Elevated Serum Heart-Type Fatty Acid-Binding Protein in the Convalescent Stage Predicts Long-Term Outcome in Patients Surviving Acute Myocardial Infarction

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Background: Little is known about the prognostic significance of elevated serum heart-type fatty acid-binding protein (H-FABP) in post-acute myocardial infarction (post-AMI) patients.

Methods and Results: A total of 1,283 post-AMI patients with available serum samples collected in the convalescent stage were studied. During a median follow-up period of 1,785 days, 176 patients (14%) had adverse events (all-cause mortality, $n=81$; non-fatal MI, $n=44$; readmission for heart failure [HF], $n=51$). Patients were divided into 2 groups according to a serum H-FABP level of 6.08 ng/ml, which was determined to be the optimal cut-off for discriminating all-cause mortality based on the maximum value of the area under the receiver operating characteristic curve. Patients with elevated H-FABP (>6.08 ng/ml, $n=224$) had a significantly higher incidence of death (18.3% vs. 3.8%, $P<0.001$) and readmission for HF (10.3% vs. 2.6%, $P<0.001$), but not of non-fatal MI (4.5% vs. 3.2%, $P=0.187$), compared to those with H-FABP <6.08 ng/ml. Multivariate Cox regression analysis indicated that elevated serum H-FABP was associated with an increased risk of mortality (hazard ratio [HR], 1.91; 95% confidence interval [CI]: 1.03–3.51, $P=0.039$) and readmission for HF (HR, 2.49; 95% CI: 1.15–5.39, $P=0.020$).

Conclusions: Elevated serum H-FABP during the convalescent stage of AMI predicted long-term mortality and readmission for HF after survival discharge in the post-AMI patients. (*Circ J* 2013; **77**: 1026–1032)

Key Words: Acute myocardial infarction; Cardiac event; Heart-type fatty acid-binding protein

Heart-type fatty acid-binding protein (H-FABP) is an abundant cytoplasmic protein in myocardial tissue,¹ and is rapidly released into the circulation at an earlier stage of acute myocardial infarction (AMI) than other biomarkers such as troponin and creatine kinase (CK). Because H-FABP quickly disappears from the blood,² this protein biomarker has been used in clinical practice to diagnose AMI at an early phase.^{3–8} Several reports have shown that elevated H-FABP in the acute phase of AMI is associated with an increased risk of cardiac events,^{9–11} but few studies have investigated the clinical significance of serum H-FABP level in the convalescent stage of AMI.

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In patients with chronic heart failure (HF), it has been reported that increased serum H-FABP could reflect ongoing myocardial damage that causes progressive deterioration of ventricular function, and thus predict worse outcome.^{12–14} Therefore, we hypothesized that elevated H-FABP level documented in the convalescent stage could reflect ongoing myocardial damage after AMI and thus predict worse outcome in post-AMI patients.

In the present study we (1) investigated whether elevated serum H-FABP was a predictor of adverse events in patients

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surviving AMI; (2) determined the optimal cut-off value for H-FABP for predicting high risk for mortality; and (3) compared the predictive accuracy of adverse events (as assessed using the C-statistics, calculated as the area under the receiver operating characteristic curve; AUC), between H-FABP, cardiac troponin-T and left ventricular end-diastolic dimension (LVDd).

Methods

Source of Study Data

The Osaka Acute Coronary Insufficiency Study (OACIS) is a prospective, multicenter observational study in which 25 collaborating hospitals from the Osaka region of Japan record demographic, procedural, and outcome data, as well as collect and store blood samples from patients with AMI. A detailed description of the OACIS registry has been published elsewhere.^{15–19} The study protocol was approved by the ethics committee of each participating hospital.

Subjects

Among 8,603 patients with AMI who were registered in the OACIS between 1998 and 2008, we included all patients fulfilling the following criteria: (1) discharge alive between 2000 and 2005; and (2) provision of a blood sample before or within 14 days of discharge. The study protocol complied with the Guidelines for Genome/Genetic Research issued by the Japanese government and was approved by each of the participating institutional ethics committees. Written informed consent was obtained from each patient.

Serum Collection and Measurement of H-FABP and Cardiac Troponin-T

At each participating hospital, fasting blood samples were collected into serum separator tubes. After separation of the clot by centrifugation of the tubes at 1,430 g for 15 min at 4°C, the serum was removed and sent to SRL (Tokyo, Japan), where samples were stored at –80°C until the initial assay. The samples were then shipped to DS Pharma Biomedical for the measurement of H-FABP using a MARKIT-M H-FABP enzyme-linked immunosorbent assay kit (DS Pharma Biomedical, Osaka, Japan). The lower and upper detection limits for the H-FABP concentration were 1.25 ng/ml and 250 ng/ml, respectively. The median timing of serum sample collection after AMI onset was 20 days (range, 14–27 days). Cardiac troponin-T was measured with a third-generation immunoassay (Elecsys Troponin T; Roche Diagnostics, Indianapolis, IN, USA). The detection limit of the assay was 0.01 ng/ml.

Data Collection

Research cardiologists and trained research nurses or coordinators recorded data concerning sociodemographic variables, medical history, therapeutic procedures, and clinical events during the hospital stay. Clinical data after discharge were obtained at 3 and 12 months after the onset of AMI, and annually thereafter up to 5 years. The clinical endpoint of this study was primarily all-cause mortality. To explore the underlying mechanism, readmission for HF and non-fatal MI were also included as study endpoints. Non-fatal MI was defined as the occurrence of symptoms used for the diagnosis of AMI.¹⁸ Readmission for HF was defined using the Framingham Heart Study criteria.²⁰

Statistical Analysis

After confirming that serum H-FABP was higher in post-AMI

Figure 1. Serum heart-type fatty acid-binding protein (H-FABP) distribution in post-acute myocardial infarction patients.

patients who died from any cause, we determined the best cut-off point for balancing the sensitivity and specificity of all-cause mortality with the point on the curve closest to the upper left-hand corner of the AUC.²¹ To verify the estimated cut-off value, repeated random sub-sampling validation was conducted.²² C-statistics, as assessed by the AUC, were then used to assess predictive accuracy.²³ According to the optimal cut-off value for H-FABP concentration, patients were then divided into 2 groups. Categorical variables were compared between the 2 groups using the χ^2 test. All continuous variables are described as mean $\pm$ SD and were compared using Student's t-test. For continuous variables not normally distributed, the variables are given as median (25th–75th percentile) and compared using Mann-Whitney U-test. Rates of cardiac events, including all-cause mortality, non-fatal MI, and readmission for HF, following discharge for the 2 groups are described using the Kaplan-Meier method and compared using the log-rank test. Multivariate logistic regression analysis was used to identify factors associated with elevated H-FABP. The variables used in model 1 were age, male gender, body mass index, diabetes mellitus (DM), hypertension, dyslipidemia, smoking, previous MI, peak CK $\geq 3,000$ (IU/L), Killip $\geq$ II on admission, reperfusion therapy, and estimated glomerular filtration rate (eGFR). Step-wise regression analysis (model 2) was then performed to validate the determinants detected in model 1. Cox regression models were used to examine whether elevated H-FABP was associated with an increased risk of all-cause mortality, non-fatal MI, and readmission for HF. All analyses were performed using PASW Statistics, version 18 (SPSS, Chicago, IL, USA). Statistical significance was defined as $P < 0.05$ or 95% confidence intervals (95% CI) that did not include 1.0.

Results

A total of 1,283 post-AMI patients were included in the present study; 77% were male and the mean age was 64 ± 11 years. The median serum H-FABP concentration collected at a median of 20 days after AMI onset was 3.67 ng/ml (2.84–5.21; **Figure 1**). Because serum H-FABP was significantly higher in patients who died from any cause than surviving patients (6.09 ng/ml,

Table 1. Baseline Patient Characteristics vs. Serum H-FABP Level

	H-FABP (ng/ml)		P-value
	≤6.08 (n=1,059)	>6.08 (n=224)	
Age (years)	62.0±10.4	71.0±10.4	<0.001
Male	78.6	71.0	0.018
BMI (kg/m ²)	23.9±3.2	23.1±4.0	0.012
Diabetes mellitus	29.4	38.8	0.007
Hypertension	54.4	72.5	<0.001
Dyslipidemia	50.2	38.1	0.001
Smoking	71.5	53.6	<0.001
Previous MI	10.5	13.4	0.233
Onset to admission time <24 h	87.0	86.5	0.825
Peak CK ≥3,000 IU/L	35.8	33.3	0.571
Killip class ≥II on admission	8.7	18.8	<0.001
Reperfusion therapy	92.6	86.6	0.005
eGFR (ml·min ⁻¹ ·1.73 m ⁻²)	69.9±18.3	46.6±24.1	<0.001
LVDd (mm)	50.3±5.9	51.5±7.4	0.034
cTnT (ng/ml)	0.01 (0.01–0.05)	0.05 (0.01–0.38)	<0.001
ACEI or ARB	75.9	64.5	0.001
β-blocker	44.1	48.6	0.234
Statin	39.9	25.5	<0.001
Antiplatelet therapy	99.1	98.6	0.445

Data given %, mean ± SD or median (25th–75th percentile).

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CK, creatinine kinase; cTnT, cardiac troponin T; eGFR, estimated glomerular filtration rate; H-FABP, heart-type fatty acid-binding protein; LVDd, left ventricular end-diastolic dimension; MI, myocardial infarction.

Table 2. Factors Associated With Elevated H-FABP (>6.08 ng/ml)

	Model 1 [†]		Model 2 [‡]	
	OR (95% CI)	P-value	OR (95% CI)	P-value
eGFR	0.94 (0.93–0.95)	<0.001	0.94 (0.93–0.95)	<0.001
Age	1.07 (1.05–1.10)	<0.001	1.08 (1.06–1.10)	<0.001
Diabetes mellitus	1.69 (1.12–2.54)	0.013	1.71 (1.14–2.56)	0.010
Killip class ≥II	1.60 (0.89–2.89)	0.118	– (–)	–
BMI	0.98 (0.92–1.04)	0.515	– (–)	–
Hypertension	1.40 (0.92–2.16)	0.120	– (–)	–
Dyslipidemia	0.93 (0.62–1.39)	0.726	– (–)	–
Reperfusion therapy	0.92 (0.43–1.96)	0.823	– (–)	–
Male	1.06 (0.65–1.72)	0.816	– (–)	–
Peak CK ≥3,000 (IU/L)	1.09 (0.72–1.66)	0.694	– (–)	–
Previous MI	0.99 (0.56–1.74)	0.973	– (–)	–
Smoking	0.88 (0.57–1.37)	0.583	– (–)	–

[†]Variables considered to be associated with elevated H-FABP were inserted into multivariate logistic regression model. [‡]Stepwise regression analysis was further performed in order to validate the factors identified in model 1. CI, confidence interval; OR, odds ratio. Other abbreviations as in Table 1.

3.92–13.3 ng/ml vs. 3.57 ng/ml, 2.78–4.95 ng/ml; $P<0.001$), we determined the optimal cut-off value of serum H-FABP for discriminating between the risk of all-cause mortality and survival. The optimal cut-off was estimated to be 6.08 ng/ml with C-statistics of 0.68.

Patients with elevated serum H-FABP >6.08 ng/ml ($n=224$) were more likely to be older and female, and to have DM, hypertension, HF defined as Killip class ≥2 on admission, and multivessel disease compared to those with H-FABP ≤6.08 ng/ml ($n=1,059$; **Table 1**). In addition, patients with elevated H-FABP were less likely to have dyslipidemia, smoking, obesity, and reperfusion therapy, and were less likely to receive angiotensin-converting enzyme inhibitors, angiotensin receptor block-

ers, or statins (**Table 1**).

Multivariate logistic regression analysis indicated that advanced age, DM, and decreased eGFR were significantly associated with elevated H-FABP (**Table 2**). To clarify the effect of infarct size on H-FABP concentration, correlations were examined. No significant correlation between serum H-FABP concentrations and peak CK was detected (**Figure 2**).

During a median follow-up period of 1,785 days, 81 patients died, 44 had non-fatal reinfarction, and 51 were rehospitalized for HF (**Table 3**). Kaplan-Meier curves showed that patients with elevated H-FABP had a significantly higher incidence of death (18.3% vs. 3.8%, $P<0.001$; **Figure 3A**) and readmission for HF (10.3% vs. 2.6%, $P<0.001$; **Figure 3B**) than those

Figure 2. Correlation of serum heart-type fatty acid-binding protein (H-FABP) concentration with peak creatinine kinase (CK).

without, although no significant differences in the rate of non-fatal MI was detected between the 2 groups (4.5% vs. 3.2%, $P=0.187$; **Figure 3C**). Multivariate Cox regression analysis also showed that elevated serum H-FABP was associated with an increased risk of all-cause mortality (hazard ratio [HR], 1.91; 95% CI: 1.03–3.51; $P=0.039$) and readmission for HF (HR, 2.49; 95% CI: 1.15–5.39; $P=0.020$; **Table 4**); no association was observed between elevated serum H-FABP and the risk of non-fatal MI (HR, 1.40; 95% CI: 0.55–3.57; $P=0.475$; **Table 4**).

The predictive accuracy of all-cause mortality and readmission for HF, assessed with the C-statistics for these 2 factors, was greater for H-FABP (0.730 and 0.724, respectively) compared with that for cardiac troponin-T (0.634 and 0.600, respectively) and LVDd (0.587 and 0.622, respectively) measured before discharge in the present subjects.

Discussion

In the present study, we found that elevated H-FABP is associated with an increased risk of all-cause mortality, and readmission for HF following AMI, but not of non-fatal MI. From the present analysis of 1,283 AMI patients, the optimal cut-off value for serum H-FABP was 6.08 ng/ml. The factors associated with elevated H-FABP were advanced age, DM, and impaired renal function.

To our knowledge, this is the first study to investigate the clinical impact of serum H-FABP concentration at the convalescent stage in post-AMI patients. H-FABP level in the present patients was skewed towards lower concentrations, given that the median and mean were 3.67 ng/ml and 5.74 ng/ml, respectively (**Figure 1**). Considering that the cut-off of H-FABP to diagnose MI is >6.2 ng/ml in the clinical setting, as measured by commercially available kits,² 18% of the present patients had elevated H-FABP in the 20 days after AMI onset. Although it is presently unclear why H-FABP remains high in the convalescent stage of AMI, it is possible that myocardial damage is ongoing during this stage.^{12,13}

Table 3. Outcome Following Discharge for AMI

Outcome	H-FABP (ng/ml)		P-value
	≤6.08 (n=1,059)	>6.08 (n=224)	
All-cause mortality, n (%)	40 (3.8)	41 (18.3)	<0.001
Non-fatal MI, n (%)	34 (3.2)	10 (4.5)	0.187
Readmission for HF, n (%)	28 (2.6)	23 (10.3)	<0.001

AMI, acute MI; HF, heart failure. Other abbreviations as in Table 1.

Table 4. Correlation of Elevated Serum H-FABP and Outcome

Outcome	Adjusted HR† (95% CI)	P-value
All-cause mortality	1.91 (1.03–3.51)	0.039
Non-fatal MI	1.40 (0.55–3.57)	0.475
Readmission for HF	2.49 (1.15–5.39)	0.020

†Adjustment for age, gender, BMI, classical coronary risk factors (hypertension, dyslipidemia, diabetes mellitus, and smoking), history of previous MI, reperfusion therapy, Killip class on admission, chronic kidney disease defined as eGFR <60 ml·min⁻¹·1.73 m⁻², and medication at discharge (ACEI and/or ARB, β-blockers, and statins).

HR, hazard ratio. Other abbreviations as in Tables 1–3.

Elevated serum H-FABP in the acute stage of AMI or acute coronary syndrome (ACS) appears to be a useful predictor of cardiac events after the onset of disease. The relationship between serum H-FABP at a mean of 40 hours and cardiac events during a 10-month follow-up period in 2,287 ACS patients was investigated in the Orbofiban in Patients with Unstable Coronary Syndromes (OPUS)-TIMI 16 trial. The authors found that elevated H-FABP (>8.0 ng/ml) was associated with an increased risk of death (HR, 2.7) and congestive HF (HR, 2.4). Kilcullen et al demonstrated the prognostic importance of H-FABP level evaluated 12–24 hours after the onset of ACS in the Evaluation of Methods and Management of Acute Coronary Events (EMMACE)-2 study, which consisted of 1,448 ACS patients, in that quartiles of H-FABP level strongly predicted 12-month mortality on multivariate analysis.⁹ In addition, Viswanathan et al reported an association between elevated H-FABP and increased risk of 12-month mortality and myocardial reinfarction in 955 patients with suspected ACS.¹¹ But because these previous studies investigated only the impact of H-FABP level on ≤12-month outcomes in acute ACS patients, it remained unclear whether H-FABP is a useful predictor of cardiac events in patients surviving the acute stage of AMI. In this regard, the present findings are of marked clinical significance in the setting of secondary prevention after AMI, because the prognostic impact of elevated H-FABP on subsequent adverse events in post-AMI patients was examined during a relatively long follow-up period of approximately 5 years. Notably, we found that elevated serum H-FABP is associated with an increased risk of all-cause mortality and readmission for HF. With respect to the predictive accuracy of all-cause mortality and readmission for HF, the C-statistics for these 2 factors were larger for H-FABP compared with those for both troponin-T and LVDd in the current subjects, suggesting that H-FABP is superior to troponin-T and LVDd for predicting subsequent adverse events in post-AMI patients. Therefore, the present findings suggest that the measurement of serum H-FABP in a single blood sample collected during the convalescent stage may predict long-term outcome, such

as all-cause mortality and rehospitalization for HF, with higher accuracy than troponin T and LVDd in post-AMI patients.

The correlation between elevated H-FABP and outcome in AMI patients has been examined using cut-offs determined between the highest and 3 lower quartiles.^{9–11} Although this approach has been used to estimate cut-off values in several epidemiological studies, it is not necessarily optimal to predict subsequent outcomes. Therefore, we determined the optimal cut-off value of serum H-FABP, which was found to be 6.08 ng/ml with a C-statistic of 0.68, discriminating all-cause mortality. The C-statistic was 0.67 for a cut-off value of 5.21 ng/ml, which was determined from the value between the 3rd and highest quartiles in the present patients. Although these C-statistics were similar between the 2 cut-offs, the optimal cut-off value calculated in the present study may provide adequate risk stratification to predict subsequent cardiac outcome in the clinical practice setting. Indeed, the sensitivity, specificity, and positive and negative predictive values were 51%, 85%, 18%, and 96%, respectively, for the optimal cut-off value of 6.08 ng/ml, and 57%, 77%, 14%, and 96%, respectively, for the cut-off value determined from the 3rd and highest quartiles, showing that the former cut-off value had higher specificity and positive predictive value. We also attempted to determine whether elevated H-FABP is attributable to necrosis of infarcted areas, but did not detect a significant correlation for H-FABP with peak CK (Figure 2), suggesting that serum H-FABP is not associated with infarct size.

We found that advanced age, DM, and impaired renal function, as indicated by decreased eGFR, are associated with increased serum H-FABP concentration (Table 2). We speculate that elevated H-FABP in post-AMI patients results from either increased secretion of H-FABP from the myocardium or impaired excretion of H-FABP from the kidney.^{24,25} Akbal et al reported that H-FABP is significantly elevated in patients with metabolic syndrome, particularly in diabetic patients.²⁶ We previously reported that post-AMI diabetic patients have an increased risk of admission for HF and that high-sensitivity C-reactive protein (hs-CRP) in the convalescent stage of AMI is significantly higher in diabetic patients who were readmitted for HF than in those who were not.¹⁷ Scirica et al also reported that hs-CRP in the convalescent stage of ACS is significantly higher in patients rehospitalized for HF.²⁷ Considering that aging is associated with increased vascular inflammation, it is possible that myocardial injury associated with aging, metabolic disorders, and inflammatory reactions coordinately induced elevation of serum H-FABP, resulting in an increased risk of all-cause mortality and readmission for HF in the present patients.

Kleine et al found that H-FABP concentration remains elevated even 25 hours after AMI onset in patients with renal insufficiency, whereas it normalizes within 10 hours in patients with normal renal function.²⁵ These findings suggest that the excretion of H-FABP may be prolonged in patients with renal dysfunction, resulting in worse outcome in relation to impaired renal function. Indeed, all-cause mortality ($P<0.001$) and readmission for HF ($P=0.037$) were significantly higher in patients with elevated serum H-FABP than in those without among patients with impaired renal function with $eGFR<50\text{ ml}\cdot\text{min}^{-1}\cdot 1.73\text{ m}^{-2}$. We note that a linear relationship between elevated H-FABP and increased risk of all-cause mortality ($P=0.018$) and readmission for HF ($P=0.039$) was also seen, even in patients with $eGFR\geq 50\text{ ml}\cdot\text{min}^{-1}\cdot 1.73\text{ m}^{-2}$, indicating that elevated H-FABP serves as a predictor of these adverse outcomes in patients with normal renal function. Advanced age may be involved in elevated serum H-FABP through both increased

secretion from heart tissue and decreased secretion from the kidney. It should be stressed, however, that the factors of age, DM, and impaired renal function might account for a small fraction of the increased incidence of all-cause mortality and readmission for HF observed in the present study, although the coefficient of determination was not significant (data not shown). Therefore, elevation of serum H-FABP might be attributable to yet undetermined underlying factors associated with myocardial injury and inflammation, among others. Interestingly, the present results show that there is no relationship between peak CK in the acute stage of AMI and elevated H-FABP, suggesting that higher serum H-FABP concentration does not necessarily cause subsequent mortality through increased infarct size.

Study Limitations

Several limitations of the present study warrant mention. First, although the OACIS is a multicenter observational prospective study and represents the real-world situation regarding the management and outcome of AMI, the present study was conducted retrospectively and included only patients who provided written informed consent, and may have been influenced by the presence of selection bias. Second, left ventricular ejection fraction (LVEF) was not assessed before discharge, even though LVEF is considered to be associated with an increased risk of adverse events. Instead, Killip class and peak CK activity were used to investigate predictors of elevated H-FABP, and the relationship between elevated H-FABP and mortality. Third, we did not have sufficient information on the treatment of patients, including the use of percutaneous coronary intervention for myocardial ischemia after discharge. Therefore, the present observations may need to be confirmed in various cohorts.

Conclusions

Elevated serum H-FABP served as an accurate predictor of long-term outcome, including all-cause mortality and readmission for HF, in the 1,283 present post-AMI patients. Patients with H-FABP $>6.08\text{ ng/ml}$ during the convalescent stage of AMI may be treated as at high risk for subsequent adverse events.

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Disclosures

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Appendix 1

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