was defined using the following formula: ([BW at discharge] − [BW on admission])/(BW on admission) × 100 (%). From 6 months of data after discharge, annualized eGFR slopes were estimated by a linear mixed effects model for time-dependent eGFR.

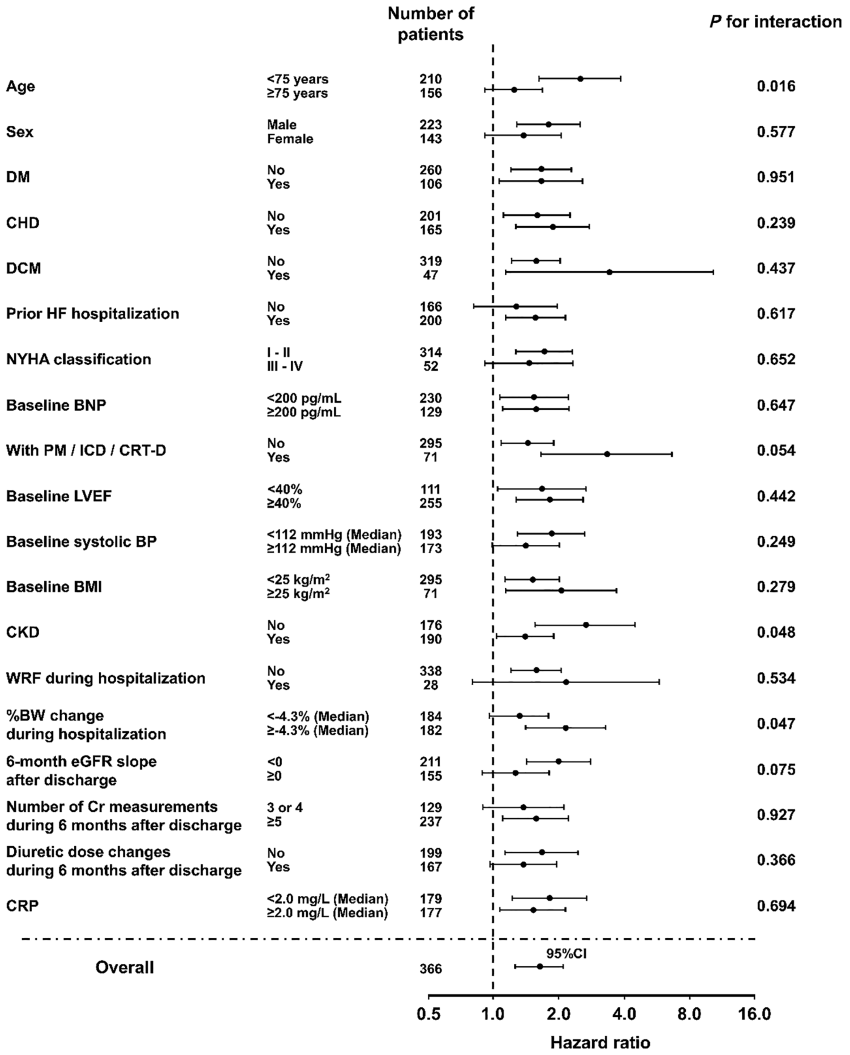
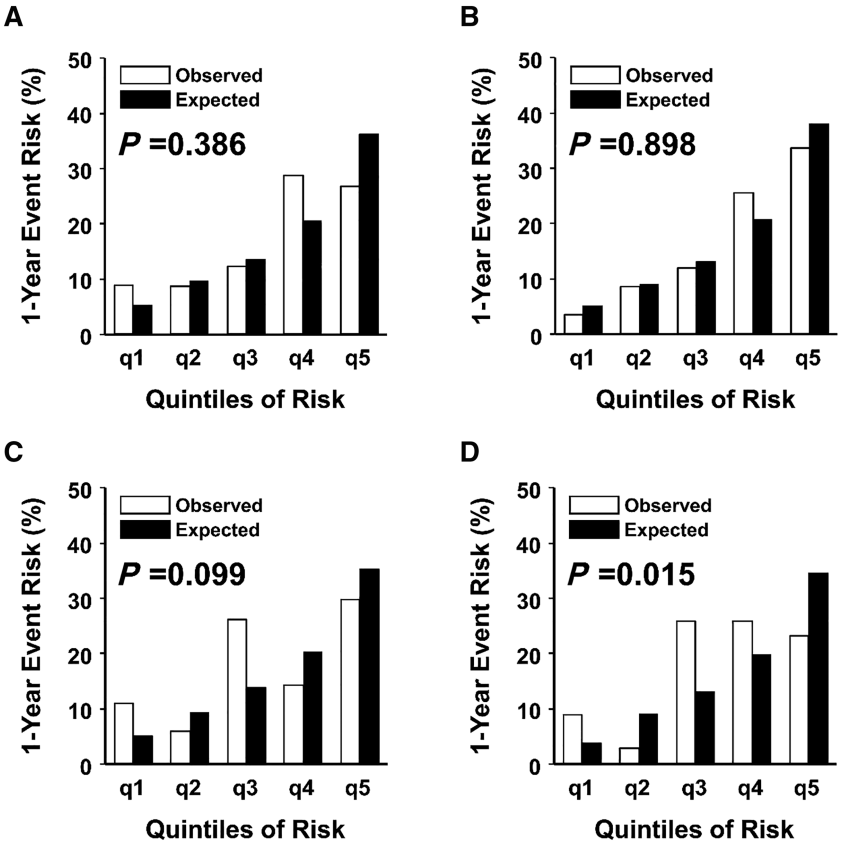



**Table 3** Non-categorical NRI and IDI using six specified factors

| Risk prediction models for 1-year death or HF hospitalization | | NRI (%) | *P*-value | IDI (%) | *P*-value |
|---|---|---|---|---|---|
| Model 1 | Six factors[a] | Ref. | - | Ref. | - |
| Model 2 | Model 1 + eGFR | −2.40 | >0.90 | 0.02 | >0.90 |
| Model 3 | Model 1 + BNP | −9.25 | >0.90 | 0.18 | 0.54 |
| Model 4 | Model 1 + EGV | 48.45 | 0.02 | 5.12 | 0.01 |
| Model 5 | Model 1 + eGFR + EGV | | | | |
| | vs. Model 4 | 9.66 | 0.63 | 0.37 | 0.63 |
| | vs. Model 2 | 64.83 | 0.001 | 5.46 | 0.007 |
| Model 6 | Model 1 + BNP + EGV | | | | |
| | vs. Model 4 | −9.25 | >0.90 | 0.12 | 0.58 |
| | vs. Model 3 | 42.85 | 0.03 | 5.06 | 0.01 |

BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; EGV, eGFR variability; HF, heart failure; IDI, integrated discrimination improvement; NRI, net reclassification improvement; Ref, reference.
[a]Age, past HF hospitalization, LVEF, haemoglobin levels, loop diuretics and aldosterone antagonists.

**Figure 5** Comparisons of observed and expected event risks across quintiles of risks estimated by Cox regression models with six specified factors.The six factors (age, past HF hospitalization, LVEF, loop diuretics, aldosterone antagonists and haemoglobin levels) were selected by the backward stepwise method in an analysis in the derivation cohort. The outcome was a composite of death and HF hospitalization within 1 year. Cox regression models included covariates as follows: (A) the six factors alone, (B) the six factors and log-transformed eGFR variability, (C) the six factors and log-transformed BNP and (D) the six factors and eGFR. *P*-values were estimated by the Hosmer–Lemeshow tests.




hypotension with severe aortic valve stenosis,[26] paroxysmal arrhythmia and on-and-off states of cardiotonic agents.

Congestive kidney failure may also be a common pathophysiology explaining high EGV and adverse HF outcomes. Previous studies showed an association of venous congestion with changes in renal function. The risk of worsening renal function (WRF) was reported to be higher in patients with higher central venous pressure[27,28] or those who underwent less fluid removal during their initial ADHF treatments.[29] A higher incidence of improving renal function following WRF (high EGV) was observed in patients with greater signs of venous congestion, including hepatojugular reflux, severe tricuspid regurgitation and right ventricular dysfunction.[30,31] On the other hand, venous congestion and right-sided cardiac dysfunction are independent predictors of mortality and HF hospitalization.[30,32] Consistently, in the present subgroup analyses, EGV predicted cardiac outcomes, particularly in patients who experienced modest fluid removal during the hospitalization.

On subgroup analyses, the relationship between EGV and cardiac outcomes was weak in patients with CKD, though significant. Compared with non-CKD patients, CKD patients have more cardiovascular risk factors, including hypertension, anaemia, diabetes mellitus, dyslipidaemia and prior cardiovascular disease.[33] Therefore, in CKD, these risk factors might have overshadowed the effect of EGV. This may also be true in the elderly, in whom the association of EGV with cardiac outcomes was not significant. Otherwise, the 'healthy survivor effect'[34] might explain this effect modification by age. Patients who survived to an older age despite high EGV are likely to tolerate the effect of EGV, showing lower risks of cardiac events than younger patients.

This study has several limitations. First, the inclusion and exclusion criteria might have created a selection bias. It is unclear whether the present results can be extrapolated to extremely severe HF patients who had cardiac events within 6 months after discharge. Second, as a baseline model, the MAGGIC prediction model, which was originally developed for predicting death,[7] not for predicting a composite event, was used. However, the present study showed that this model predicted the composite outcome. Indeed, this model was validated in a large cohort for predicting the composite

outcome (death and HF hospitalization).[35] Moreover, the present results were confirmed using other baseline risk prediction models. Third, although the consistent association between EGV and the study outcome was confirmed across the subgroup of the New York Heart Association classification, BNP at baseline and diuretic dose changes, the possibility that different HF stages and treatments, including the quantity of diuretics, affected the present results cannot be excluded. Finally, this observational study cannot prove a direct causal relationship between EGV and cardiac outcomes.

In summary, in patients who had survived HF hospitalization, higher EGV was significantly associated with increased risk of subsequent death and HF hospitalization, regardless of LVEF. Risk prediction models with EGV could have better performance than those with BNP or eGFR in real-world HF patients. Moreover, EGV improved risk prediction even in patients whose BNP or eGFR levels were already measured. The present data highlight that physicians should follow up HF patients with fluctuating renal function carefully considering risks of future cardiac events. Further studies are warranted to identify therapeutic interventions that can reduce EGV and, if any, to clarify the effect of therapeutic EGV reduction on patients' outcomes.

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Drs Oka and Hamano designed the study. Drs Oka, Hamano, Ohtani, Tanaka, Nakamoto, Sera, Hikoso and Nishino and Prof Sakata collected the data. Drs Oka and Hamano analysed the data. All authors participated in data interpretation. Dr Oka drafted the manuscript. All authors revised the manuscript and approved the final version of the manuscript.

## Conflict of interest

None.

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## Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Inclusion and exclusion criteria.
**Table S2.** Baseline characteristics of the patients in the two cohorts.
**Table S3.** Associations of EGV as a continuous variable with composite cardiac events in Cox regression and negative binomial regression analyses.
**Table S4.** Associations of EGV as a continuous variable with composite cardiac events in sensitivity analyses.
**Table S5.** Comparisons of model fitting and discrimination among various Cox regression models with six specified factors, the MAGGIC score, or the EMPHASIS-HF score.
**Table S6.** Non-categorical NRI and IDI using six specified factors in patients with CKD.
**Table S7.** Non-categorical NRI and IDI using the MAGGIC score.
**Table S8.** Non-categorical NRI and IDI using the EMPHASIS-HF score.
**Figure S1.** Associations between EGV stratified by quartiles and the number of cardiac events.
**Figure S2.** Associations between EGV stratified by quartiles and cardiac events in a sensitivity analysis using eGFR data at 4 specific time points.
**Figure S3.** Associations between EGV stratified by quartiles and cardiac events in a sensitivity analysis using eGFR estimated by the CKD-EPI formula.
**Figure S4.** Comparisons of observed and expected event risks across quintiles of risks estimated by Cox regression models with the MAGGIC score.
**Figure S5.** Comparisons of observed and expected event risks across quintiles of risks estimated by Cox regression models with the EMPHASIS-HF score.

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