Value of Placental Growth Factor as a Predictor of Adverse Events During the Acute Phase of Acute Decompensated Heart Failure

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Background: Few biomarkers, even B-type natriuretic peptide (BNP), can predict the long-term outcome in patients with acute decompensated heart failure (ADHF) on the first day of admission. Placental growth factor (PIGF), a member of the vascular endothelial growth factor family of cytokines, is a key molecule in cardiorenal syndrome and a predictor of adverse events in chronic kidney disease patients. However, its significance in ADHF patients remains poorly understood.

Methods and Results: We studied 408 ADHF patients admitted between April 2011 and December 2016 by measuring their PIGF levels on the first day of admission. Primary endpoints were all-cause and cardiovascular (CV) death. Patients were divided into 2 groups according to PIGF quartiles. Kaplan-Meier analysis revealed that the high PIGF group (quartile 4; ≥12.6 pg/mL) had a worse prognosis than the low PIGF group (quartiles 1–3; <12.6 pg/mL) in terms of all-cause (hazard ratio [HR], 1.56; 95% confidence interval [CI], 1.13–2.14; P<0.01) and CV death (HR, 1.68; 95% CI, 1.04–2.66; P<0.05). After adjustment for covariates, PIGF remained an independent predictor of all-cause and CV death.

Conclusions: PIGF on the first day of admission was significantly associated with both all-cause and CV death, suggesting that it provides novel prognostic information in the acute phase of ADHF.

Key Words: Acute decompensated heart failure; Biomarkers; Outcomes; Placental growth factor

A cute decompensated heart failure (ADHF) is a complex syndrome with a poor prognosis, especially in patients with concurrent chronic kidney disease (CKD). Prompt and accurate clinical evaluation of the severity of ADHF by examining and measuring physiological, hemodynamics, and biochemical parameters is essential for optimal management. However, recent guidelines do not recommend measuring any specific biomarkers for this purpose, as none have been adopted in routine clinical use despite the number of clinical studies performed. Even plasma B-type natriuretic peptide (BNP), while very useful in differentiating ADHF from non-cardiac causes of acute dyspnea, is controversial as a prognostic marker in the acute phase. In this context, further studies to identify new biomarkers that have clinical value and enable us to better understand the pathophysiology and prognosis in the acute phase of ADHF are still necessary.

In ADHF, renal dysfunction resulting from decreased renal blood flow is independently associated with death, and its pathophysiology has been recently advocated as cardiorenal syndrome (CRS). We have previously suggested that the placental growth factor (PIGF)/fms-like tyrosine kinase 1 (Flt-1) system is a critical pathway in CRS. PIGF, a member of the vascular endothelial growth factor family of cytokines, stimulates angiogenesis via binding to the membrane-spanning receptor Flt-1 and exacerbates atherosclerosis by stimulating the migration of monocytes/macrophages into the arterial wall. As verified by our previous work, relative activation of PIGF/Flt-1 signaling in CKD contributes not only to progression of atherosclerotic lesions but also aggravation of cardiac hypertrophy and HF. We have also have demonstrated that circulating PIGF is a useful predictor of cardiovascular (CV) events, including atherosclerotic diseases and HF requiring hospitalization, in patients with CKD.
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Helsinki guidelines for clinical research protocols. Informed consent was given by all patients.

Outcomes
Primary endpoints were all-cause and CV death. CV death was defined as death from HF, MI, sudden death, stroke, or vascular disease. Vital status and the cause of death were confirmed through patient medical records by clinicians blinded to the patients’ PlGF levels. When this information was unavailable in the medical records, clinicians telephoned the patients or their families to collect the data.

Measurements
For PlGF measurement, serum samples were collected within 12h of hospitalization and at discharge. Serum samples

Table 1. Baseline Characteristics of Study Patients With Heart Failure

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Total</th>
<th>Quartile 1–3 (≤12.6 pg/mL)</th>
<th>Quartile 4 (≥12.6 pg/mL)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>74.4±12.1</td>
<td>74.0±12.4</td>
<td>75.5±11.0</td>
<td>0.3792</td>
</tr>
<tr>
<td>Sex (male, %)</td>
<td>56.6</td>
<td>54.3</td>
<td>63.7</td>
<td>0.0925</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.8±4.5</td>
<td>23.6±4.3</td>
<td>24.4±4.9</td>
<td>0.2534</td>
</tr>
</tbody>
</table>

Cause of HF, %
Ischemic heart disease | 37.7 | 34.9 | 46.1 |
Dilated cardiomyopathy | 18.1 | 20.3 | 11.8 |
Hypertensive heart disease | 4.7 | 5.7 | 2.0 |
Valvular heart disease | 15.1 | 14.6 | 16.7 |

Medical history, %
Previous HF hospitalization | 31.5 | 30.5 | 34.3 | 0.4740 |
Hypertension | 72.3 | 71.6 | 74.5 | 0.5699 |
Diabetes mellitus | 42.6 | 41.1 | 47.1 | 0.2950 |
Atrial fibrillation | 44.3 | 45.4 | 41.2 | 0.4572 |

Vital signs on admission
Heart rate (beats/min) | 97.4±28.1 | 97.2±28.6 | 97.8±26.6 | 0.8886 |
SBP (mmHg) | 145.1±34.6 | 145.1±34.9 | 145.1±33.7 | 0.8424 |
DBP (mmHg) | 84.0±21.9 | 84.2±22.3 | 83.4±20.7 | 0.8568 |

Echocardiographic parameters
LAD (mm) | 46.1±8.9 | 46.2±8.9 | 45.7±8.9 | 0.8257 |
LVDd (mm) | 54.2±10.4 | 53.9±10.4 | 55.2±10.4 | 0.2730 |
LVDs (mm) | 42.5±12.6 | 42.3±12.7 | 43.1±12.2 | 0.6523 |
LVEF (%) | 43.1±16.7 | 42.9±16.6 | 43.8±16.9 | 0.5590 |

Laboratory data on admission
Hemoglobin (g/dL) | 11.6±2.4 | 11.7±2.4 | 11.2±2.4 | 0.0232 |
CRP (mg/dL) | 0.5 [0.2–1.8] | 0.5 [0.2–1.7] | 0.8 [0.3–2.7] | 0.0052 |
BUN (mg/dL) | 30.2±20.2 | 29.6±20.0 | 32.1±20.9 | 0.2045 |
eGFR (mL/min/1.73m²) | 46.0±24.5 | 46.8±24.5 | 43.9±24.5 | 0.2866 |
Sodium (mEq/L) | 138.2±4.4 | 138.1±4.5 | 138.4±4.3 | 0.9590 |
BNP (pg/mL) | 915 [501–1,629] | 980 [527–1,625] | 789 [451–1,692] | 0.4224 |

Medications at discharge, %
β-blockers | 71.8 | 72.9 | 68.0 | 0.3552 |
ACEI/ARBs | 86.5 | 87.1 | 84.5 | 0.5209 |
Diuretics | 85.5 | 86.4 | 82.7 | 0.3650 |

Data are presented as the mean±SD for continuous normally distributed variables, the median (25–75th interquartile range [IQR]) for continuous non-normally distributed variables, or n (%). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LAD, left atrial diameter; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure.

Methods
Patient Population
The present study investigated ADHF patients from the NARA-HF 3 study, as described previously.11,12 The NARA-HF 3 study recruited 696 consecutive patients following emergency admission for ADHF between April 2011 and December 2016. Diagnosis of HF was based on the criteria of the Framingham study.13 Patients with acute myocardial infarction (MI), acute myocarditis, or acute HF with acute pulmonary embolism were excluded. Among the patients included, PlGF levels were measured in 408. The present study was approved by the Nara Medical University Institutional Ethics Committee and was performed in accordance with the 1975 Declaration of Helsinki guidelines for clinical research protocols. Informed consent was given by all patients.

Outcomes
Primary endpoints were all-cause and CV death. CV death was defined as death from HF, MI, sudden death, stroke, or vascular disease. Vital status and the cause of death were confirmed through patient medical records by clinicians blinded to the patients’ PlGF levels. When this information was unavailable in the medical records, clinicians telephoned the patients or their families to collect the data.

Measurements
For PlGF measurement, serum samples were collected within 12h of hospitalization and at discharge. Serum samples
PlGF and ADHF

Cumulative event-free rates during follow-up were assessed using the Kaplan-Meier method. Univariate and multivariate analyses of event-free survival were examined using Cox proportional hazard models. An unadjusted model and 3 models for the adjustment of covariates were utilized as follows: model 1 adjusted for age and sex, model 2 adjusted for the covariates in model 1 plus systolic blood pressure (SBP) and LVEF, and model 3 adjusted for the covariates in model 2 plus hemoglobin concentration (Hb), eGFR, and BNP. When analyzing the association between BNP and study outcomes, we excluded BNP from the adjusted model. P<0.05 was considered statistically significant. JMP software for Windows version 13 (SAS Institute, Cary, NC, USA) was used for all statistical analyses.

Results

PIGF and Risks of All-Cause and CV Death

The mean age of the 408 patients was 74 (±12) years and the proportion of men was 57% (Table 1). During the mean follow-up period of 25 (13–42) months, 167 participants died, including 76 from CV causes. Supplementary Figure 1 shows the distribution of PlGF levels. To investigate the effect of PlGF on the prognosis of ADHF, patients were divided into quartiles (quartile 1; <4.5 pg/mL, quartile 2; 4.5–7.6 pg/mL, quartile 3; 7.6–12.6 pg/mL, and quartile 4; ≥12.6 pg/mL). Supplementary Figure 2 shows the Kaplan-Meier event-free survival curves for the 4 groups. The quartile 4 group tended to have a worse prognosis than the other 3 groups, but there was no significant different among the lower 3 groups in all-cause (log rank P=0.9658) and CV death (log rank P=0.9786).
To clarify the effect of higher levels of PlGF on the prognosis of ADHF, patients were divided into two categories: quartiles 1–3 (<12.6 pg/mL) and the highest quartile (quartile 4; ≥12.6 pg/mL) based on PlGF levels on admission. Crude Kaplan-Meier curves revealed that participants with a higher level of PlGF had a significantly greater risk of all-cause (log rank P=0.0054) and CV death (log rank P=0.0283) (Figure 1).

Table 1 summarizes the characteristics of the ADHF patients according to these categories. Age, sex ratio, and body mass index in the high and low PlGF groups were similar. In terms of the cause of HF, the high PlGF group had a significantly higher ratio of ischemic cardiomyopathy than the low PlGF group. There were no significant differences in SBP, diastolic BP, LVEF, and plasma BNP levels between the 2 groups. The high PlGF group exhibited significantly reduced levels of Hb and elevated levels of C-reactive protein (CRP) compared with the low PlGF group. There was no significant difference in the proportion of patients treated with β-blockers, angiotensin-converting enzyme inhibitors and/or angiotensin II receptor blockers, and diuretics on admission and at discharge between the 2 groups (Table 1).

Table 2. Cox Regression Analysis of PlGF as a Predictor of Adverse Outcomes

<table>
<thead>
<tr>
<th></th>
<th>All-cause death</th>
<th></th>
<th>CV death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;12.6 pg/mL</td>
<td>≥12.6 pg/mL</td>
<td>P value</td>
</tr>
<tr>
<td>Unadjusted HR</td>
<td>1.56 (1.13–2.14)</td>
<td>1.00</td>
<td>0.0071</td>
</tr>
<tr>
<td>Adjusted HR (model 1)</td>
<td>1.51 (1.09–2.08)</td>
<td>0.0141</td>
<td></td>
</tr>
<tr>
<td>Adjusted HR (model 2)</td>
<td>1.60 (1.14–2.22)</td>
<td>0.0064</td>
<td></td>
</tr>
<tr>
<td>Adjusted HR (model 3)</td>
<td>1.55 (1.09–2.17)</td>
<td>0.0140</td>
<td></td>
</tr>
</tbody>
</table>

Model 1: adjusted for age, sex; model 2: adjusted for age, sex, SBP, and LVEF; model 3: adjusted for age, sex, SBP, LVEF, hemoglobin, eGFR, BNP, and CRP. CI, confidence interval; CV, cardiovascular; HR, hazard ratio; PlGF, placental growth factor. Other abbreviations as in Table 1.

Figure 2. All-cause and cardiovascular (CV) death according to BNP levels. Kaplan-Meier event-free survival curves for (A) all-cause and (B) CV death in patients with BNP levels ≥1,630 pg/mL (high BNP group; n=102) compared with patients with BNP levels <1,630 pg/mL (low BNP group; n=306). BNP, B-type natriuretic peptide.
BNP and Risks of All-Cause and CV Death

We also divided patients into 2 groups according to BNP quartiles on admission (high BNP group: quartile 4, ≥1,630 pg/mL and low BNP group: quartiles 1–3, <1,630 pg/mL) as well as PlGF. Figure 2 shows the Kaplan-Meier analysis for each group based on the plasma BNP levels on admission. No significant difference in all-cause and CV death was observed between the high and low BNP groups. Additionally, elevated levels of BNP were not significantly associated with a risk of death in either the unadjusted or fully adjusted model, unlike PlGF levels (Table 3).

Factors Affecting PlGF

To identify the independent determinants of PlGF levels, we performed multiple linear regression analyses. As shown in Table 4, there was no correlation between PlGF and these other parameters.

Discussion

The present study is the first to demonstrate an association between PlGF levels on admission and long-term adverse events in patients with ADHF. The HRs of PlGF were attenuated in the fully adjusted model; however, PlGF remained independently associated with all-cause and CV death. In contrast, plasma BNP levels on admission were not associated with a risk of death in ADHF patients. These findings suggested that PlGF is a possibly useful biomarker of long-term outcome on the first day of admission for ADHF.

Using soluble Flt-1-specific knockout mice, in which PlGF/Flt-1 signaling is relatively activated, we proposed that activation of PlGF/Flt-1 signaling aggravates pressure overload-induced cardiac remodeling and HF, and that administration of an anti-PlGF neutralizing antibody ameliorates this phenomenon.9 Earlier human studies reported the significance of PlGF in HF, one of which showed that patients with chronic HF had significantly higher levels of PlGF than healthy young subjects after adjustment for factors such as age and sex.16 Another reported that patients with chronic HF in the high PlGF group had an approximately 2-fold increased risk for adverse events, but this finding was less significant after adjustment for covariates.16 Thus, it is likely that PlGF is involved in the pathophysiology of HF. However, all the earlier human studies were performed in patients with chronic HF, not ADHF. In our study, elevated PlGF levels on admission were significantly associated with all-cause and CV death in ADHF. Additionally, among the patients included in this study, PlGF at discharge was measured in 150 patients. The PlGF levels at discharge did not change significantly compared with the levels on admission (P=0.9814), suggesting that PlGF levels were not affected by hemodynamic change and indicate the patient’s basal condition. This result suggested that PlGF is a potential biomarker for risk stratification of both ADHF and CHF patients.

In this study, there was no significant factor that defined the PlGF levels. The high PlGF group exhibited significantly elevated levels of CRP compared with the low PlGF group, but as CRP was not an independent predictor regulating the PlGF levels in the analysis with continuous variables, the relationship between CRP and PlGF requires further analysis. Additionally, regarding the mechanism by which PlGF is elevated in HF, its clinical significance needs to be further investigated.

This study determined a PlGF cutoff level of 12.6 pg/mL in patients with ADHF, BECAUSE participants within the first 3 PlGF quartiles showed no significant difference in all-cause (log rank P=0.9658) or CV death (log rank P=0.9786). In a previous report on chronic HF patients, Ky et al16 revealed that the highest PlGF group (>22.7 pg/mL) had significantly worse prognosis than the other 3 groups divided by quartile. Their study, as well as ours, suggests that plasma levels of PlGF may be useful above a certain

Table 3. Cox Regression Analysis of BNP as a Predictor of Adverse Outcomes

<table>
<thead>
<tr>
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<th>All-cause death</th>
<th>CV death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;1,630 pg/mL</td>
<td>≥1,630 pg/mL</td>
</tr>
<tr>
<td>Unadjusted HR</td>
<td>1.27 (0.90–1.78)</td>
<td>0.1712</td>
</tr>
<tr>
<td>Adjusted HR (model 1)</td>
<td>1.27 (0.89–1.77)</td>
<td>0.1858</td>
</tr>
<tr>
<td>Adjusted HR (model 2)</td>
<td>1.09 (0.75–1.56)</td>
<td>0.6818</td>
</tr>
<tr>
<td>Adjusted HR (model 3)</td>
<td>1.04 (0.71–1.51)</td>
<td>0.8310</td>
</tr>
</tbody>
</table>

Model 1: adjusted for age, sex; model 2: adjusted for age, sex, SBP, and LVEF; model 3: adjusted for age, sex, SBP, LVEF, hemoglobin, eGFR, and CRP. Abbreviations as in Tables 1,2.

Table 4. Variables Affecting PlGF Levels

<table>
<thead>
<tr>
<th></th>
<th>Coefficient</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 1 year)</td>
<td>+0.03</td>
<td>(−0.04 to 0.10)</td>
<td>0.4150</td>
</tr>
<tr>
<td>CRP (per 1 mg/dL)</td>
<td>+0.15</td>
<td>(−0.11 to 0.40)</td>
<td>0.2650</td>
</tr>
<tr>
<td>Hemoglobin (per 1 g/dL)</td>
<td>−0.22</td>
<td>(−0.62 to 0.18)</td>
<td>0.2756</td>
</tr>
<tr>
<td>eGFR (per 1 mL/min/1.73 m²)</td>
<td>−0.01</td>
<td>(−0.04 to 0.03)</td>
<td>0.7293</td>
</tr>
<tr>
<td>BNP (per 100 pg/mL)</td>
<td>−0.02</td>
<td>(−0.10 to 0.06)</td>
<td>0.6548</td>
</tr>
<tr>
<td>SBP (per 10 mmHg)</td>
<td>+0.15</td>
<td>(−0.10 to 0.39)</td>
<td>0.2332</td>
</tr>
<tr>
<td>LVEF (per 1%)</td>
<td>+0.01</td>
<td>(−0.05 to 0.06)</td>
<td>0.8258</td>
</tr>
</tbody>
</table>

Abbreviations as in Tables 1,2.
threshold among patients with each disease. However, because the 2 studies used different assay kits, it is difficult to evaluate the cutoff as an absolute value. Therefore, in this study, the highest quartile (12.6 pg/mL) was taken as the cutoff level, but it is necessary to pay attention to the clinical significance of levels of 12.6 pg/mL for prediction of prognosis in patients with ADHF.

Of note in the current study, plasma BNP levels on admission were not associated with long-term all-cause or CV death in ADHF patients, in contrast to previous reports. However, we reset the BNP cutoff levels using a ROC curve (1,550 pg/mL). In high BNP group, the prognosis tended to be worse than in the low BNP group, but not significantly (P=0.0618, data not shown). Given that the plasma BNP level is widely accepted as a useful biomarker of the severity of HF, the level in the acute phase of ADHF is probably affected by many factors related to acute HF such as hemodynamic changes, acute renal injury, and/or inflammatory cytokines. In fact, interleukin-6 and IL-1β stimulate BNP production, and a reduced GFR augments BNP production and reduces clearance. It should be noted that the PlGF level in the acute phase of ADHF predicted long-term outcomes.

Study Limitations
First, this was a single-center study involving a relatively small number of ADHF patients. Second, one-third of patients were excluded because their PlGF data was unavailable (unable to be measured). Third, there are no solid data on the PlGF levels of healthy individuals, and there are differences depending on assay kit, so further study is required to evaluate the absolute cutoff value for PlGF-dependent stratification.

Conclusions
PlGF on admission was more strongly associated with both all-cause and CV death than BNP. PlGF could provide novel prognostic information in the acute phase of ADHF.

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Conflict of Interest
None declared.

References