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Original Paper

Urinary Liver-Type Fatty Acid-Binding Protein Level as a Predictive Biomarker of Acute Kidney Injury in Patients with Acute Decompensated Heart Failure

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Keywords
Acute kidney injury · Acute decompensated heart failure · Liver-type fatty acid-binding protein

Abstract
Background: There are no biological markers to predict the onset of acute kidney injury (AKI) in patients with acute decompensated heart failure (ADHF). Liver-type fatty acid-binding protein (L-FABP) levels are markedly upregulated in the proximal tubules after renal ischemia. We investigated whether urinary L-FABP is a suitable marker to predict AKI in ADHF patients. ***Methods:*** We examined 281 consecutive patients with ADHF. Serum creatinine (Cr) and L-FABP levels were measured at admission and 24 and 48 h after admission. ***Results:*** AKI developed in 104 patients (37%). Urinary L-FABP levels at admission were significantly higher in patients with AKI than in those without (33.0 vs. 5.2 μg/g Cr; $p < 0.001$). Multivariate analysis showed that baseline urinary L-FABP level was an independent predictor of AKI in ADHF patients (odds ratio 1.08, 95% confidence interval 1.05–1.12; $p < 0.001$). Receiver operating characteristic analysis showed that baseline urinary L-FABP level exhibited 94.2% sensitivity and 87.0% specificity at a cutoff value of 12.5 μg/g Cr. ***Conclusions:*** Urinary L-FABP level is useful for predicting the onset of AKI in patients with ADHF. The results of our study could help clinicians diagnose AKI in ADHF patients earlier, leading to possible improvements in the treatment of this group of patients.

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Introduction

Acute decompensated heart failure (ADHF) is a widespread adverse event that physicians face worldwide. Despite advances in chronic heart failure management, ADHF continues to be associated with poor outcomes, exemplified by 30-day readmission rates of over 20% and in-hospital mortality rates of 4–6%, both of which have not significantly improved over the past 20 years [1]. One of the strongest predictors of adverse outcomes in ADHF patients is acute kidney injury (AKI). Previous studies reported that patients with AKI exhibited higher in-hospital mortality rates and worse long-term prognoses than non-AKI patients among subjects with ADHF [2]. AKI occurs commonly in patients with ADHF and was termed cardiorenal syndrome type 1 [3]. Physicians' knowledge of cardiorenal syndrome type 1 is widening, and interactions between the kidney and heart that contribute to the progression of disease have received more attention. In clinical situations, the detection of AKI at admission is an immediate and essential problem in ADHF patients. The timely diagnosis of AKI might lead to early adjustment of the diuretic dose or might justify the use of other drugs as well as the transient early use of renal replacement therapies.

Fatty acid-binding proteins (FABPs) are small cytoplasmic proteins of 14 kDa that are abundantly expressed in the cytosol of most tissues, plus the related cellular retinoid-binding proteins. Two types of FABPs have been isolated from the human kidney. Liver-type FABP (L-FABP) is reabsorbed by the proximal tubule via megalin-dependent endocytosis and is localized in the cytoplasm of the proximal renal tubular cells [4]. Urinary L-FABP binds free fatty acids (FFAs) produced by proteinuria, oxidative stress, and toxic insults [5]. Urinary L-FABP could potentially prevent FFA-induced tubulointerstitial damage. Recent studies have shown that urinary L-FABP may be a useful biomarker of acute and progressive renal disease [6]; however, the clinical significance of urinary L-FABP measurement in patients with ADHF has not been completely investigated. Although previous studies have shown that elevated urinary L-FABP levels increase the risk of contrast-induced nephropathy in patients undergoing elective percutaneous coronary interventions [7], limited data exist regarding the effect of urinary L-FABP on AKI in ADHF patients. In the present study, we evaluated the association of admission urinary L-FABP levels with the occurrence of AKI in consecutive ADHF patients.

Methods

Study Population

We studied 281 consecutive patients with ADHF admitted to the Cardiac Intensive Care Unit at Yokosuka Kyosai Hospital between June 2015 and July 2016. ADHF was defined as either new-onset heart failure or decompensated chronic heart failure with symptoms that warranted hospitalization [8]. Based on the European Society of Cardiology guidelines for the diagnosis of ADHF, abnormal findings on an electrocardiogram or the presence of pulmonary edema on a chest X-ray and a B-type natriuretic peptide level ≥100 pg/mL are required to diagnose ADHF [9]. Furthermore, all included patients were administered diuretics or vasodilators for the treatment of ADHF. The treating physician in the cardiology department diagnosed ADHF based on the criteria within 30 min of the patients' admission. All patients had a New York Heart Association functional class of either III or IV. Patients with heart failure in whom a contrast medium was used for the diagnosis or treatment (acute aortic dissection, acute coronary syndrome, infection, etc.) were excluded from the study, as were patients who had undergone renal replacement therapy before admission. There was no limitation to the treatment strategy for ADHF, which was chosen by each of the physicians.

Evaluation of AKI

The serum creatinine (Cr) level was determined upon hospital admission and at least once a day during the Cardiac Intensive Care Unit stay until discharge; it was available for all patients who were analyzed. The

estimated glomerular filtration rate (eGFR) was estimated using the abbreviated Modification of Diet in Renal Disease equation [10]. Baseline renal insufficiency was categorized as an eGFR at the time of admission of ≤60 mL/min/1.73 m^2 [11]. AKI was determined using the AKI network (AKIN) criteria [12] and defined as a serum Cr rise >0.3 mg/dL or an increase in serum Cr ≥1.5 times the baseline levels within 48 h of admission, compared with the serum Cr level at admission.

Serum and Urinary Biomarker Measurements

Blood and urine samples were collected within 30 min of admission, in the hospital after 24 and 48 h, and between 7 days and discharge according to the patients' status. The blood and urine samples were centrifuged within 5 min at 4°C and immediately frozen at −80°C until they were analyzed. The serum levels of blood urea nitrogen, Cr, and urinary L-FABP, β_2-microglobulin (β_2-MG), and N-acetyl-β-D-glucosaminidase (NAG) were measured at each sampling point. These urine biomarkers were measured by the Special Reference Laboratory (Yokohama, Japan). Urinary L-FABP was measured with a specific enzyme-linked immunosorbent assay [13]. Urinary NAG was determined with spectrophotometry. All urinary markers were corrected using the value of urinary Cr.

Procedures

AKI was evaluated using the AKIN criteria after admission; 177 patients were allocated to the non-AKI group and 104 patients to the AKI group. The serum and urine biomarker levels were compared between the non-AKI and AKI groups. The factors that were significantly different between the non-AKI and AKI groups based on the univariate analysis were selected for inclusion in a multivariate logistic regression model.

Statistical Analysis

IBM® SPSS® software version 21.0 (IBM, Armonk, NY, USA) was used for baseline descriptive analyses. The normality of the data was verified using the Kolmogorov-Smirnov test. Categorical data were expressed as absolute frequencies and percentages, which were compared using the χ^2 test or the Fisher exact test, as appropriate. Continuous variables were expressed as means ± standard deviations if they were normally distributed and as medians with interquartile ranges if they were not normally distributed; and they were compared using the Student *t* test or the Mann-Whitney U test, respectively. The whole study population was stratified according to the occurrence of AKI. Univariate predictors of AKI for the ADHF patients whose level of significance was $p < 0.1$ were entered into the multivariate regression model. The receiver operating characteristic curve was analyzed to determine the cutoff value of baseline urinary L-FABP for predicting AKI. A probability value of $p < 0.05$ was considered statistically significant.

Results

Patient Characteristics and AKI

Of the 281 patients included in this study, 63.7% were male, with a mean age of 75.7 ± 12.9 years. One hundred fifteen (40.9%) patients had ischemic heart disease, and 166 (59.1%) patients had nonischemic heart disease, including valvular heart disease (n = 31), hypertensive heart disease (n = 19), dilated cardiomyopathy (n = 18), hypertrophic cardiomyopathy (n = 6), arrhythmia (n = 51), and other heart diseases (n = 41). The etiology of ADHF was similar between the 2 groups. The average left ventricular ejection fraction on admission was 49.7 ± 16.2%.

Patient characteristics, including baseline values and medications at admission, with respect to the presence of AKI are listed in Table 1. The rate of diabetes mellitus was significantly higher in the AKI group than in the non-AKI group. Serum levels of blood urea nitrogen, Cr, C-reactive protein, B-type natriuretic peptide, and cardiac troponin I were significantly higher in the AKI group than in the non-AKI group. The serum levels of eGFR and hemoglobin were significantly lower in the AKI group than in the non-AKI group. No significant differences were observed between the AKI group and the non-AKI group regarding the medication at admission.

Table 1. Patient characteristics

	Total (n = 281)	Non-AKI (n = 177)	AKI (n = 104)	p value
Age, years	75.7±12.9	75.5±12.5	77.9±11.8	0.12
Male, *n* (%)	179 (63.7)	115 (65.0)	64 (61.5)	0.61
LVEF on admission, %	49.7±16.2	50.6±16.7	48.0±15.2	0.19
Etiology, *n* (%)				
Ischemic heart disease	115 (40.9)	67 (37.9)	48 (46.2)	0.21
Valvular heart disease	31 (11.0)	17 (9.6)	14 (13.5)	0.33
Hypertensive heart disease	19 (6.8)	13 (7.3)	6 (5.8)	0.80
Dilated cardiomyopathy	18 (6.4)	14 (7.9)	4 (3.8)	0.21
Hypertrophic cardiomyopathy	6 (2.1)	4 (2.3)	2 (1.9)	1.00
Arrhythmia	51 (18.1)	36 (20.3)	15 (14.4)	0.26
Others	41 (14.6)	26 (14.7)	15 (14.4)	1.00
Past medical history				
Hypertension, *n* (%)	196 (69.8)	120 (67.8)	76 (73.1)	0.42
Dyslipidemia, *n* (%)	89 (31.7)	55 (31.1)	34 (32.7)	0.79
LDL cholesterol, mg/dL	91.0±36.1	92.8±36.2	87.8±35.9	0.31
Diabetes mellitus, *n* (%)	93 (33.1)	49 (27.7)	44 (42.3)	0.01
HbA1c, %	6.4±1.2	6.4±1.2	6.4±1.1	0.94
COPD, *n* (%)	36 (18.2)	21 (17.2)	15 (19.7)	0.71
PAD, *n* (%)	16 (5.7)	7 (4.0)	9 (8.7)	0.11
Laboratory data				
BUN, mg/dL	25.7±15.7	23.1±12.2	30.2±19.6	<0.001
Cr, mg/dL	1.18±0.55	1.05±0.40	1.41±0.68	<0.001
eGFR, mL/min/1.73 m^2	50.3±24.9	56.2±27.1	40.2±16.4	<0.001
Hb, g/dL	11.8±2.2	12.1±2.0	11.1±2.3	<0.001
CRP, mg/dL	1.12 (0.25–4.92)	0.58 (0.13–3.63)	2.40 (0.63–7.25)	<0.001
BNP, pg/mL	368 (162–850)	311 (143–754)	442 (228–1441)	0.002
cTnI, ng/mL	0.07 (0.03–0.27)	0.05 (0.03–0.15)	0.11 (0.04–0.77)	<0.001
Medication on admission, *n* (%)				
ACE-I or ARB	125 (44.5)	72 (40.7)	53 (51.0)	0.11
β-Blocker	90 (32.0)	53 (29.9)	37 (35.6)	0.36
Diuretics	122 (43.4)	72 (40.7)	50 (48.1)	0.26

Values are means ± standard deviations or medians with interquartile ranges in parentheses, unless otherwise indicated. AKI, acute kidney injury; LVEF, left ventricular ejection fraction; LDL, low-density lipoprotein; HbA1c, hemoglobin A1c; COPD, chronic obstructive pulmonary disease; PAD, peripheral artery disease; BUN, blood urea nitrogen; Cr, creatinine; eGFR, estimated glomerular ejection fraction; Hb, hemoglobin; CRP, C-reactive protein; BNP, B-type natriuretic peptide; cTnI, cardiac troponin I; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Urinary Biomarkers and AKI

The levels of urinary β_2-MG, L-FABP, and NAG in the AKI group were significantly higher at baseline and 24 and 48 h afterwards than those in the non-AKI group. The urinary level of L-FABP significantly decreased at 48 h compared to the values at admission in the AKI group but was unchanged in the non-AKI group (Table 2).

The Urinary L-FABP Level as an Independent Prognostic Parameter for AKI

Univariate analysis showed that several clinicopathological parameters, including diabetes mellitus, serum levels of baseline B-type natriuretic peptide, cardiac troponin I, C-reactive protein, hemoglobin, blood urea nitrogen, and Cr and urinary levels of β_2-MG, L-FABP, and NAG were associated with the occurrence of AKI in ADHF patients (Table 3).

Table 2. Serial changes of urinary biomarkers

	Total (*n* = 281)	Non-AKI (*n* = 177)	AKI (*n* = 104)	*p* value
Urinary β_2-MG, μg/L				
Baseline	533 (132–2,722)	303 (89–946)	2,948 (449–10,407)	<0.001
At 24 h	837 (200–4,003)	343 (140–1,453)	4,003 (718–13,174)	<0.001
At 48 h	910 (233–3,949)	410 (145–1,573)	3,130 (773–11,705)	<0.001
Urinary L-FABP, μg/g Cr				
Baseline	10 (3.8–25.3)	5.2 (2.8–9.6)	33.0 (18.0–72.0)	<0.001
At 24 h	7.0 (2.8–22.8)	4.1 (2.2–8.2)	26.7 (9.6–53.8)	<0.001
At 48 h	6.4 (3.1–16.9)	4.7 (2.5–7.8)	19.1 (7.0–45.0)	<0.001
Urinary NAG, U/g Cr				
Baseline	14.3 (8.7–23.1)	12.8 (7.2–18.6)	16.7 (12.1–27.1)	<0.001
At 24 h	12.9 (7.5–18.9)	11.9 (6.7–18.1)	13.8 (10.1–21.0)	0.010
At 48 h	12.9 (7.5–19.1)	12.0 (6.7–18.5)	13.6 (9.8–20.6)	0.049

Values are presented as medians (interquartile ranges). AKI, acute kidney injury; β_2-MG, β_2-microglobulin; L-FABP, liver-type fatty acid-binding protein; Cr, creatinine; NAG, N-acetyl-β-D-glucosaminidase.

Table 3. Analysis of factors related to AKI

	Univariate			Multivariate		
	p	OR	95% CI	*p*	OR	95% CI
DM	0.012	1.92	1.15–3.19	0.23	1.74	0.71–4.28
BNP, pg/mL	0.008	1.00	1.00–1.00	0.56	1.00	1.00–1.00
cTnI, ng/mL	0.004	1.15	1.05–1.27	0.07	1.13	0.99–1.29
CRP, mg/dL	<0.001	1.10	1.04–1.15	0.31	1.04	0.96–1.12
Hb, g/dL	<0.001	0.80	0.71–0.90	0.92	0.99	0.78–1.25
BUN, mg/dL	0.001	1.03	1.01–1.05	0.28	0.97	0.92–1.02
Cr, mg/dL	<0.001	4.17	2.31–7.53	0.06	3.18	0.96–10.57
Urinary β_2-MG, μg/L	<0.001	1.00	1.00–1.00	0.10	1.00	1.00–1.00
Urinary L-FABP, μg/g Cr	<0.001	1.07	1.05–1.10	<0.001	1.08	1.05–1.12
Urinary NAG, U/g Cr	0.001	1.03	1.01–1.04	0.45	0.99	0.95–1.02

AKI, acute kidney injury; OR, odds ratio; CI, confidence interval; DM, diabetes mellitus; BNP, B-type natriuretic peptide; cTnI, cardiac troponin I; CRP, C-reactive protein; Hb, hemoglobin; BUN, blood urea nitrogen; Cr, creatinine; β_2-MG, β_2-microglobulin; L-FABP, liver-type fatty acid-binding protein; NAG, N-acetyl-β-D-glucosaminidase.

Multivariate regression analysis showed that the urinary level of baseline L-FABP was an independent predictor of the occurrence of AKI in ADHF patients after admission.

Diagnostic Value of the L-FABP Level

The receiver operating characteristic curves are shown in Figure 1. The urinary L-FABP level that demonstrated an optimal balance between sensitivity and specificity to detect the occurrence of AKI (94.2 and 87.0%, respectively; area under the curve 0.930, 95% confidence interval 0.895–0.965) was overall 12.5 μg/g Cr for the ADHF patients.

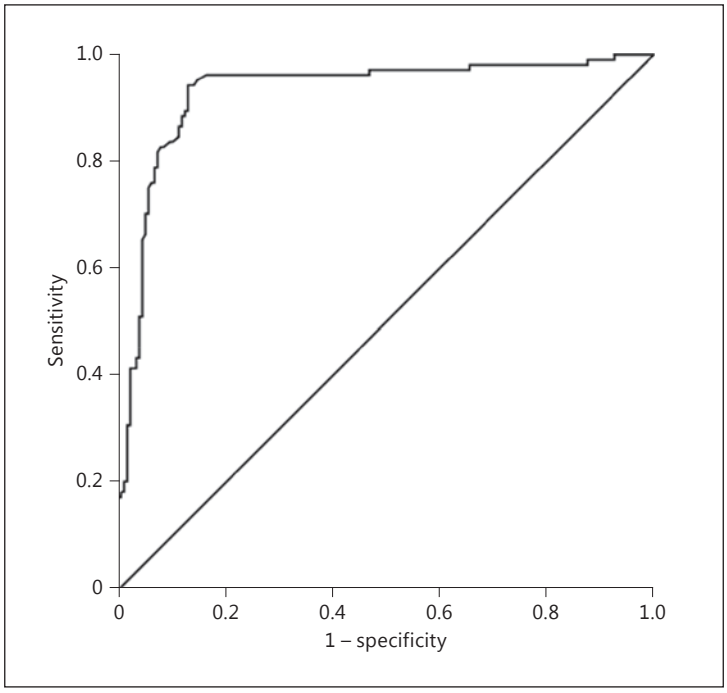

Fig. 1. Receiver-operating characteristic analysis for urinary liver-type fatty acid-binding protein in acute kidney injury.

Discussion

The present study demonstrated that levels of urinary biomarkers, such as β_2-MG, L-FABP, and NAG, were all higher in ADHF patients who developed AKI than in those without AKI. Among these biomarkers, the urinary L-FABP level at baseline was the only independent predictor of AKI after multivariate regression analysis, and its cutoff value was 12.5 μg/g Cr with 94.2% sensitivity and 87.0% specificity. Measuring urinary L-FABP to detect the occurrence of AKI earlier may be advantageous in terms of additive therapeutic strategies and may lead to an improvement in the clinical outcomes of patients who experience ADHF.

AKI in ADHF Patients

Previous studies have reported that the occurrence of AKI in patients who are hospitalized for ADHF is a strong and consistent independent predictor of adverse outcomes. Furthermore, those with AKI often require a longer hospital stay [14]. In most reports, AKI is defined as a change in serum Cr ≥0.3 mg/mL during hospitalization, and it has been reported to be associated with an increased risk for long-term cardiovascular mortality and morbidity in ADHF patients [15]. In a retrospective study of 200,063 hospitalized ADHF patients, Kociol et al. [15] found that 17.8% of the total cohort developed AKI, of which 64.5% were readmitted and 35.4% died within 1 year. Cowie et al. [11] reported that 33% of the patients in their study developed AKI, as defined by an increase in serum Cr of 0.3 mg/dL from baseline during the hospital stay, and showed that the mortality rate was higher in the AKI group than in the non-AKI group during the hospital stay (12 vs. 2%), rising to 28% in total by 6 months compared to 18% in patients without AKI.

The risk, injury, failure, loss, and end-stage renal disease (RIFLE) criteria are the standard method for evaluating AKI in intensive care patients [16]. A recent classification for AKI, based on the RIFLE criteria, has been proposed by the AKIN [12], and the Kidney Disease Improving Global Guidelines recommended that clinicians should effectively adopt the AKIN criteria [17]. The AKIN diagnostic criteria for AKI specify an abrupt (within 48 h) absolute

increase in the serum Cr concentration ≥0.3 mg/dL from baseline; a percentage increase in the serum Cr concentration of ≥50%; or oliguria of <0.5 mL/kg per hour for more than 6 h. Therefore, we adopted the AKIN diagnostic criteria in our study.

Urinary L-FABP Levels and AKI

The urinary L-FABP level is increasingly being used as a diagnostic marker in patients with various conditions and suspected AKI [18, 19]. Nakamura et al. [18] showed that the baseline urinary L-FABP level was significantly higher in the contrast-induced AKI group than in the non-contrast-induced AKI group, suggesting that this is a predictive marker for contrast-induced AKI in patients with moderate chronic kidney disease. Obata et al. [19] reported that urinary L-FABP is a sensitive biomarker of AKI in patients treated with abdominal aortic aneurysm repair, and preoperative urinary L-FABP can predict the postoperative development of AKI, especially in patients treated with endovascular aneurysm repair. Consistent with these reports, the present study suggests that the baseline urinary L-FABP level may be useful in predicting the development of AKI in patients with ADHF.

Mechanisms for Detecting AKI by Urinary L-FABP Levels

Our study showed that the level of baseline urinary L-FABP was an independent predictor of the occurrence of AKI in ADHF patients. In this study, although the levels of urinary biomarkers, such as β_2-MG, L-FABP, and NAG, were all higher in ADHF patients who developed AKI than in those without AKI, urinary L-FABP level at baseline was the only independent predictor of AKI. The baseline level of urinary L-FABP was significantly higher than that 48 h after admission in the AKI group, but the level of other urinary biomarkers was not significantly changed between that at admission and that 48 h after admission in the AKI group. The elevation of baseline urinary L-FABP was induced by some complex and diverse factors. These factors are likely to cause insidious structural and/or functional kidney injury, the degree of which cannot be quantified by a conventional urine test or serum Cr measurement. It is well known that several substances that are involved in the pathophysiologic process of kidney injury and renal tubular cell death are released into urine. Among them, urinary L-FABP may be one of the most promising new biomarkers to detect occult yet substantial kidney disease; elevated levels of this biomarker predict the future appearance of solid kidney disease after treatment that is potentially detrimental to the kidney, as well as predict the acute worsening of prevalent nephropathies [5]. L-FABP is an intracellular lipid chaperone that selectively binds unsaturated FAs or lipid peroxidation products and transports them to mitochondria or peroxisomes, where they are metabolized by β-oxidization [13]. FAs are important in mammals as mediators of signal transduction for metabolic regulation and are rarely present in the free state in biological fluids because of their hydrophobic character and cytotoxicity. Overproduction of FFAs induces oxidative stress and production of inflammatory cytokines by increasing mitochondrial reactive oxygen species and subsequently leads to tubulointerstitial damage [20]. It is well established that FFA levels are increased in patients with ADHF and renal ischemia [21]. Evidence indicates that the activation of L-FABP in proximal tubules could be triggered not only by overproduction of FFAs but also by tubular ischemia [22]. Systemic hypoxia caused by ADHF induces both renal parenchymal and tubulointerstitial ischemia. Hypoxia correlates with transcriptional activation of L-FABP, because the promoter region of L-FABP contains the binding sites of hepatocyte nuclear factor and hypoxia-inducible factor-1 [23]. Therefore, urinary L-FABP levels may be high, especially in AKI patients with ADHF.

Study Limitations

Despite its novel findings, our study has the following limitations. First, because of the small sample size in a single center, the statistical power for detecting the impact of urinary

L-FABP on the incidence of AKI might be inadequate. Our results could be generalized if data based on more samples from multiple international centers were collected. Second, urinary L-FABP levels can be affected by treatment with various medications, such as angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers [24]. However, no significant differences in the concomitant use of such medications were observed between the AKI group and the non-AKI group (Table 1).

Conclusions

The present study demonstrated that baseline urinary L-FABP level is an effective biomarker for predicting the occurrence of AKI in ADHF patients and demonstrates an optimal balance between sensitivity and specificity. The results of our study could help clinicians diagnose AKI in ADHF patients earlier, leading to possible improvements in the treatment of this group of patients.

Statement of Ethics

The institutional review board at Yokosuka Kyosai Hospital approved the study protocol.

Disclosure Statement

The authors have no conflicts of interest to declare.

References

1 Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al: Heart disease and stroke statistics – 2015 update: a report from the American Heart Association. Circulation 2015;131:e29–e322.
2 Smith GL, Vaccarino V, Kosiborod M, Lichtman JH, Cheng S, Watnick SG, et al: Worsening renal function: what is a clinically meaningful change in creatinine during hospitalization with heart failure? J Card Fail 2003;9:13–25.
3 Ronco C, Haapio M, House AA, Anavekar N, Bellomo R: Cardiorenal syndrome. J Am Coll Cardiol 2008;52:1527–1539.
4 Yamamoto T, Yamamoto A, Watanabe M, Matsuo T, Yamazaki N, Kataoka M, et al: Classification of FABP isoforms and tissues based on quantitative evaluation of transcript levels of these isoforms in various rat tissues. Biotechnol Lett 2009;31:1695–1701.
5 Kamijo A, Sugaya T, Hikawa A, Okada M, Okumura F, Yamanouchi M, et al: Urinary excretion of fatty acid-binding protein reflects stress overload on the proximal tubules. Am J Pathol 2004;165:1243–1255.
6 Kamijo A, Kimura K, Sugaya T, Yamanouchi M, Hikawa A, Hirano N, et al: Urinary fatty acid-binding protein as a new clinical marker of the progression of chronic renal disease. J Lab Clin Med 2004;143:23–30.
7 Bachorzewska-Gajewska H, Poniatowski B, Dobrzycki S: NGAL (neutrophil gelatinase-associated lipocalin) and L-FABP after percutaneous coronary interventions due to unstable angina in patients with normal serum creatinine. Adv Med Sci 2009;54:221–224.
8 Gheorghiade M, Zannad F, Sopko G, Klein L, Pina IL, Konstam MA, et al: Acute heart failure syndromes: current state and framework for future research. Circulation 2005;112:3958–3968.
9 McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, et al: ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33:1787–1847.
10 Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D: A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130:461–470.
11 Cowie MR, Komajda M, Murray-Thomas T, Underwood J, Ticho B; POSH Investigators: Prevalence and impact of worsening renal function in patients hospitalized with decompensated heart failure: results of the prospective outcomes study in heart failure (POSH). Eur Heart J 2006;27:1216–1222.

12 Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A; Acute Kidney Injury Network: Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007;11:R31.
13 Veerkamp JH, Peeters RA, Maatman RG: Structural and functional features of different types of cytoplasmic fatty acid-binding proteins. Biochim Biophys Acta 1991;1081:1–24.
14 Gottlieb SS, Abraham W, Butler J, Forman DE, Loh E, Massie BM, et al: The prognostic importance of different definitions of worsening renal function in congestive heart failure. J Card Fail 2002;8:136–141.
15 Kociol RD, Greiner MA, Hammill BG, Phatak H, Fonarow GC, Curtis LH, et al: Long-term outcomes of Medicare beneficiaries with worsening renal function during hospitalization for heart failure. Am J Cardiol 2010;105:1786–1793.
16 Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P: Acute renal failure: Definition, outcome measures, animal models, fluid therapy and information technology needs – the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004;8:204–212.
17 Khwaja A: KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract 2012;120:179–184.
18 Nakamura T, Sugaya T, Node K, Ueda Y, Koide H: Urinary excretion of liver-type fatty acid-binding protein in contrast medium-induced nephropathy. Am J Kidney Dis 2006;47:439–444.
19 Obata Y, Kamijo-Ikemori A, Ichikawa D, Sugaya T, Kimura K, Shibagaki Y, et al: Clinical usefulness of urinary liver-type fatty-acid-binding protein as a perioperative marker of acute kidney injury in patients undergoing endovascular or open-abdominal aortic aneurysm repair. J Anesth 2016;30:89–99.
20 Sasaki H, Kamijo-Ikemori A, Sugaya T, Yamashita K, Yokoyama T, Koike J, et al: Urinary fatty acids and liver-type fatty acid binding protein in diabetic nephropathy. Nephron Clin Pract 2009;112:148–156.
21 Matthys E, Patel Y, Kreisberg J, Stewart JH, Venkatachalam M: Lipid alterations induced by renal ischemia: pathogenic factor in membrane damage. Kidney Int 1984;26:153–161.
22 Yamamoto T, Noiri E, Ono Y, Doi K, Negishi K, Kamijo A, et al: Renal L-type fatty acid-binding protein in acute ischemic injury. J Am Soc Nephrol 2007;18:2894–2902.
23 Noiri E, Doi K, Negishi K, Tanaka T, Hamasaki Y, Fujita T, et al: Urinary fatty acid-binding protein 1: an early predictive biomarker of kidney injury. Am J Physiol Renal Physiol 2009;296:669–679.
24 Nakamura T, Inoue T, Sugaya T, Kawagoe Y, Suzuki T, Ueda Y, et al: Beneficial effects of olmesartan and temocapril on urinary liver-type fatty acid-binding protein levels in normotensive patients with immunoglobin A nephropathy. Am J Hypertens 2007;20:1195–1201.