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# High-Sensitivity Cardiac Troponin T Predicts Non-Cardiac Mortality in Heart Failure

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***Background:*** Cardiac troponins are independent predictors of cardiac mortality in patients with heart failure (HF). Recently, elevation of troponins was described in non-cardiac diseases such as stroke and infection, among others, but it remains unclear whether high-sensitivity troponin T (hs-TnT) predicts non-cardiac mortality in HF patients.

***Methods and Results:*** Four-hundred and forty-four consecutive HF patients admitted to hospital for the treatment of decompensated HF were divided into 2 groups based on median hs-TnT: group L (<0.028 ng/ml, n=220) and group H (≥0.028 ng/ml, n=224). We compared all-cause mortality and echocardiographic findings between the 2 groups. In the follow-up period (mean 472 days), 77 deaths (49 cardiac deaths and 28 non-cardiac deaths) were observed. The event-free rate was significantly lower in group H than in group L for non-cardiac death (P=0.025), cardiac death (P<0.001), and all-cause mortality (P<0.001). On multivariate Cox proportional hazard analysis, high hs-TnT was found to be an independent predictor of non-cardiac death (P=0.042), cardiac death (P<0.001) and all-cause mortality (P<0.001) in HF patients after adjusting for risk factors. Regarding echocardiographic parameters, left ventricular wall thickness was higher (P<0.001), and ejection fraction was lower (P=0.011) in group H than in group L.

***Conclusions:*** Hs-TnT is an independent predictor not only of cardiac mortality, but also of non-cardiac mortality in HF patients. (*Circ J* 2014; **78:** 890–895)

**Key Words:** High-sensitivity troponin T; Non-cardiac death; Cardio-renal function; Prognosis

Cardiac troponins (cTn) are sensitive and specific markers of myocardial damage used for the diagnosis of acute coronary syndrome.[1,2] It has been reported that elevated blood cTn is correlated with severity of disease and with adverse all-cause mortality in heart failure (HF) patients, not only those hospitalized[3–5] but outpatients as well.[6–10] Previous studies, however, reported all-cause mortality only in the absence of a classification of cardiac death or non-cardiac death. Hence, the association of cTn and non-cardiac mortality in HF remains unclear. Even though no sources other than the myocardium have been found for cTn, several non-cardiac conditions such as stroke and infection are associated with a minor increase in cTn,[11,12] but it remains unclear whether higher cTn predicts non-cardiac mortality in HF patients.

The aim of the present study was therefore to investigate the association of higher high-sensitivity cardiac troponin T (hs-TnT) with non-cardiac mortality in HF patients and cardio-renal function.

## Methods

### Subjects and Study Protocol

We retrospectively analyzed 621 consecutive patients who were hospitalized at Fukushima Medical University Hospital for the treatment of decompensated HF between 2009 and 2012. The diagnosis of decompensated HF was defined based on the Framingham criteria.[13] Patients with missing data for hs-TnT (n=117), or who had acute coronary syndrome (n=16), residual ischemia (n=25), pulmonary thromboembolism (n=5), dialysis (n=7), or documented cancer (n=3), and those who underwent chemotherapy (n=2) or had an unidentified cause of death (n=2), were excluded. Finally, we analyzed 444 patients. These patients were divided into 2 groups based on median hs-TnT: group L (hs-TnT <0.028 ng/ml, n= 220) and group H (hs-TnT

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**Table 1. Clinical Subject Features**

| | Group L (n=220) | Group H (n=224) | P-value |
|---|---|---|---|
| **Age (years)** | 65.6±13.9 | 68.4±14.1 | 0.034 |
| **Male** | 133 (60.5) | 149 (66.5) | 0.201 |
| **Body mass index (kg/cm²)** | 23.5±4.0 | 22.9±4.1 | 0.123 |
| **SBP (mmHg)** | 121.0±17.7 | 118.4±21.4 | 0.295 |
| **DBP (mmHg)** | 73.7±11.4 | 71.8±12.5 | 0.220 |
| **Heart rate (beats/min)** | 68.6±13.9 | 70.9±14.9 | 0.211 |
| **Body temperature (°C)** | 36.5±0.6 | 36.4±0.8 | 0.893 |
| **Ischemic etiology** | 31 (14.1) | 35 (15.6) | 0.650 |
| **Comorbidity** | | | |
| Hypertension | 157 (71.4) | 166 (74.1) | 0.525 |
| Diabetes | 79 (35.9) | 92 (41.1) | 0.284 |
| Dyslipidemia | 83 (37.7) | 72 (32.1) | 0.233 |
| Atrial fibrillation | 88 (44.0) | 72 (32.1) | 0.093 |
| Chronic kidney disease | 94 (42.7) | 171 (76.3) | <0.001 |
| Anemia | 76 (34.5) | 139 (62.1) | <0.001 |
| COPD | 39 (17.7) | 46 (20.5) | 0.452 |
| **Medications** | | | |
| ACEI | 122 (55.5) | 116 (51.8) | 0.448 |
| ARB | 62 (28.2) | 53 (23.7) | 0.281 |
| β-blockers | 179 (81.4) | 176 (78.6) | 0.479 |
| **Laboratory data** | | | |
| White blood cell (×10³/μl) | 7.18±2.87 | 7.54±3.75 | 0.183 |
| Neutrophils (%) | 66.7±11.2 | 68.4±12.0 | 0.278 |
| Lymphocytes (%) | 23.4±9.9 | 22.0±9.8 | 0.379 |
| Monocytes (%) | 7.7±2.3 | 7.4±2.7 | 0.326 |
| Eosinophils (%)† | 1.0 (1.0) | 1.0 (1.0) | 0.988 |
| Basophils (%)† | 0 (1.0) | 0 (1.0) | 0.683 |
| Hemoglobin (g/dl) | 13.1±2.3 | 11.9±2.3 | <0.001 |
| BNP (pg/ml)† | 267.0 (445) | 600.7 (1053) | <0.001 |
| eGFR (ml·min⁻¹·1.73 m⁻²) | 63.9±19.4 | 45.7±24.8 | <0.001 |
| Cystatin C (mg/L) | 1.33±0.44 | 2.03±1.28 | <0.001 |
| C-reactive protein (mg/dl)† | 0.32 (1) | 0.43 (1) | 0.069 |
| Sodium (mEq/L) | 139.0±4.3 | 138.7±4.4 | 0.472 |
| Troponin T (ng/ml)† | 0.015 (0.010) | 0.056 (0.077) | <0.001 |

Data given as mean±SD, n (%) or †median (IQR).
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BNP, B-type natriuretic peptide; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

≥0.028 ng/ml, n= 224). We compared the clinical features and results from several examinations of both groups, such as general laboratory tests and echocardiography, performed on hospital admission. Residual ischemia was diagnosed on coronary angiography, cardiac magnetic resonance imaging, and myocardial perfusion scintigraphy. Hypertension was defined as the recent use of antihypertensive drugs, systolic blood pressure ≥140 mmHg, and/or diastolic pressure ≥90 mmHg. Diabetes was defined as the recent use of insulin or anti-diabetic drugs, fasting blood glucose ≥126 mg/dl, and/or hemoglobin $A_{1c}$ ≥6.5%. Dyslipidemia was defined as the recent use of cholesterol-lowering drugs, triglyceride ≥150 mg/dl, low-density lipoprotein cholesterol ≥140 mg/dl, and/or high-density lipoprotein cholesterol <40 mg/dl. Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate (eGFR) <60 ml·min$^{-1}$·1.73 m$^{-2}$, using the Modification of Diet in Renal Disease formula.[14] Anemia was defined as hemoglobin <12.0 g/dl in female subjects and <13.0 g/dl in male subjects.[15] Chronic obstructive pulmonary disease was defined as forced expiratory volume in 1s/forced vital capacity <70% on spirometry according to the Global Initiative for Chronic Obstructive Lung Disease and the American Thoracic Society/European Respiratory Society guidelines.[16,17] Patients were followed up for cardiac death, non-cardiac death, and all-cause mortality. Cardiac death included death due to ventricular fibrillation or worsening HF. Non-cardiac death included death due to stroke, respiratory failure, infection, sepsis, cancer, digestive hemorrhage, among other reasons. Status and date of deaths were obtained from the patients' medical records. If these data were unavailable, status was ascertained by a telephone call to the patients' referring hospital physician. Written informed consent was obtained from all study subjects. The study protocol was approved by the ethics committee of Fukushima Medical University.

### B-Type Natriuretic Peptide, Cystatin C and hs-TnT Measurement

A blood sample was obtained from each patient at Fukushima Medical University upon hospital admission. Plasma B-type

**Table 2. Echocardiographic Data**

| | Group L (n=220) | Group H (n=224) | P-value |
|---|---|---|---|
| Interventricular septum thickness (mm) | 10.4±2.2 | 11.4±3.0 | <0.001 |
| Left ventricular end-diastolic dimension (mm) | 53.1±10.4 | 54.0±10.6 | 0.391 |
| Left ventricular end-systolic dimension (mm) | 39.4±12.6 | 41.7±12.7 | 0.087 |
| Posterior wall thickness (mm) | 10.8±2.8 | 11.3±2.6 | 0.045 |
| Left ventricular end-diastolic volume (ml) | 115.3±55.4 | 127.8±61.9 | 0.043 |
| Left ventricular end-systolic volume (ml) | 63.5±42.9 | 75.0±47.3 | 0.015 |
| LVEF (%) | 48.3±15.4 | 44.3±14.5 | 0.011 |
| Left atrial volume (ml) | 83.0±58.5 | 88.1±69.1 | 0.476 |
| Mitral valve E'(cm/sec) | 6.9±5.4 | 5.7±2.6 | 0.013 |
| Mitral valve E/E' | 13.8±7.3 | 16.9±7.9 | <0.001 |
| Inferior vena cava diameter (mm) | 15.2±4.9 | 15.9±5.5 | 0.237 |
| SPAP (mmHg) | 34.4±14.8 | 33.7±13.2 | 0.670 |
| Right atrial end systolic area ($cm^2$) | 19.2±10.7 | 20.8±16.5 | 0.425 |
| Right ventricular area-diastolic ($cm^2$) | 17.2±6.8 | 16.3±6.4 | 0.381 |
| Right ventricular area-systolic ($cm^2$) | 10.2±4.5 | 9.8±4.8 | 0.496 |
| RV-FAC (%) | 42.5±14.2 | 43.5±15.6 | 0.645 |

Data given as mean±SD.
E/E', ratio of the peak transmitral velocity during early diastole to the peak mitral valve annular velocity during early diastole; LVEF, left ventricular ejection fraction; RV-FAC, right ventricular fractional area change; SPAP, systolic pulmonary artery pressure.

natriuretic peptide (BNP) was measured using a specific immunoradiometric assay (Shionoria BNP kit; Shionogi, Osaka, Japan). Cystatin C was measured using particle-enhanced immunoturbidimetric assay (Tina-quant cystatin C; Roche Diagnostics, Mannheim, Germany). hs-TnT was measured using electrochemiluminescence immunoassay (Elecsys Troponin T hs; Roche Diagnostics, Rotkreuz, Switzerland). This assay's working range is reported as 0.003–10 ng/ml, with interassay coefficients of variation of 3.1% at 24ng/L, and 1.3% at 300 ng/L. The lower limit of quantification is 13 ng/L, the lowest limit of detection is 5ng/L, and the limit of the blank is 3 ng/L as listed by the manufacturer. The gender-specific 99 th percentile concentration limit as established in a healthy population (male, 18 ng/L; female, 8 ng/L) was adopted to differentiate normal values of hs-TnT from abnormal ones.[18]

### Echocardiography

Echocardiography was performed blind by an experienced echocardiographer using the standard techniques. Echocardiographic parameters investigated included left ventricular volume, left ventricular ejection fraction (LVEF), left atrial volume, ratio of early transmitral flow velocity to mitral annular velocity (mitral valve E/E'), inferior vena cava diameter, systolic pulmonary artery pressure (SPAP), right atrial end-systolic area, and right ventricular area, right ventricular fractional area change (RV-FAC), and so on.[17] LVEF was calculated using a modification of the Simpson's method. Mitral valve E/E' was calculated using transmitral Doppler flow and tissue Doppler imaging. SPAP was calculated by adding the right atrial pressure (estimated by the diameter and collapsibility of the inferior vena cava) to the systolic trans-tricuspid pressure gradient.[19] RV-FAC, defined as (end-diastolic area–end-systolic area)/end-diastolic area×100, is a measure of right ventricular systolic function.[19] All recordings were performed on ultrasound systems (ACUSON Sequoia; Siemens Medical Solutions USA, Mountain View, CA, USA).

### Statistical Analysis

Normally distributed data are presented as mean±SD, non-normally distributed data as median (interquartile range), and categorical variables as numbers and percentages. Characteristics between the 2 groups were compared using independent Student's t-test for normally distributed data and the Mann-Whitney U-test for non-normally distributed data, whereas the chi-squared test was used for categorical variables. Kaplan-Meier analysis was used to describe event-free rate and log-rank test was used for initial comparisons. Univariate and multivariate Cox proportional hazard analysis were used to analyze predictors of events and to adjust for confounding factors. Univariate parameters with $P<0.10$ were used in multivariate analysis. $P<0.05$ was considered significant for all comparisons. These analyses were done using SPSS version 21.0 (IBM, Armonk, NY, USA).

## Results

As shown in Tables 1,2, group H had (1) lower hemoglobin and eGFR; (2) higher BNP and cystatin C; (3) larger left ventricular wall thickness, greater left ventricular volume and mitral valve E/E'; and (4) lower LVEF. In contrast, right heart function (right atrial and ventricular areas and RV-FAC) did not differ between the 2 groups. In summary, group H had left ventricular hypertrophy, left ventricular systolic dysfunction, renal dysfunction, anemia, and similar right heart function.

During the follow-up period (mean 472 days), there were 49 cardiac deaths (group L, n=10; group H, n=39) and 28 non-cardiac deaths (group L, n=9; group H, n=19). Details of cardiac and non-cardiac deaths are as follows: group L: HF deaths, n=5; ventricular fibrillation, n=5; cancer, n=3; infection/sepsis, n=2; respiratory failure and/or pneumonia, n=1; stroke, n=1; digestive hemorrhage, n=1; and renal failure, n=1; group H: HF deaths, n=32; ventricular fibrillation, n=7; respiratory failure and/or pneumonia, n=4; infection/sepsis, n=4; stroke, n=3; cancer, n=3; digestive hemorrhage, n=2; renal failure, n=2; and aortic aneurysm, n=1. As shown in Figure, the event-free rate

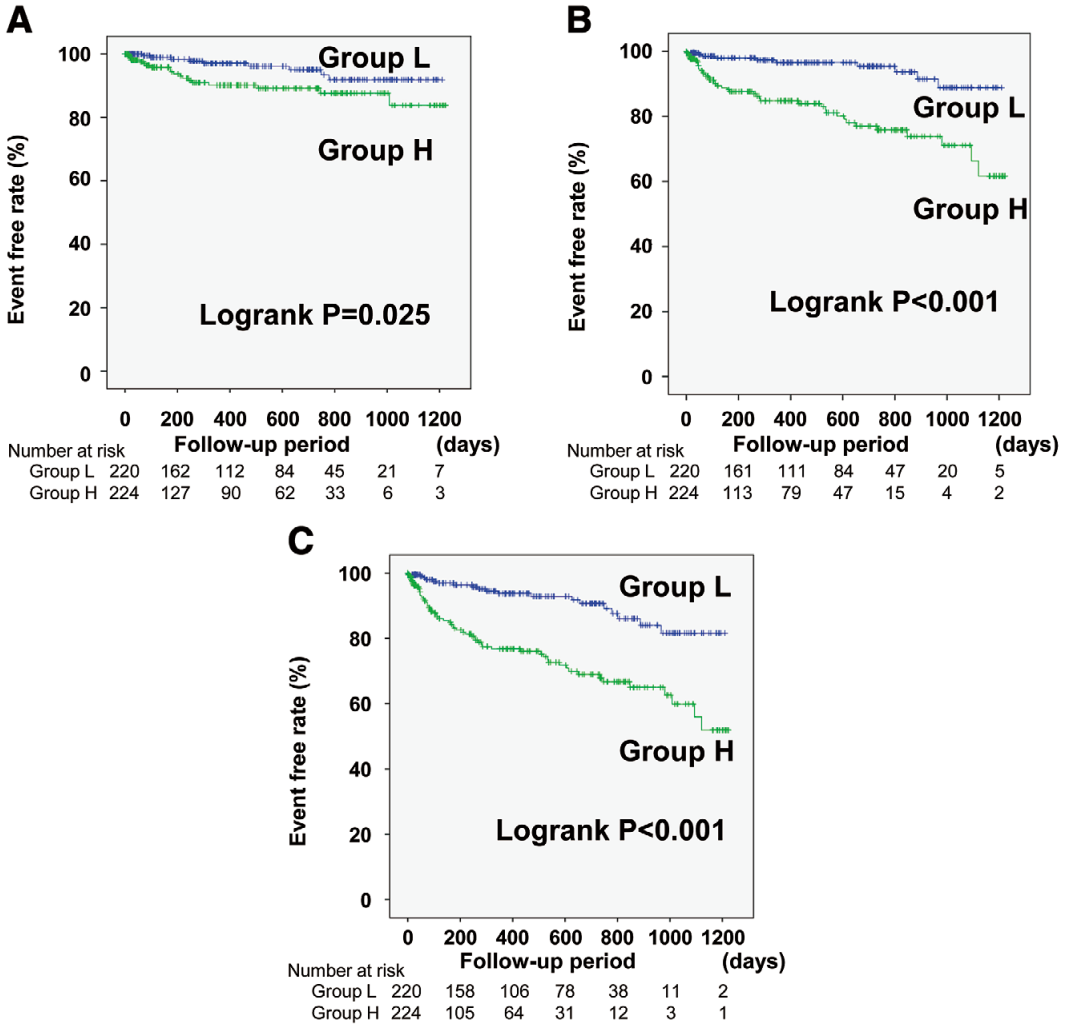


**Figure.** Kaplan-Meier curves for (**A**) non-cardiac death, (**B**) cardiac death, and (**C**) all-cause mortality in group L and group H.

**Table 3. Prognostic Value of Higher hs-TnT in HF**

| Event | HR | 95% CI | P-value |
|---|---|---|---|
| **Non-cardiac death** | | | |
| Unadjusted | 2.413 | 1.092–5.336 | 0.030 |
| Adjusted for gender and age | 2.321 | 1.046–5.150 | 0.038 |
| Multivariate Cox proportional model† | 2.293 | 1.030–5.103 | 0.042 |
| **Cardiac death** | | | |
| Unadjusted | 4.459 | 2.229–8.920 | <0.001 |
| Adjusted for gender and age | 4.464 | 2.228–8.943 | <0.001 |
| Multivariate Cox proportional model† | 3.970 | 1.902–8.289 | <0.001 |
| **All-cause mortality** | | | |
| Unadjusted | 3.438 | 2.047–5.773 | <0.001 |
| Adjusted for gender and age | 3.408 | 2.026–5.733 | <0.001 |
| Multivariate Cox proportional model† | 2.865 | 1.625–5.049 | <0.001 |

†The following factors were analyzed after adjustment for gender and age: presence of ischemic etiology, atrial fibrillation, chronic kidney disease, anemia, reduced left ventricular ejection fraction, and higher B-type natriuretic peptide.
CI, confidence interval; HF, heart failure; HR, hazard ratio; hs-TnT, high-sensitivity troponin T.

was significantly lower in group H than in group L for non-cardiac death (P=0.025), cardiac death (P<0.001), and all-cause mortality (P<0.001).

To examine the prognostic value of higher hs-TnT in HF patients, the Cox proportional hazard model was used (**Table 3**). On univariate and multivariate Cox proportional hazard analysis, we assessed the following factors, known to affect the risk of mortality in HF patients after adjusting for gender and age: presence of ischemic etiology, atrial fibrillation, CKD, anemia, reduced LVEF (<50%), higher (>median) BNP, and higher hs-TnT. With respect to non-cardiac death in HF patients, higher hs-TnT was an independent predictor in multivariate analysis (hazards ratio [HR], 2.293; 95% confidence interval [CI]: 1.030–5.103, P=0.042). With respect to cardiac death in HF patients, higher hs-TnT was an independent predictor (HR, 3.970; 95% CI: 1.902–8.289, P<0.001); and with respect to all-cause mortality in HF patients, higher hs-TnT was an independent predictor (HR, 2.865; 95% CI: 1.625–5.049, P<0.001). In summary, high hs-TnT was an independent predictor of cardiac, non-cardiac and all-cause mortality.

## Discussion

To the best of our knowledge, the present study is the first to show the utility of hs-TnT for predicting not only cardiac mortality but also detailed non-cardiac mortality in hospitalized HF patients with left ventricular hypertrophy, systolic dysfunction and impaired renal function.

Concerning measurement of cTn, large-scale population-based epidemiological studies have shown that multiple factors such as aging, male gender, hypertension, diabetes mellitus and reduced renal function are associated with low-grade increases of cTn.[1,20] In addition, even though cTn are specific proteins of the myocardium, recent studies have shown that they are occasionally elevated in non-cardiac diseases.[11,12] Namely, elevation of cTn has been described in diabetes,[20] arterial hypertension, renal dysfunction,[21] sepsis,[22] stroke,[23] digestive hemorrhage,[24] chronic obstructive pulmonary disease,[25] sleep-disordered breathing,[26,27] acute respiratory distress syndrome,[28] acute pulmonary embolism,[29,30] and aortic dissection,[11] but has never been fully explained. Furthermore, elevated hs-TnT is a strong predictor of all-cause mortality in hospitalized patients in general with primary non-cardiac conditions such as orthopedic, gastrointestinal, hematological, oncological, pulmonary, neurological, and infectious disease.[31]

Several underlying mechanisms for the association between increase of hs-TnT and non-cardiac mortality in HF patients should be considered. The mechanism behind cTn release still remains unclear, but it may be due to cardiac stress including inflammation, sympathetic nervous activity, hypoxia, hyper or hypotension, or other reasons. Inflammatory mediators from multiple organs (lung, kidney, vascular etc.) present in the systemic circulation due to comorbidities including pulmonary disease, CKD, and arteriosclerosis, have been proposed to exist in HF.[32,33] Moreover, significant associations between cTnT and inflammatory markers have been reported.[34] Pro-inflammatory cytokines such as tumor necrosis factor-$\alpha$, interleukin-1$\beta$ and interleukin-6 derived from activated neutrophils could increase the permeability of cardiomyocyte cell membrane and promote cTn release or apoptosis of cardiomyocytes.[35] In patients with infection, cTn release may result from transient loss in membrane integrity,[36] direct cytotoxicity of bacterial endotoxins, microvascular thrombotic dysfunction, and reperfusion damage.[37] In patients with stroke, cTn is increased approximately 10% and is associated with adverse outcome.[38] Exaggerated catecholamine release leads to excessive release of intracellular calcium ions, and subsequently reversible cardiomyocyte dysfunction.[38] In hospitalized non-cardiac patients, potential etiologies for increased cTn include subendocardial damage secondary to increased wall stress, and oxygen supply/demand mismatch.

In this study, higher hs-TnT was associated with not only left ventricular hypertrophy and systolic dysfunction, but also the presence of potential comorbidities through cardiac stress. These conditions may then cause additional cardiac damage through cardiac wall stress and/or inflammation and other problems. With regard to potential clinical implications, the low-grade myocardial damage reflected by hs-TnT in HF patients underscores the need to understand the pathogenic, especially immunologic, mechanisms of HF and its comorbidities, in order to develop new strategies for the prevention and treatment of non-cardiac diseases such as stroke, infection, respiratory failure, and other disease.

### Study Limitations

The present study was a retrospective analysis of a single institution. The number of subjects was relatively small; hence, prospective studies with a larger subject group are needed.

## Conclusions

Higher hs-TnT was an independent predictor of not only cardiac death but also non-cardiac mortality in HF patients. HF patients with high hs-TnT had left ventricular hypertrophy and systolic dysfunction, and renal dysfunction. These mechanisms may in part contribute to the adverse prognosis of HF patients.

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### Disclosures

Conflicts of Interest: None.

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