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ORIGINAL ARTICLE

Urinary liver-type fatty acid-binding protein as a prognostic marker in patients with acute heart failure

Tsutomu Sunayama[1], Shoichiro Yatsu[1], Yuya Matsue[1,2]*, Taishi Dotare[1], Daichi Maeda[1,3], Sayaki Ishiwata[1], Yutaka Nakamura[1], Shoko Suda[1], Takao Kato[1], Masaru Hiki[1], Takatoshi Kasai[1,2] and Tohru Minamino[1,4]

[1]*Department of Cardiovascular Biology and Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan;* [2]*Cardiovascular Respiratory Sleep Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan;* [3]*Department of Cardiology, Osaka Medical and Pharmaceutical University, Osaka, Japan; and* [4]*Japan Agency for Medical Research and Development-Core Research for Evolutionary Medical Science and Technology (AMED-CREST), Japan Agency for Medical Research and Development, Tokyo, Japan*

Abstract

Aims Urinary liver-type fatty acid-binding protein (L-FABP) is expressed in proximal tubular epithelial cells and excreted into the urine during tubular injury. We hypothesized that high urinary L-FABP is associated with poor prognosis in patients with acute heart failure (AHF).

Methods and results We analysed 623 patients (74 ± 13 years old; 60.0% male patients) with AHF. Urinary L-FABP levels were measured at the time of admission and adjusted for the urinary creatinine concentration. The primary endpoint was all-cause mortality. The median value and interquartile range of urinary L-FABP levels were 6.66 and 3.37–21.1 μg/gCr, respectively. Urinary L-FABP levels were significantly correlated with both beta-2 microglobulin and cystatin C levels; the correlation with the former was higher than that with the latter. During the follow-up of 631 (interquartile range: 387–875) days, 142 deaths occurred. A high tertile of urinary L-FABP level was associated with high mortality; this association was retained after adjusting for other covariates (second tertile hazard ratio 1.40, P = 0.152 vs. first tertile; third tertile hazard ratio 1.94, P = 0.005 vs. first tertile).

Conclusions Urinary L-FABP is more closely associated with tubular dysfunction than with glomerular dysfunction. Tubular dysfunction, which was evaluated based on urinary L-FABP levels, in patients with AHF is associated with all-cause mortality and is independent of pre-existing risk factors. L-FABP should be considered for use in the prognosis of AHF.

Keywords Urinary liver-type fatty acid-binding protein; Acute heart failure; Tubular dysfunction; Beta-2 microglobulin; Prognosis

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**Correspondence to: Yuya Matsue and Shoichiro Yatsu, Department of Cardiovascular Biology and Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan. Phone: +81-3-3813-3111; Fax: +81-3-5689-0627. Email: yuya8950@gmail.com; syatsu@juntendo.ac.jp*

Introduction

Renal dysfunction is a major complication of acute and chronic heart failure[1] and is associated with poor prognosis.[2] Creatinine is the most important biomarker for renal function, particularly for glomerular function; previous studies revealed a strong correlation between the prognosis of renal disorders and reduced estimated glomerular filtration rate (eGFR) calculated using serum creatinine levels.

Tubular dysfunction is another form of renal impairment that occurs in patients with heart failure. As renal tubules have the highest oxygen consumption in the kidney, tubular dysfunction is common, particularly during reduced tissue perfusion and hypoxia including heart failure.[3] Therefore, tubular dysfunction defined by associated biomarkers is thought to be associated with poor prognosis in patients with heart failure. This hypothesis has been tested in several observational studies involving patients with chronic heart failure that have demonstrated its prognostic capability[4–6]; however, some of these studies included a limited number of patients and showed conflicting results for acute heart failure (AHF).[7–9] Therefore, although cardio-renal interactions may play important roles in patients with AHF, it remains unknown whether tubular function can be analysed to predict clinical outcomes in this population.

Liver-type fatty acid-binding protein (L-FABP) is an endogenous antioxidant protein expressed in proximal tubular epithelial cells and is released into the tubular lumen in response to ischaemia or oxidative stress.[10] Therefore, urinary L-FABP is considered as a marker of tubular injury; a previous study showed that the correlation of urinary L-FABP with renal ischaemia is higher than that for several other urinary markers.[10] The clinical implications of urinary L-FABP have been shown in several settings.[11–13] However, because AHF is also associated with reduced renal blood flow and hypoxia, L-FABP may be a tubular marker that is more specific to the dysfunction exacerbated by heart failure. One study focused on urinary L-FABP in 138 patients with AHF and found an association between higher levels of L-FABP and worsening renal function during hospitalization[14]; however, its clinical and prognostic implications remain unclear. Therefore, we examined the clinical implication and prognostic role of urinary L-FABP in patients with AHF.

Methods

Study population

We performed retrospective analysis of a database (Juntendo database for Acute Heart Failure: JEDI-AHF) of all patients with AHF who were hospitalized in a high-care unit or coronary-care unit of Juntendo University Hospital (Tokyo, Japan) from January 2015 to December 2019. Consecutive patients with AHF aged >18 years with confirmed AHF diagnoses by experienced cardiologists according to the Framingham criteria[15] were included in the study. We excluded cases in which brain-type natriuretic peptide (BNP) values at admission were <100 pg/mL, as the primary diagnosis of these cases was less likely to have been heart failure.[16,17] We further excluded patients with AHF who presented with acute coronary syndrome, primary pulmonary hypertension, and pericardial disease or those under maintained haemodialysis. Baseline data including patient characteristics, medical history, prescription at the time of admission and discharge, and events were recorded in the database. A history of heart failure was regarded as having been diagnosed of heart failure before index admission.

All patients who require high-care unit/coronary-care unit admission in our department are expected to undergo comprehensive cardiovascular and renal biomarker assessments as routine practice at the time of admission, or at least within 24 h of admission, as they are at a high risk for developing future cardiovascular and renal adverse events.

The primary outcome in this study was all-cause mortality. All participants were notified regarding their participation in the study, and it was explained that they were free to opt out of participation at any time. Our study complied with the Declaration of Helsinki and Japanese Ethical Guideline for Medical and Health Research involving Human Subjects. As this was an observational study without invasive procedures or interventions, written informed consent was not required under the 'Ethical Guidelines for Medical and Health Research Involving Human Subjects' issued by Japanese Ministry of Health, Labor, and Welfare. The Institutional Review Board of Juntendo University Hospital approved the study protocol, including opt-out informed consent.

All patients were followed from the date of index admission until June 2020; outcome data were obtained during a clinical visit or by reviewing medical records for all recorded deaths. The endpoint was all-cause mortality.

Urinary liver-type fatty acid-binding protein and beta-2 microglobulin analyses

Liver-type fatty acid-binding protein levels were measured by chemiluminescent enzyme immunoassay on a Lumipulse® G1200 analyser (Fujirebio corporation, Chuo, Tokyo, Japan). Urinary L-FABP levels were expressed as μg/gCr (creatinine, g), and the reference value was <8.5 μg/gCr.[18] Urinary beta-microglobulin (beta-2 MG) and cystatin C levels were measured according to standard clinical laboratory methods and were expressed as μg/gCr and mg/dL, respectively. All analyses were performed immediately after collecting blood and urine samples.

Statistical analysis

Normally distributed continuous variables are expressed as the means ± standard deviations, whereas abnormally distributed variables are presented as the medians and interquartile ranges. Categorical variables are expressed as numbers and percentages. The cohort was classified into three groups according to L-FABP levels corrected for urinary creatinine concentration. Group differences were evaluated using one-way analysis of variance or Kruskal–Wallis test for continuous variables, and χ^2 or Fisher's exact test for dichotomous variables, as appropriate. The method of fractional polynomials was used to identify optimal transformations.[19]

Correlations between L-FABP, beta-2 MG, and cystatin C were evaluated via Pearson's correlation coefficient tests. Survival was evaluated using the Kaplan–Meier method and was compared with log-rank statistics. We also performed univariate and multivariable Cox regression analysis using age, gender, systolic blood pressure haemoglobin, left ventricular ejection fraction, eGFR, serum sodium, log-transformed N-terminal pro B-type natriuretic peptide (NT-proBNP) at baseline, and history of hypertension, diabetes, coronary artery disease, and heart failure as adjustment variables. The primary outcome was all-cause mortality. For

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Cox regression analysis, we performed multiple imputation creating 20 data sets using a chained-equations procedure.[20] Multiple imputation was used to factor the missing covariate data in our data set. Multiple imputation is a general approach to deal with missing data that are available in several commonly used statistical packages. It aims to allow for uncertainty in the missing data by creating several different plausible imputed data sets and appropriately combining results obtained from each. We created 20 data sets using a chained-equations procedure. Parameter estimates were obtained for each data set and then combined to produce an integrated result as described by Barnard and Rubin.[21]

To evaluate whether considering urinary L-FABP can yield incremental prognostic information in addition to pre-existing prognostic factors, we constructed receiver operating characteristic (ROC) curves for logistic regression models of baseline model including all variables used for adjustment in Cox regression (age, gender, systolic blood pressure haemoglobin, left ventricular ejection fraction, eGFR, serum sodium, log-transformed NT-proBNP at baseline, and history of hypertension, diabetes, coronary artery disease, and heart failure), baseline model + A1MG, baseline model + B2MG, and baseline model + NAG. Increases in the areas under the ROC curves (AUCs) were evaluated using DeLong's method,[22] and the net reclassification improvement (NRI) was calculated to evaluate the additive prognostic value of each tubular marker.[23]

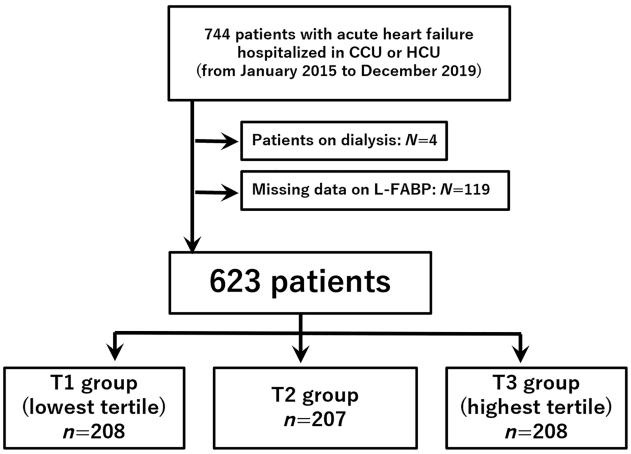
A two-tailed $P < 0.05$ was considered to indicate significant results in all analyses. Statistical analyses were performed using R Version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria; ISBN 3-900051-07-0, URL http://www.R-project.org).

Results

A total of 744 patients were eligible for inclusion. After excluding 123 patients (4 were on dialysis; data on L-FABP and cystatin C were missing for 117 and 2 patients, respectively), we analysed the records of the 623 remaining patients (*Figure 1*). Their average age was 74 ± 13 years, and 60.0% were male patients. Raw measurements of urinary L-FABP levels varied from 0.20 to 11 471.9 μg and 0.56 to 32 776.9 μg/gCr after correcting for urinary creatinine concentrations. The patients were stratified into three L-FABP tertiles: T1 (lowest), T2, and T3 (highest). Patient clinical characteristics at admission are presented in *Table 1*. The highest L-FABP tertile was associated with high systolic blood pressure, history of hypertension, diabetes, and coronary artery disease. Additionally, the high tertile was associated with low haemoglobin, poor renal function, and a high C-reactive protein and NT-proBNP.

Figure 2 shows the correlations between L-FABP, cystatin C, and beta-2 MG. Although both cystatin C and beta-2 MG showed significant positive correlations with L-FABP, the correlation coefficient and *R*-squared values were higher for beta-2 MG than for cystatin C. The *R*-squared values of the linear regression models constructed using log L-FABP as a dependent variable using log beta-2 MG and cystatin C individually as independent variables were 0.37 and 0.16, respectively. Moreover, including cystatin C in the model with only beta-2 MG yielded only a small increase in the *R*-squared value from 0.37 to 0.39.

Figure 1 Flow chart of subject selection. CCU, coronary-care unit; HCU, high-care unit; L-FABP, liver-type fatty acid-binding protein.



During the follow-up of 631 days (interquartile range: 387–875), 142 deaths occurred. In Kaplan–Meier analysis, the high L-FABP tertile was found to be associated with increased mortality (*Figure 3*). In Cox regression, log-transformed L-FABP in a continuous scale was associated with all-cause death, and this association remained significant even after adjusting for other prognostic factors [hazard ratio 1.16, 95% confidence interval (CI): 1.03–1.29, $P = 0.012$] (*Table 2*). As an exploratory analysis, we defined the optimal cut-off value of L-FABP as 5.7 μg/gCr according to ROC analysis and found that patients with L-FABP > 5.7 μg/gCr had a 1.66-fold higher risk of mortality than those with L-FABP ≤ 5.7 μg/gCr in the adjusted Cox model (hazard ratio 1.66, 95% CI 1.12–2.47, $P = 0.011$). Moreover, we performed sensitivity analysis to investigate whether the association between urinary L-FABP and mortality was retained even when death was confined to cardiovascular death. Of the 142 all-cause deaths, 81 deaths were cardiovascular death, and adjusted Cox regression analysis showed that the log L-FABP was significantly associated with cardiovascular death even after adjusting for other covariates (hazard ratio 1.17, 95% CI: 1.01–1.35, $P = 0.039$) *Table 2*.

Finally, to test the incremental prognostic predictability of urinary L-FABP compared with that of the pre-existing tubular marker, we calculated whether adding these two

Table 1 Patient characteristics stratified by urinary L-FABP tertiles

Variables	T1 $N = 208$	T2 $N = 207$	T3 $N = 208$	P value
L-FABP [μg/gCr, min–max]	2.53 [0.56–4.33]	6.94 [4.40–14.53]	47.51 [15.0–32 776.9]	—
Age (years)	72 ± 14	76 ± 12	76 ± 12	<0.001
Male (%)	146 (70.2)	114 (55.1)	130 (62.5)	0.006
SBP (mmHg)	130 ± 25	133 ± 26	139 ± 29	0.003
DBP (mmHg)	79 ± 19	78 ± 21	79 ± 23	0.886
Heart rate (bpm)	92 ± 28	90 ± 28	91 ± 26	0.774
NYHA III/IV at admission (%)	123 (59.4)	120 (58.3)	138 (67.6)	0.103
Electrocardiogram rhythm at admission (%)				
Sinus rhythm	80 (38.6)	86 (42.0)	118 (56.7)	0.007
Atrial fibrillation/flatter	101 (48.8)	91 (44.4)	67 (32.2)	
Pacing	21 (10.1)	20 (9.8)	15 (7.2)	
Others	5 (2.4)	8 (3.9)	8 (3.8)	
LVEF (%)	44 [31–61]	54 [34–64]	52 [36–64]	0.024
Ischaemic aetiology (%)	29 (14.1)	38 (18.4)	40 (19.9)	0.284
Cardiac implantable electronic device (%)				0.576
Pacemaker	21 (10.1)	26 (12.6)	19 (9.1)	
ICD	2 (1.0)	1 (0.5)	2 (1.0)	
CRT-P	0	1 (0.5)	0	
CRT-D	7 (3.4)	5 (2.4)	2 (1.0)	
Valvular disease (%)				
Aortic valve regurgitation (moderate/severe)	16 (7.7)	8 (3.9)	11 (5.3)	0.231
Aortic valve stenosis (moderate/severe)	14 (6.7)	11 (5.3)	14 (6.7)	0.789
Mitral valve regurgitation (moderate/severe)	51 (24.5)	52 (25.1)	46 (22.1)	0.749
Mitral valve stenosis (moderate/severe)	2 (1.0)	6 (2.9)	3 (1.4)	0.296
Tricuspid valve regurgitation (moderate/severe)	16 (7.7)	8 (3.9)	11 (5.3)	0.231
Past medical history (%)				
Heart failure	101 (48.6)	101 (48.8)	81 (38.9)	0.071
Hypertension	95 (46.8)	103 (50.0)	134 (65.0)	<0.001
Diabetes	52 (25.0)	60 (29.0)	88 (42.3)	<0.001
COPD	10 (5.0)	14 (7.0)	17 (8.4)	0.387
CAD	40 (19.8)	64 (31.7)	71 (35.0)	0.002
Prescription at admission (%)				
Loop diuretics	103 (50.7)	88 (43.1)	87 (42.4)	0.175
ACE-I/ARB	73 (36.1)	86 (42.4)	96 (47.1)	0.082
Beta-blocker	80 (38.5)	86 (41.5)	84 (40.4)	0.811
MRA	44 (21.2)	44 (21.3)	30 (14.4)	0.125
Prescription at discharge (%)				
Loop diuretics	180 (88.7)	168 (84.0)	145 (79.2)	0.040
ACE-I/ARB	144 (70.9)	131 (65.5)	121 (66.1)	0.446
Beta-blocker	162 (79.8)	145 (72.5)	129 (70.5)	0.084
MRA	111 (54.7)	99 (49.5)	63 (34.4)	<0.001
Laboratory data at admission				
Haemoglobin (g/dL)	12.7 ± 2.7	11.8 ± 2.3	11.2 ± 2.3	<0.001
Creatinine (mg/dL)	0.96 [0.77–1.19]	0.98 [0.74–1.35]	1.40 [0.97–2.23]	<0.001
eGFR (mL/min/1.73 m^2)	73.9 ± 26.7	70.9 ± 37.4	50.8 ± 33.6	<0.001
Blood urea nitrogen (mg/dL)	19 [16–26]	24 [18–30]	31 [21–44]	<0.001
Sodium (mEq/L)	140 ± 4	140 ± 4	139 ± 5	0.229
Potassium (mEq/L)	4.3 ± 0.6	4.3 ± 0.7	4.4 ± 0.8	0.409
C-reactive protein (mg/dL)	0.55 [0.25–1.43]	1.10 [0.33–3.45]	2.20 [0.78–6.25]	<0.001
NT-proBNP (pg/dL)	3249 [1648–5753]	5346 [2704–9677]	8248 [3441–19 884]	<0.001
Urinary beta-2-microglobulin (μg/gCr)	150 [73–359]	467 [118–1967]	6938 [1369–23 751]	<0.001
Cystatin C (mg/dL)	1.12 [0.99–1.40]	1.32 [1.08–1.83]	1.79 [1.35–2.46]	<0.001

ACE-I, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; L-FABP, liver-type fatty acid-binding protein; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure. Variables are expressed as the mean ± standard deviation, median [interquartile range] or *n* (%).

tubular markers to the baseline model would significantly increase the ROC AUC and/or NRI (*Table 3*). Although AUC was not increased by adding tubular biomarkers, only urinary L-FABP (NRI: 0.197, 95% CI: 0.011–0.384, $P = 0.038$), but not urinary beta-2 MG (NRI: 0.035, 95% CI: −0.134–0.205, $P = 0.682$), yielded a significant NRI. Moreover, using urinary L-FABP rather than urinary beta-2-MG in addition to the baseline model was associated with better model prediction (NRI: 0.198, 95% CI: 0.012–0.385, $P = 0.037$).

Figure 2 Scatter plots of correlations of L-FABP levels with those of beta-2 MG and cystatin C. L-FABP, liver-type fatty acid-binding protein; beta-2 MG, beta-2 microglobulin.

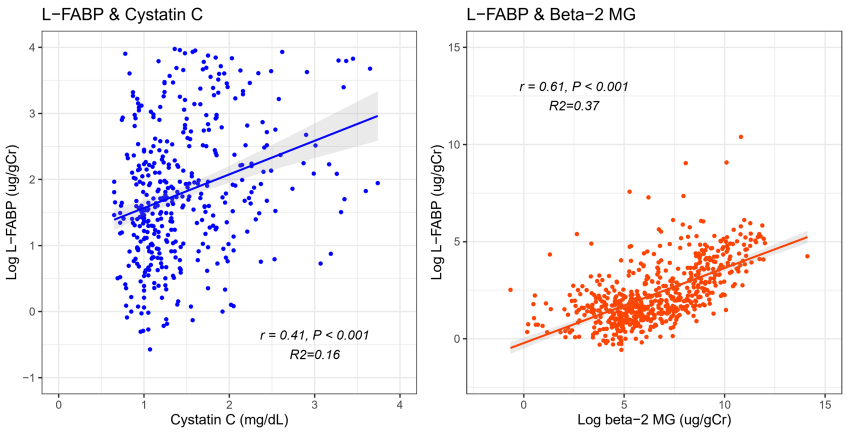


Figure 3 Kaplan–Meier curves for all-cause mortality stratified by L-FABP level tertiles. L-FABP, liver-type fatty acid-binding protein.

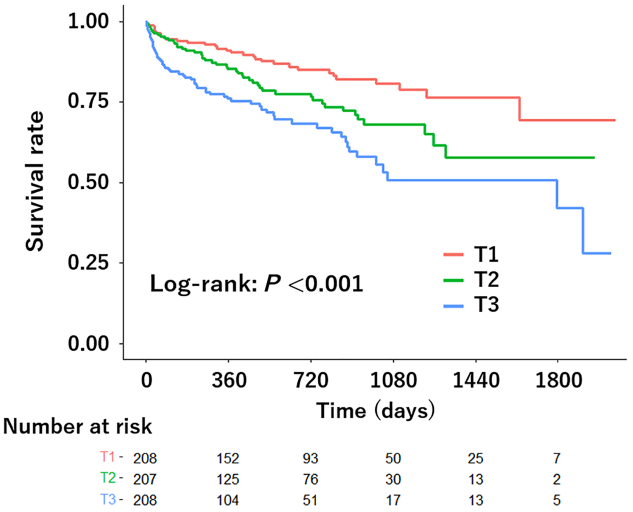


Table 2 Cox regression for all-cause mortality

	Unadjusted model			Adjusted model[a]		
Group	HR	95% CI	*P* value	HR	95% CI	*P* value
Log-urinary L-FABP	1.27	1.16–1.39	<0.001	1.16	1.03–1.29	0.012

CI, confidence interval; HR, hazard ratio; L-FABP, liver-type fatty acid-binding protein.
[a]Adjusted for age, gender, systolic blood pressure haemoglobin, left ventricular ejection fraction, eGFR, serum sodium, log NT-proBNP at baseline, and history of hypertension, diabetes, coronary artery disease, and heart failure.

Discussion

We determined the clinical and prognostic value of L-FABP for patients with AHF. We found that although L-FABP was significantly correlated with both beta-2 MG and cystatin C, its correlation with beta-2 MG was higher than that with cystatin C, suggesting that L-FABP is a tubular marker rather than a glomerular marker. Urinary L-FABP was associated with both all-cause and cardiovascular mortality, and this association was independent of pre-existing prognostic factors of heart failure. Moreover, urinary L-FABP, but not beta-2-MG, provided additive prognostic information in addition to pre-existing prognostic factors.

Although several urinary biomarkers have been shown to be associated with glomerular or tubular renal damage, renal dysfunction is generally characterized by a decreased glomerular filtration rate that represents glomerular function, whereas tubular function is not widely considered. However, several biomarkers associated with tubular dysfunction have been shown to be predictive of poor clinical outcomes in patients with chronic heart failure. A previous study showed that tubular damage assessed by analysing urinary kidney injury molecule 1 and *N*-acetyl-*β*-D-glucosaminidase, both of which are associated with tubular function, is a significant prognostic factor independent of glomerular function in patients with chronic heart failure.[24] In addition, several reports have described associations between tubular damage and disease progression in the chronic phase of kidney and heart failure.[4,25,26] However, very few studies have evaluated the limited number of patients with AHF; moreover, they showed conflicting results regarding the clinical and prognostic implications of tubular dysfunction at admission. Kawai *et al.* measured serum beta-2 MG levels in 131 patients with AHF and found that high levels were significantly associated with a higher risk of cardiovascular events.[7] In contrast, the Acute Kidney Injury N-gal Evaluation of Symptomatic Heart Failure

Table 3 Comparison of prognostic values between baselined and updated models

		Updated model	
		Baseline model + beta-2 MG (AUC: 0.66, 95% CI 0.61–0.71)	Baseline model + L-FABP (AUC: 0.67, 95% CI 0.62–0.72)
Baseline model	Baseline model (AUC: 0.66, 95% CI 0.61–0.71)	$AUC_{comparison}$: $P = 0.704$, NRI: 0.035 (−0.134–0.205), $P = 0.682$	$AUC_{comparison}$: $P = 0.230$, NRI: 0.197 (0.011–0.384), $P = 0.038$
	Baseline model + beta-2 MG (AUC: 0.66, 95% CI 0.61–0.71)	—	$AUC_{comparison}$: $P = 0.231$, NRI: 0.198 (0.012–0.385), $P = 0.037$

AUC, area under the curve; CI, confidence interval; L-FABP, liver-type fatty acid-binding protein; MG, macroglobulin; NRI, net reclassification improvement.

Study, including 927 patients with AHF, showed that plasma neutrophil gelatinase-associated lipocalin is not as useful as creatinine for predicting adverse short-term outcomes and that it is not independently associated with short-term outcomes after adjusting for other covariates.[27]

Fatty acid-binding proteins are a family of cytoplasmic proteins found in all tissues that exhibit fatty acid metabolism; L-FABP, a member of this family, is an endogenous antioxidant protein spanning 14 kDa and is expressed in proximal tubular epithelial cells.[10] This protein is released into the tubular lumen in response to ischaemia or oxidative stress.[28] In addition, L-FABP levels are considered to increase in the early phase of acute kidney injury and can be used to identify patients with a high susceptibility to renal stress.[29] Beta-2 MG is a histologically established tubular injury marker[30,31]; we found a stronger correlation between L-FABP and beta-2 MG than between L-FABP and cystatin C. This finding supports that increased L-FABP reflects tubular dysfunction rather than glomerular dysfunction, even in the acute phase of AHF.

Several studies have focused on the clinical importance of L-FABP in multiple conditions including diabetes,[32] septic shock,[33] acute kidney injury after surgery (particularly cardiac),[11] and coronary catheterization.[13] For AHF, Okubo *et al*. reported that elevated urinary L-FABP levels are an independent predictor of increased creatinine and showed a non-significant tendency to be associated with subsequent heart failure rehospitalization in 138 patients.[14] However, this study included small population and short follow-up period of 1 year, which may have affected the results and conclusion. Moreover, the lack of the association between urinary L-FABP and mortality may be attributed to reduced statistical power because of the relatively small patient sample. Naruse *et al*. similarly reported that urinary L-FABP levels during admission are independent predictors of mortality and acute kidney injury in patients hospitalized in medical cardiac intensive care units.[34] However, the patient population in this study was heterogeneous and included patients other than those with heart failure; additionally, L-FABP was not normalized to the urinary creatinine concentration. We used urinary L-FABP levels corrected for the urine creatine concentration measured for the same urine sample and described their association with mortality in AHF. Additionally, we compared L-FABP levels with those of well-established glomerular and tubular markers obtained simultaneously. This suggests that L-FABP acts as a tubular marker rather than as a glomerular marker in AHF.

There were some strengths to our study. First, L-FABP was associated with not only all-cause death but also cardiovascular death. As our study included a large number of elderly patients, non-negligible patients may die from non-cardiovascular disease; however, our study clearly showed that urinary L-FABP is associated with death due to cardiovascular causes, indicating that this tubular marker is strongly associated with the cardio-renal axis. Moreover, adding L-FABP to pre-existing prognostic factors significantly improved the prognostic values, whereas adding beta-2 MG did not, although these two biomarkers showed a good correlation. Our study suggests that urinary L-FABP is a tubular biomarker and promising prognostic biomarker for patients with AHF; however, its therapeutic implications remain unknown and should be evaluated in further studies.

This study has several limitations. First, we measured urinary L-FABP only at admission and thus could not assess changes in L-FABP levels. Second, this was a single-centre, retrospective observational study involving a limited number of patients. Larger scale, multicentre prospective studies are needed to confirm our results. Third, urinary L-FABP levels can be affected by treatment with multiple medications including angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers,[35] and we were unable examine the impact of such treatments on our results. Finally, we did not obtain data on clinical characteristics such as the trigger of decompensation and lung oedema.

Conclusion

We demonstrated that urinary L-FABP, a novel tubular marker, may provide prognostic information in patients with acute heart failure that cannot be achieved using known prognostic factors and tubular markers. The therapeutic implications of this association should be evaluated in further studies.

Conflict of interest

Y.M. and T.Kas. are affiliated with a department endowed by Philips Respironics, ResMed, Teijin Home Healthcare, and Fukuda Denshi, and Y.M. received an honorarium from Otsuka Pharmaceutical Co and Novartis Japan. Other authors have nothing to declare.

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