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Original Paper

Clinical Usefulness of Urinary Liver Fatty Acid-Binding Protein Excretion for Predicting Acute Kidney Injury during the First 7 Days and the Short-Term Prognosis in Acute Heart Failure Patients with Non-Chronic Kidney Disease

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Keywords
Acute decompensated heart failure · Acute kidney injury · Worsening renal function · Liver fatty acid-binding protein · Neutrophil gelatinase-associated lipocalin · Mortality

Abstract
Background: The clinical significance of urinary liver fatty acid-binding protein (u-LFABP) in acute heart failure (AHF) patients remains unclear. ***Methods and Results:*** The u-LFABP levels on admission of 293 AHF patients were analyzed. The patients were divided into 2 groups according to the u-LFABP quartiles (Q1, Q2, and Q3 = low u-LFABP [L] group vs. Q4 = high u-LFABP [H] group). We evaluated the diagnostic and prognostic value of u-LFABP and compared the findings between the chronic kidney disease (CKD; *n* = 165) and non-CKD patients (*n* = 128). Acute kidney injury (AKI) during the first 7 days was evaluated based on the RIFLE criteria. In the non-CKD group, the number of AKI patients during the first 7 days was significantly greater in the H group (70.0%) than in the L group (45.6%). A multivariate logistic regression model indicated that the H group (odds ratio: 3.850, 95% confidence interval [CI] 1.128–13.140) was independently associated with AKI during the first 7 days. The sensitivity and specificity of u-LFABP for predicting AKI were 63.6 and 59.7% (area under the ROC curve 0.631) at 41.9 ng/mg × cre. A Cox regression model identified the H group (hazard ratio: 13.494, 95% CI 1.512–120.415) as an independent predictor of the 60-day mortality. A Kaplan-Meier curve, including all-cause death within 60 days, showed a significantly poorer survival

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rate in the H group than in the L group (p = 0.036). ***Conclusions:*** The u-LFABP level is an effective biomarker for predicting AKI during the first 7 days of hospitalization and an adverse outcome in AHF patients with non-CKD.

Introduction

Since the proposal of cardio-renal syndrome, which describes diseases that involve both heart failure and acute or chronic kidney disease (CKD) [1], kidney damage has become a topic of discussion in patients with acute heart failure (AHF). We have reported acute kidney injury (AKI) on admission in patients with AHF [2]. In that previous report, AKI was found to be already involved in approximately 30% of patients with AHF, with the rate increasing to around 70% over the course of hospitalization [2]. We further investigated the relationship between the degree of AKI, as evaluated by the Risk, Injury, Failure, Loss and End Stage (RIFLE) criteria, and the long-term prognosis, concluding that patients with AKI, especially class I and F patients, had a worse long-term prognosis than those without AKI [3]. Our findings further suggested that the presence of AKI on admission, especially the exacerbation of AKI at admission, was associated with a poor prognosis [4].

The mechanisms and pathophysiology of AKI in AHF patients are multifactorial and still poorly understood. Based on the understanding of the mechanisms involved, several urinary biomarkers have been investigated for their utility in detecting or predicting AKI. For example, levels of neutrophil gelatinase-associated lipocalin (NGAL) and liver fatty acid-binding protein (LFABP), which reflect the presence of renal tubular injury, have been suggested as candidates for detecting or predicting AKI in AHF patients in particular [1, 5–8]. However, we concluded in a previous report that these urinary biomarkers were not appropriate for the detection of AKI on admission [9].

AKI at admission was reported to be caused by venous congestion [10], and subsequent worsening of AKI after or during treatment has been suggested to be due to renal proximal tubular injury. We therefore hypothesized that urinary levels of LFABP (u-LFABP) might be the most suitable biomarker for the early detection of proximal tubular injury, and the u-LFABP level at admission might be useful for the prediction of AKI during the acute phase of AHF. In the present study, we examined the utility of the urinary u-LFABP level on admission for predicting AKI during the first 7 days of hospitalization in patients with AHF.

Methods

Subjects

A total of 293 AHF patients admitted to the intensive care unit of Nippon Medical School Chiba Hokusoh Hospital between March 2010 and March 2014 were enrolled in this study. AHF was defined as either new-onset HF or decompensation of chronic HF with symptoms sufficient to warrant hospitalization [11]. Based on the ECS guidelines for the diagnosis of AHF, an abnormal electrocardiogram or the presence of pulmonary edema on chest X-ray and a b-type natriuretic peptide level of ≥100 pg/mL are required to diagnose AHF [12].

Furthermore, all included patients were administered diuretics or vasodilators for the treatment of AHF. The treating physician in the emergency department diagnosed AHF based on these criteria within 30 min of admission, and patients were formally enrolled in the present study by filling out a form. All patients had a New York Heart Association (NYHA) functional class of either III or IV. The patients who met any of the following criteria were admitted to the ICU: (1) requiring high-flow oxygen inhalation (including mechanical support) to treat orthopnea; (2) requiring inotrope or mechanical support due to low blood pressure; and (3) requiring various types of diuretics to improve general or lung edema. All patients in the present study

received either diuretics or vasodilators for the treatment of AHF after admission. All of the data were retrospectively retrieved from the hospital medical records. Patients who had undergone renal replacement therapy before admission were excluded. There were no limitations regarding the treatment of AHF, and the treatment strategy was chosen by each subject's attending physician.

Urinary Biomarker Excretion and Serum Biomarker Measurements

The urine and blood samples were collected within 30 min of admission (day 1), in the hospital after 72 h (day 4) and between days 7 and 21 (before discharge). They were centrifuged within 5 min of collection at 4°C and immediately frozen at –80°C until analysis. The serum levels of blood urea nitrogen, creatinine, β_2-microglobin, α_1-microglobin, osmolality, heart-type fatty acid-binding protein, high-sensitivity troponin-T, N-terminal pro-brain-type natriuretic peptide, brain-type natriuretic peptide, and procollagen III peptide were measured on admission. In addition, the urine blood urea nitrogen, creatinine, osmolality, NGAL, LFABP, β_2-microglobulin, N-acetyl-β-D-glucosaminidase (NAG), and albumin excretion were also measured on admission. These urine and serum biomarkers were measured by the Special Reference Laboratory (SRL©, Tokyo, Japan). The level of u-LFABP was measured with an enzyme-linked immunosorbent assay (ELISA) using a human LFABP ELISA kit (Kyowa Medex Co., Tokyo, Japan). The level of urinary NGAL was measured using the NGAL ELISA Kit (R&D Systems Inc., Minneapolis, MN, USA). The lower and upper limits of detection for the urinary NGAL (u-NGAL) concentration were 4 and 500 pg/mL, respectively, and the lower limit for the u-LFABP was 2.9 pg/mL. u-LFABP and NGAL were obtained from all 293 patients on day 1; other urinary biomarkers were measured in 267 patients on admission (data for 26 patients were not collected). Furthermore, the u-LFABP samples were obtained from 272 patients on day 4 (4 patients died, and 17 samples were not collected) and 236 patients before discharge (15 patients died within 14 days of admission, 7 patients were discharged within 7 days of admission, and the data for 36 patients were not collected). The u-NGAL samples were obtained from 274 patients on day 4 and 235 patients before discharge.

Evaluation of AKI

Because the urine output could not be precisely measured in the general ward, the majority of patients with AHF receive treatment with diuretics which influence the urine output. We evaluated the presence of AKI using only the creatinine criteria of the RIFLE classification [13]. AKI was defined based on the ratio of the serum creatinine value recorded on admission to the baseline creatinine value, the AKI during the first 7 days defined as the ratio of the maximum serum creatinine value during first 7 days to the baseline creatinine value, and the AKI during hospitalization defined as the ratio of the maximum serum creatinine value during hospitalization to the baseline creatinine value. Patients were classified as having either no AKI or class R (risk), class I (injury) or class F (failure) AKI. "No AKI" was diagnosed as an increase in the serum creatinine level <1.5-fold baseline, class R as an increase in the serum creatinine level ≥1.5-fold baseline, class I as increase in the serum creatinine level ≥2.0-fold baseline and class F as increase in the serum creatinine level ≥3.0-fold baseline. Patients who were receiving continuous renal replacement therapy (CRRT) were defined as class F.

With regard to the baseline level of creatinine, in CKD patients, the baseline level was defined as the lowest value recorded during admission. In patients without CKD (non-CKD) patients, the lower of either the lowest creatinine value during hospitalization or the Modification of Diet in Renal Disease (MDRD) creatinine level was used as the baseline creatinine value. The MDRD creatinine levels were calculated using the MDRD equation, as recommended by the Acute Dialysis Quality Initiative. The MDRD equation for serum creatinine was calculated assuming a glomerular filtration rate (GFR) of 75 mL/min/1.73 m^2 [14, 15].

CKD was diagnosed based on the creatinine value observed within 1 year. Furthermore, among patients in whom the creatinine value had not been measured within 1 year before admission, those who had been previously diagnosed with CKD in the past or at another institution were considered to have CKD. CKD was defined as a syndrome comprising a >3-month history of a low GFR (<60 mL/min/1.73 m^2) [16]. Patients who did not have medical records at Chiba Hokusoh Hospital for the 3 months before admission were diagnosed with CKD using the previous 3 months' data from another institution. Kidney damage, as identified by abnormal findings in the urine and imaging tests, was used to diagnose CKD in some patients in the present study; therefore, CKD was diagnosed only by a >3-month history of low GFR. In the present study, 165 of 293 patients (56.3%) were diagnosed with CKD.

Procedures

The patients were divided into 2 groups according to the u-LFABP quartiles (Q1, Q2, and Q3 = low u-LFABP group, n = 220 vs. Q4 = high u-LFABP group, n = 73). We evaluated the presence of AKI on admission,

during the first 7 days and during hospitalization and also compared the diagnostic and prognostic value of u-LFABP between CKD (n = 165) and non-CKD patients (n = 128). The receiver-operating characteristic (ROC) curves for the urine biomarkers were calculated to predict the optimal cut-off values, and the sensitivity, specificity, and area under the ROC curve (AUC) were determined to indicate the optimal values for predicting AKI on admission, AKI during the first 7 days and AKI during hospitalization.

The factors that were significantly different between the low and high LFABP groups on a univariate analysis were selected for inclusion in a multivariate logistic regression model. The biomarkers predicting AKI during the first 7 days were investigated using a multivariate logistic regression model in the non-CKD and CKD patients.

The patients were clinically followed-up at a routine outpatient clinic. The prognoses of the patients who were followed-up at other institutes were determined by telephone contact. The patients were assigned to 1 of 2 groups based on levels of biomarkers (low vs. high) by the quantiles of each biomarker, including NGAL, NAG, and albumin excretion (Q1, Q2, and Q3 = low group vs. Q4 = high group). The prognostic value for the 60-day mortality was evaluated using the Cox regression hazard model and Kaplan-Meier curve.

Statistical Analyses

All data were statistically analyzed using the SPSS 22.0 J software program (SPSS Japan Institute, Tokyo, Japan). All numerical data were expressed as the medians (25–75% interquartile range). The Mann-Whitney U test was used to compare 2 groups (low u-LFABP group vs. high u-LFABP group), and the Friedman test was used to compare 3 groups (time-dependent change in u-LFABP and u-NGAL). Comparisons of all proportions were performed with a χ^2 analysis. The significant biomarkers indicating AKI during the first 7 days were determined using the multivariate logistic regression model. ROC curves were calculated to predict the cutoff values, and the sensitivity, specificity, and AUC were determined. A p value <0.05 was considered to be statistically significant.

The prognostic value of each biomarker in the low and high groups was assessed using a Cox regression hazard model. A Cox regression analysis was performed to obtain the hazard ratio for 60-day mortality. A multivariate analysis was performed using the variables with a p value of <0.05 in the univariate analysis to examine their independent associations with the 60-day mortality. The survival rates were analyzed between the groups determined based on the quantile of each biomarker and were assigned as low or high biomarkers using Kaplan-Meier curves. Significant differences were calculated using the log-rank test.

Results

Patients' Characteristics and u-LFABP Levels

The median (range) u-LFABP levels were 57.8 (14.9 to 183.9) ng/mg × cre. The distribution of the u-LFABP levels in the AHF patients overall is shown in Figure 1a. Among all 293 patients, the u-LFABP levels were <100 ng/mg × cre in 184 (62.8%) and >1,000 ng/mL in 23 (7.8%). Both the u-LFABP and u-NAGL levels were significantly decreased on day 4 and before discharge compared with the values observed on day 1 (Fig. 1b, c).

The patient cohort comprised 66.9% males with a median age of 74 years. One hundred and ninety-two (65.5%) patients had new-onset HF, 125 (42.7%) had ischemic heart disease and 168 (57.3%) had non-ischemic heart disease, including cardiomyopathy (n = 37), hypertensive heart disease (n = 45), and valvular disease (n = 61). Most patients were NYHA class IV (75.1%). The median left ventricular ejection fraction (LVEF) on admission was 41.0%. The etiology of HF was similar in the low and high u-LFABP groups. There were significantly more patients with new-onset HF; the systolic blood pressure, pulse rate, and lactate levels were significantly higher, and the serum levels of total bilirubin were significantly lower in the high u-LFABP group than in the low u-LFABP group (Table 1).

The serum levels of β_2-microglobulin, α_1-microgloburin, creatinine, and heart-type fatty acid-binding protein were significantly higher in the high u-LFABP group than in the low u-LFABP group, as were the urinary NGAL, β_2-microglobulin, NAG, and albumin excretion (Table 1).

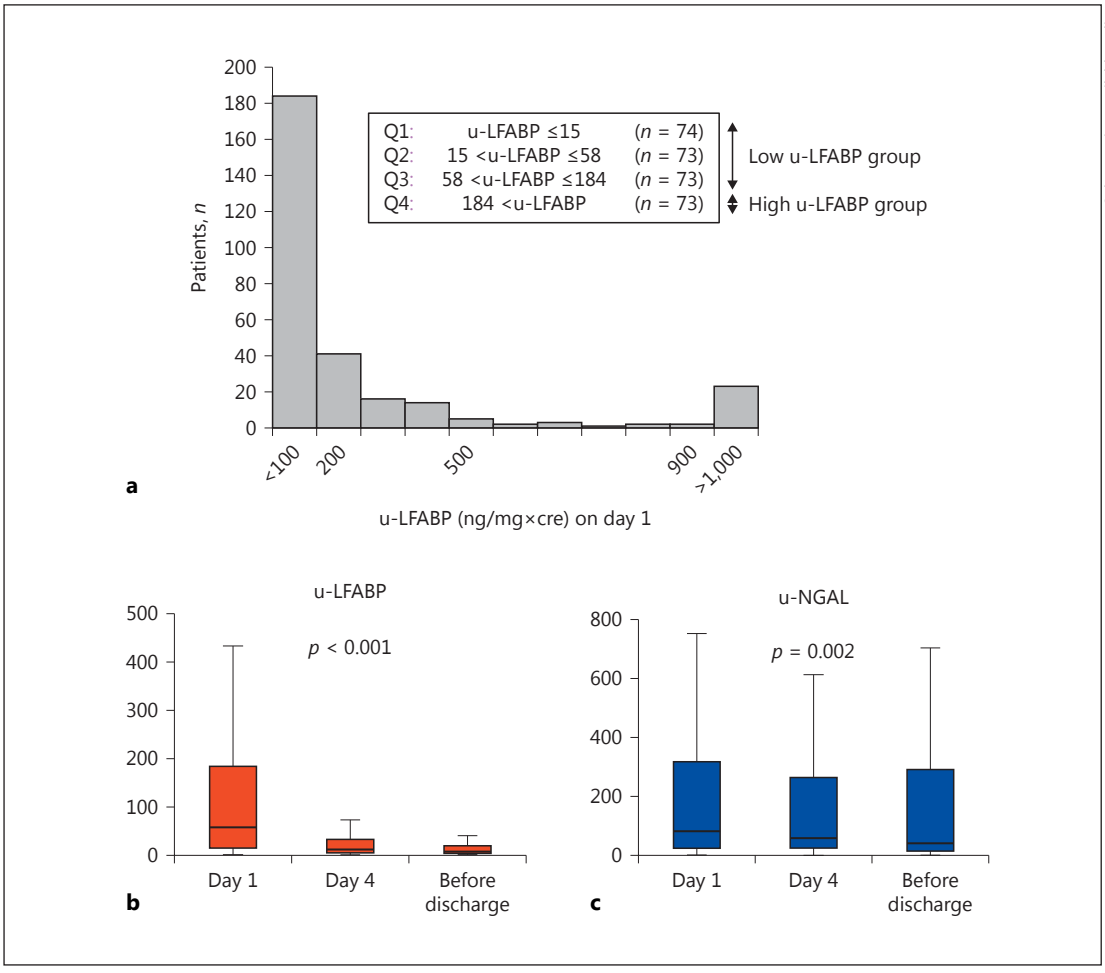

Fig. 1. a The distribution of the urinary liver fatty acid-binding protein (u-LFABP) levels. The median value among all 293 acute heart failure patients was 57.8 ng/mg × cre. The u-LFABP levels were <100 ng/mg × cre in 184 patients (62.8%) and >1,000 ng/mL in 23 patients (7.8%). **b** The u-LFABP levels were significantly decreased on day 4 and before discharge compared with the values observed on day 1. **c** The urinary neutrophil gelatinase-associated lipocalin (u-NGAL) levels were significantly decreased on day 4 and before discharge compared with the values observed on day 1 in the AKI patients.

Evaluation of AKI in Each CKD and Non-CKD Patient

There were significantly more patients with AKI during the first 7 days in the high u-LFABP group (70.0%) than in the low u-LFABP group (45.9%) among non-CKD patients. However, there was no significant difference in the proportion between the low u-LFABP group (36.5%) and the high u-LFABP group (44.8%) among CKD patients. Regarding the rate of patients with AKI on admission and during hospitalization, no significant difference was noted between the low and high u-LFABP groups or between the CKD and non-CKD patients (Table 2).

The results of the ROC curves are shown in Table 3. u-LFABP proved valuable based on the AUC for detecting AKI during the first 7 days in non-CKD patients. In contrast, only u-NGAL was a significant biomarker for detecting AKI during the first 7 days in CKD patients. The value of serum u-LFABP that produced the optimal balance between the sensitivity and specificity for predicting the AKI during the first 7 days (63.6 and 59.7%; AUC = 0.662, 95% confi-

Table 1. Patients' characteristics and u-LFABP levels

Characteristic	Low u-LFABP			High u-LFABP	*p* value
	Q1 (*n* = 74)	Q2 (*n* = 73)	Q3 (*n* = 73)	Q4 (*n* = 73)	
Age, years	72 (65–80)	77 (70–83)	77 (68–82)	76 (66–84)	0.249
Type, new onset	43 (58.1%)	48 (65.8%)	46 (63.0%)	55 (75.3%)	0.047
Etiology, ischemia	29 (39.2%)	33 (45.2%)	38 (52.1%)	25 (34.3%)	0.103
Gender, male	55 (74.3%)	46 (63.0%)	53 (72.6%)	42 (57.5%)	0.062
Past medical history					
Hypertension, yes	43 (58.1%)	51 (69.9%)	61 (83.6%)	55 (75.3%)	0.457
Diabetes mellitus, yes	33 (44.6%)	38 (52.1%)	47 (64.4%)	38 (52.1%)	0.892
Dyslipidemia, yes	32 (43.2%)	35 (47.9%)	43 (58.9%)	32 (43.8%)	0.418
Vital signs and status					
Systolic blood pressure, mm Hg	146 (111–169)	162 (132–183)	162 (141–186)	174 (150–200)	<0.001
Pulse, beats/min	98 (83–118)	108 (94–130)	107 (94–128)	115 (95–130)	0.046
LVEF, %	38 (26–52)	39 (27–50)	36 (26–50)	41 (32–50)	0.117
NYHA, IV	48 (64.9%)	58 (79.5%)	56 (76.7%)	58 (79.5%)	0.352
Arterial blood gas					
pH	7.41 (7.30–7.45)	7.38 (7.29–7.45)	7.30 (7.20–7.39)	7.28 (7.14–7.34)	<0.001
PCO_2, mm Hg	35 (31–47)	37 (31–49)	46 (37–58)	47 (36–60)	0.011
PO_2, mm Hg	101 (72–146)	86 (65–137)	85 (65–123)	91 (64–131)	0.778
HCO_3^-, mmol/L	22.3 (20.1–24.4)	22.1 (19.2–24.2)	22.4 (20.2–25.0)	20.5 (17.1–22.5)	<0.001
SaO_2, %	98 (94–99)	96 (91–98)	95 (92–98)	96 (91–97)	0.038
Lactate, mmol/L	1.5 (1.2–3.3)	1.7 (1.2–2.9)	1.8 (1.1–2.8)	2.2 (1.3–4.6)	0.022
Laboratory data					
Total bilirubin, mg/dL	0.7 (0.5–1.2)	0.8 (0.5–1.0)	0.5 (0.4–0.7)	0.5 (0.3–0.7)	0.001
Uric acid, mg/dL	7.0 (5.8–8.0)	6.9 (5.2–8.0)	6.9 (5.6–8.2)	6.6 (5.2–8.6)	0.922
Sodium, mmol/L	140 (137–142)	140 (137–141)	140 (138–142)	140 (138–143)	0.064
Potassium, mmol/L	4.5 (3.9–4.7)	4.3 (3.8–4.8)	4.1 (3.8–4.6)	4.3 (3.8–4.7)	0.906
Hemoglobin, g/dL	12.8 (10.9–14.0)	12.4 (10.8–13.7)	11.7 (9.5–13.2)	11.8 (9.9–13.6)	0.325
CRP, mg/dL	0.68 (0.16–2.36)	0.94 (0.29–5.80)	1.04 (0.15–4.31)	0.67 (0.20–2.98)	0.293
BNP, pg/mL	726 (433–1,381)	700 (414–1,691)	850 (541–1,546)	730 (439–1,753)	0.699
Serum biomarkers					
β_2-Macroglobulin, mg/L	3.0 (2.2–4.3)	3.6 (2.8–5.6)	4.5 (3.0–7.0)	4.7 (3.2–7.6)	0.020
α_1-Microgloburin, ng/L	19.1 (13.5–23.6)	20.7 (17.1–29.5)	25.2 (19.8–43.8)	24.2 (17.8–51.0)	0.019
Osmolality, mOsm/L	293 (287–300)	295 (289–300)	297 (292–306)	302 (296–307)	<0.001
BUN, mg/dL	23.7 (18.9–34.4)	25.3 (18.1–37.6)	26.0 (18.1–40.3)	30.3 (17.5–42.6)	0.496
Creatinine, mg/dL	1.09 (0.81–1.51)	1.10 (0.88–1.73)	1.27 (0.90–2.22)	1.31 (0.98–2.30)	0.019
NTproBNP, pg/mL	4,855 (2,231–10,460)	6,357 (2,782–13,753)	7,241 (3,012–17,867)	6,706 (2,971–15,390)	0.333
Hs-TropT, ng/mL	0.064 (0.031–0.285)	0.065 (0.033–0.127)	0.067 (0.044–0.139)	0.052 (0.033–0.126)	0.313
PIIIP, U/mL	0.9 (0.7–1.1)	1.0 (0.8–1.2)	1.2 (0.9–1.4)	1.1 (0.9–1.5)	0.009
HFABP, ng/mL	9.8 (6.5–21.0)	12.8 (8.4–26.6)	14.8 (8.5–27.1)	18.5 (10.9–38.5)	0.002
Urinary biomarkers					
NGAL, ng/mg × cre	20.9 (10.8–56.6)	61.9 (22.9–164.8)	119.3 (41.6–388.0)	350.0 (89.6–736.3)	<0.001
β_2-Microglobulin, μg/mg × cre	94 (36–236)	470 (135–2,177)	2,685 (447–8,225)	10,150 (1,182–37,456)	<0.001
NAG, U/mg × cre	12.0 (7.3–16.3)	14.6 (10.8–22.5)	17.4 (11.1–23.6)	22.8 (14.4–36.4)	<0.001
Albumin, mg/g × cre	164 (65–289)	360 (137–838)	984 (471–2,212)	2,201 (691–5,417)	<0.001
Osmolality, mOsm/L	519 (397–693)	422 (351–534)	431 (349–576)	417 (367–540)	0.130
BUN, mg/dL	532 (367–895)	478 (266–678)	419 (287–579)	361 (257–586)	0.002
Creatinine, mg/dL	105 (57–178)	82 (36–127)	69 (43–122)	57 (36–88)	0.001
Medication (cases) during the first 5 days					
Furosemide, yes	65 (87.8%)	67 (91.8%)	68 (93.2%)	68 (93.2%)	0.637
Nitroglycerin, yes	20 (27.0%)	31 (42.5%)	45 (61.6%)	45 (61.6%)	0.010
Nicorandil, yes	13 (17.6%)	11 (15.1%)	15 (20.5%)	12 (16.4%)	0.861
Carperitide, yes	35 (47.3%)	33 (45.2%)	40 (54.8%)	42 (57.5%)	0.226
Dopamine, yes	5 (6.8%)	3 (4.1%)	3 (4.1%)	9 (12.3%)	0.056
Dobutamine, yes	19 (25.7%)	9 (12.3%)	8 (11.0%)	5 (6.9%)	0.051
ACE-I/ARBm, yes	27 (36.5%)	23 (31.5%)	33 (45.2%)	25 (34.3%)	0.675
β-Blocker, yes	25 (33.8%)	28 (38.4%)	14 (19.2%)	22 (30.1%)	1.000
Spironolactone, yes	32 (43.2%)	27 (37.0%)	22 (30.1%)	22 (30.1%)	0.325

Table 1 (continued)

Characteristic	Low u-LFABP			High u-LFABP	*p* value
	Q1 (*n* = 74)	Q2 (*n* = 73)	Q3 (*n* = 73)	Q4 (*n* = 73)	
AKI					
AKI on admission, yes	18 (24.3%)	16 (21.9%)	20 (27.4%)	21 (28.8%)	0.358
AKI during first 7 days, yes	29 (39.2%)	31 (42.5%)	32 (43.8%)	42 (57.5%)	0.022
AKI during hospitalization, yes	41 (55.4%)	43 (58.9%)	41 (56.2%)	51 (69.9%)	0.054

u-LFABP, urinary liver fatty acid-binding protein; LVEF, left ventricular ejection fraction measured by echocardiography; NYHA, New York Heart Association; CRP, C-reactive protein; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; BUN, blood urea nitrogen; NTproBNP, N-terminal pro-brain-type natriuretic peptide; Hs-TropT, high-sensitivity troponin T; PIIIP, procollagen III peptide; HFABP, heart-fatty acid-binding protein; NGAL, neutrophil gelatinase-associated lipocalin; NAG, N acetyl-β-D-glucosaminidase; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; AKI, acute kidney injury. *p* value, between the low u-LFABP group and the high u-LFABP group, determined by the Mann-Whitney U test or the χ^2 test. All numerical data were expressed as the medians (25–75% interquartile range).

Table 2. Evaluation of AKI between the high LFABP group and the low LFABP group in non-CKD and CKD patients

	Non-CKD (*n* = 128)			CKD (*n* = 165)		
	low LFABP	high LFABP	*p* value	low LFABP	high LFABP	*p* value
AKI on admission, yes	27 (27.6%)	15 (50.0%)	0.047	27 (22.1%)	7 (16.3%)	0.515
AKI during first 7 days, yes	45 (45.9%)	21 (70.0%)	0.042	47 (36.5%)	21 (48.8%)	0.206
AKI during hospitalization, yes	64 (65.3%)	22 (73.3%)	0.387	62 (50.8%)	28 (65.1%)	0.075

AKI, acute kidney injyury; LFABP, liver fatty acid-binding protein; CKD, chronic kidney disease.

Table 3. Diagnostic value of the urinary biomarkers in non-CKD and CKD patients

AKI during first 7 days	Non-CKD			CKD		
	AUC	95% CI	*p* value	AUC	95% CI	*p* value
Urinary biomarkers						
LFABP, ng/mg × cre	0.662	0.564–0.761	0.003	0.529	0.434–0.625	0.540
NGAL, ng/mg × cre	0.613	0.511–0.716	0.036	0.616	0.523–0.709	0.016
NAG, U/mg × cre	0.581	0.477–0.685	0.134	0.546	0.451–0.641	0.340
Albumin, mg/g × cre	0.505	0.398–0.611	0.927	0.462	0.365–0.558	0.424
β_2-Microglobulin, μg/mg × cre	0.623	0.520–0.725	0.023	0.492	0.394–0.589	0.865

AKI, acute kidney injury; CKD, chronic kidney disease; HR, hazard ratio; CI, confidence interval; LFABP, liver fatty acid-binding protein; NGAL, neutrophil gelatinase-associated lipocalin; NAG, N-acetyl-β-D-glucosaminidase.

dence interval [CI] 0.564–0.761, $p = 0.002$) was 41.9 ng/mg × cre for non-CKD patients. The multivariate logistic regression model for indicating the presence of AKI during first 5 days found that the most useful specific biomarker was u-LFABP (Q4 = high u-LFABP group, odds ratio: 3.850; 95% CI 1.128–13.140, $p = 0.031$) in non-CKD patients, with no biomarker found in CKD patients (Table 4).

Table 4. The results of the univariate and multivariate logistic regression analyses for the detection of AKI in non-CKD or CKD patients

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Non-CKD						
u-LFABP						
Q1 (≤15 ng/mg × cre)	1.000			1.000		
Q2 (16–58 ng/mg × cre)	1.222	0.464–3.217	0.684	1.325	0.418–4.205	0.633
Q3 (59–183 ng/mg × cre)	2.226	0.821–6.037	0.116	2.031	0.606–6.805	0.251
Q4 (≥184 ng/mg × cre)	3.300	1.204–9.042	0.020	3.850	1.128–13.140	0.031
Adjusting factors						
NGAL (≥320 ng/mg × cre)	2.115	0.791–5.655	0.135			
NAG (≥24.8 U/mg × cre)	2.872	0.985–8.374	0.053			
Albumin (≥1,950 ng/mg × cre)	0.942	0.408–2.627	0.942			
β_2-Microglobulin (≥6,750 ng/mg × cre)	2.667	0.960–7.408	0.060			
Age (per 1-year increase)	1.002	0.974–1.030	0.913			
SBP (per 10 mm Hg increase)	0.946	0.869–1.031	0.208			
LVEF (per 10% increase)	0.913	0.753–1.107	0.353			
Sodium (per 1.0 mmol/L increase)	0.893	0.813–0.981	0.018	0.895	0.799–1.002	0.055
Hemoglobin (per 1.0 g/dL increase)	0.893	0.775–1.030	0.119			
Creatinine (per 0.1 mg/dL increase)	1.664	1.335–2.076	<0.001	1.613	1.291–2.015	<0.001
Hs-TropT (per 0.01 ng/mL increase)	0.998	0.992–1.004	0.526			
BNP (per 100 pg/mL increase)	1.032	0.991–1.075	0.127			
CKD						
u-LFABP						
Q1 (≤15 ng/mg × cre)	1.000					
Q2 (16–58 ng/mg × cre)	1.086	0.442–2.670	0.857	1.212	0.440–3.341	0.710
Q3 (59–183 ng/mg × cre)	0.793	0.322–1.953	0.614	0.759	0.261–2.209	0.613
Q4 (≥184 ng/mg × cre)	1.533	0.631–3.727	0.346	1.967	0.675–5.732	0.215
Adjusting factors						
NGAL (≥320 ng/mg × cre)	1.897	0.975–3.690	0.059			
NAG (≥24.8 U/mg × cre)	1.392	0.655–2.958	0.390			
Albumin (≥1,950 ng/mg × cre)	1.176	0.577–2.396	0.655			
β_2-Microglobulin (≥6,750 ng/mg × cre)	1.910	0.938–3.886	0.074			
Age (per 1-year increase)	0.971	0.942–1.000	0.048	0.991	0.957–1.026	0.624
SBP (per 10 mm Hg increase)	0.897	0.825–0.974	0.010	0.910	0.824–1.006	0.065
LVEF (per 10% increase)	1.050	0.868–1.270	0.618			
Sodium (per 1.0 mmol/L increase)	0.901	0.842–0.963	0.002	0.916	0.851–0.985	0.019
Hemoglobin (per 1.0 g/dL increase)	0.990	0.958–1.022	0.522			
Creatinine (per 0.1 mg/dL increase)	1.037	1.012–1.062	0.004	1.031	1.004–1.060	0.026
Hs-TropT (per 0.01 ng/mL increase)	1.007	1.001–1.013	0.023	1.005	0.998–1.012	0.206
BNP (per 100 pg/mL increase)	1.008	0.991–1.025	0.362			

AKI, acute kidney injury; CKD, chronic kidney disease; OR, odds ratio; CI, confidence interval; LFABP, liver fatty acid-binding protein; NGAL, neutrophil gelatinase-associated lipocalin; NAG, N-acetyl-β-D-glucosaminidase; SBP, systolic blood pressure; LVEF, left ventricular ejection fraction measured on echocardiography; Hs-TropT, high-sensitivity troponin T; BNP, brain-type natriuretic peptide.

Relationship between the u-LFABP Level and the Short-Term Prognosis

Twenty-six of the 293 patients died within 60 days of follow-up, including 10 of the 128 patients with no-CKD patients and 16 of the 165 patients with CKD patients. The multivariate Cox regression model indicated that u-LFABP levels (Q4 = high u-LFABP group, hazard ratio: 13.494, 95% CI 1.512–121.415; $p = 0.020$) were independent predictors of 60-day mortality

Table 5. Cox regression analysis of the associations between the 60-day mortality and the clinical findings, including urinary biomarkers in non-CKD or CKD patients

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Non-CKD						
u-LFABP						
Q1 (≤15 ng/mg × cre)	1.000			1.000		
Q2 (16–58 ng/mg × cre)	1.113	0.070–17.790	0.940	1.427	0.089–22.832	0.802
Q3 (59–183 ng/mg × cre)	3.811	0.396–36.641	0.247	6.134	0.619–60.780	0.121
Q4 (≥184 ng/mg × cre)	6.466	0.755–55.369	0.088	13.494	1.512–120.415	0.020
Adjusting factors						
NGAL (≥320 ng/mg × cre)	0.564	0.071–4.453	0.587			
NAG (≥24.8 U/mg × cre)	1.428	0.357–5.711	0.614			
Albumin (≥1,950 ng/mg × cre)	1.327	0.276–6.391	0.724			
β_2-Microglobulin (≥6,750 ng/mg × cre)	1.287	0.267–6.195	0.753			
Age (per 1-year increase)	1.027	0.968–1.088	0.377			
SBP (per 10 mm Hg increase)	0.839	0.716–0.984	0.030	0.785	0.667–0.924	0.004
LVEF (per 10% increase)	1.033	0.737–1.449	0.848			
Sodium (per 1.0 mmol/L increase)	1.004	0.869–1.160	0.955			
Hemoglobin (per 1.0 g/dL increase)	0.975	0.763–1.244	0.837			
Creatinine (per 0.1 mg/dL increase)	1.000	0.992–1.007	0.941			
Hs-TropT (per 0.01 ng/mL increase)	1.003	0.997–1.009	0.328			
BNP (per 100 pg/mL increase)	1.023	0.981–1.066	0.285			
CKD						
u-LFABP						
Q1 (≤15 ng/mg × cre)	1.000					
Q2 (16–58 ng/mg × cre)	0.953	0.307–2.957	0.934	2.642	0.660–10.569	0.170
Q3 (59–183 ng/mg × cre)	0.133	0.016–1.102	0.061	0.450	0.046–4.452	0.495
Q4 (≥184 ng/mg × cre)	0.422	0.106–1.690	0.223	1.706	0.333–8.731	0.521
Adjusting factors						
NGAL (≥320 ng/mg × cre)	0.997	0.347–2.871	0.996			
NAG (≥24.8 U/mg × cre)	1.680	0.574–4.916	0.344			
Albumin (≥1,950 ng/mg × cre)	0.355	0.080–1.573	0.173			
β_2-Microglobulin (≥6,750 ng/mg × cre)	0.356	0.080–1.578	0.174			
Age (per 1-year increase)	0.999	0.955–1.046	0.975			
SBP (per 10 mm Hg increase)	0.737	0.638–0.851	<0.001	0.836	0.714–0.977	0.025
LVEF (per 10% increase)	0.868	0.621–1.214	0.409			
Sodium (per 1.0 mmol/L increase)	0.895	0.865–0.927	<0.001	0.917	0.873–0.964	0.001
Hemoglobin (per 1.0 g/dL increase)	0.970	0.794–1.184	0.970			
Creatinine (per 0.1 mg/dL increase)	0.999	0.972–1.028	0.968			
Hs-TropT (per 0.01 ng/mL increase)	1.000	0.995–1.005	0.999			
BNP (per 100 pg/mL increase)	1.006	0.986–1.027	0.542			

CKD, chronic kidney disease; HR, hazard ratio; CI, confidence interval; LFABP, liver fatty acid-binding protein; NGAL, neutrophil gelatinase-associated lipocalin; NAG, N-acetyl-β-D-glucosaminidase; SBP, systolic blood pressure; LVEF, left ventricular ejection fraction measured on echocardiography; Hs-TropT, high-sensitivity troponin T; BNP, brain-type natriuretic peptide.

for no-CKD patients; however, they were not significant predictors for CKD patients (Table 5). The Kaplan-Meier survival curves showed that the prognosis, including all-cause death and HF events, was significantly poorer in the high u-LFABP group than in the low u-LFABP group for non-CKD patients (Fig. 2a). However, all biomarkers could not predict the prognosis using the Kaplan-Meier curve for CKD patients (Fig. 3).

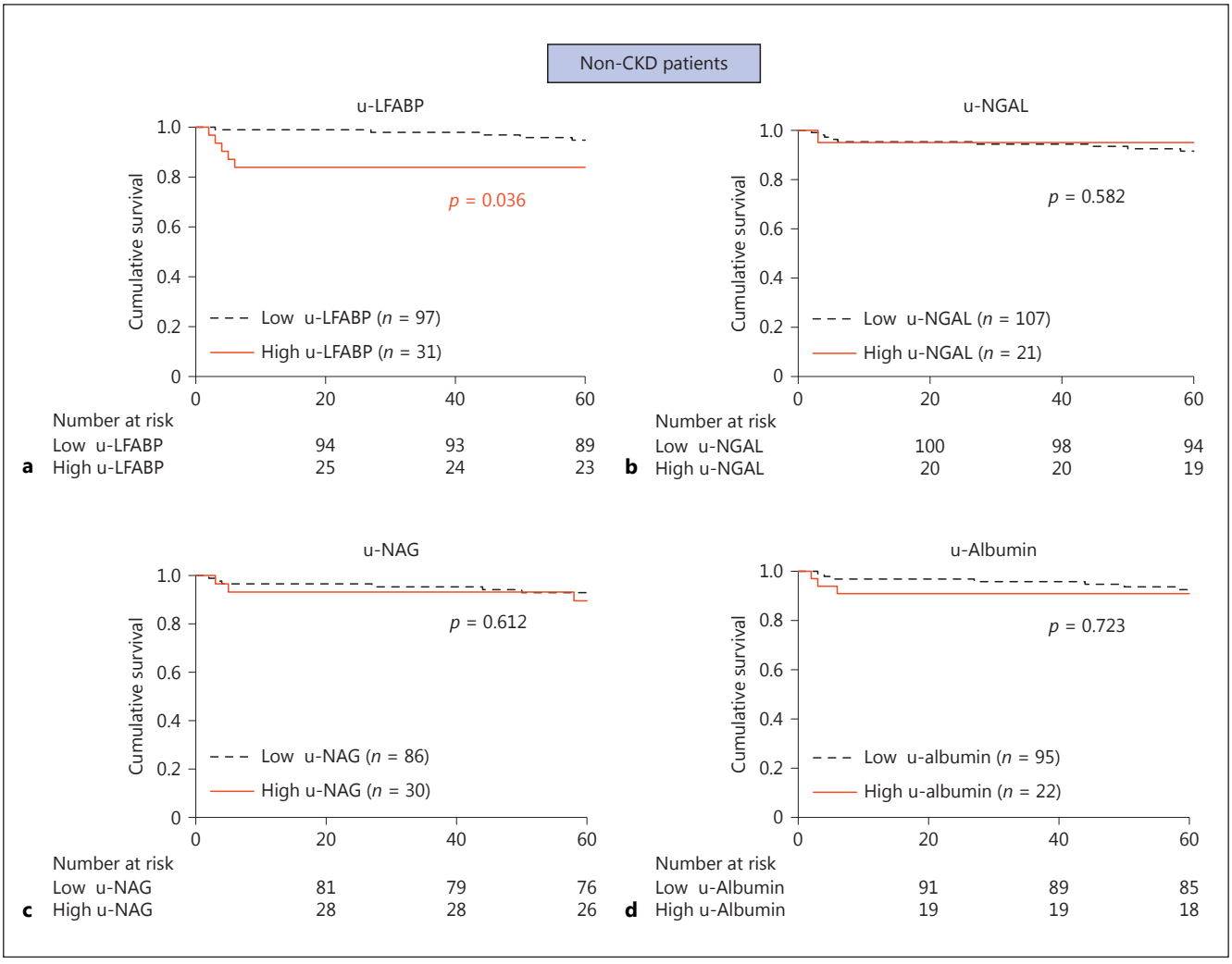

Fig. 2. Kaplan-Meier curves based on the differences in each biomarker in non-CKD patients. **a** The all-cause death rate was significantly higher in the high urinary liver fatty acid-binding protein (u-LFABP) group than in the low u-LFABP group ($p = 0.036$). **b** The all-cause death rate was not markedly different between the high urinary neutrophil gelatinase-associated lipocalin (u-NGAL) group and the low u-NGAL group. **c** The all-cause death rate was not markedly different between the high urinary N-acetyl-β-D-glucosaminidase (u-NAG) group and the low u-NAG group. **d** The all-cause death rate was not markedly different between the high u-albumin group and the low u-albumin group.

Discussion

Utility of u-LFABP and NGAL for Evaluating the Presence of AKI

u-LFABP is a fatty acid-binding protein with a molecular weight of approximately 14 kDa that belongs to the lipocalin family. It is found in the cytoplasm of human proximal tubular cells [17] and binds fatty acids and transports them to mitochondria or peroxisomes, where the fatty acids are β-oxidized [18].

Fatty acids 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 hydro-

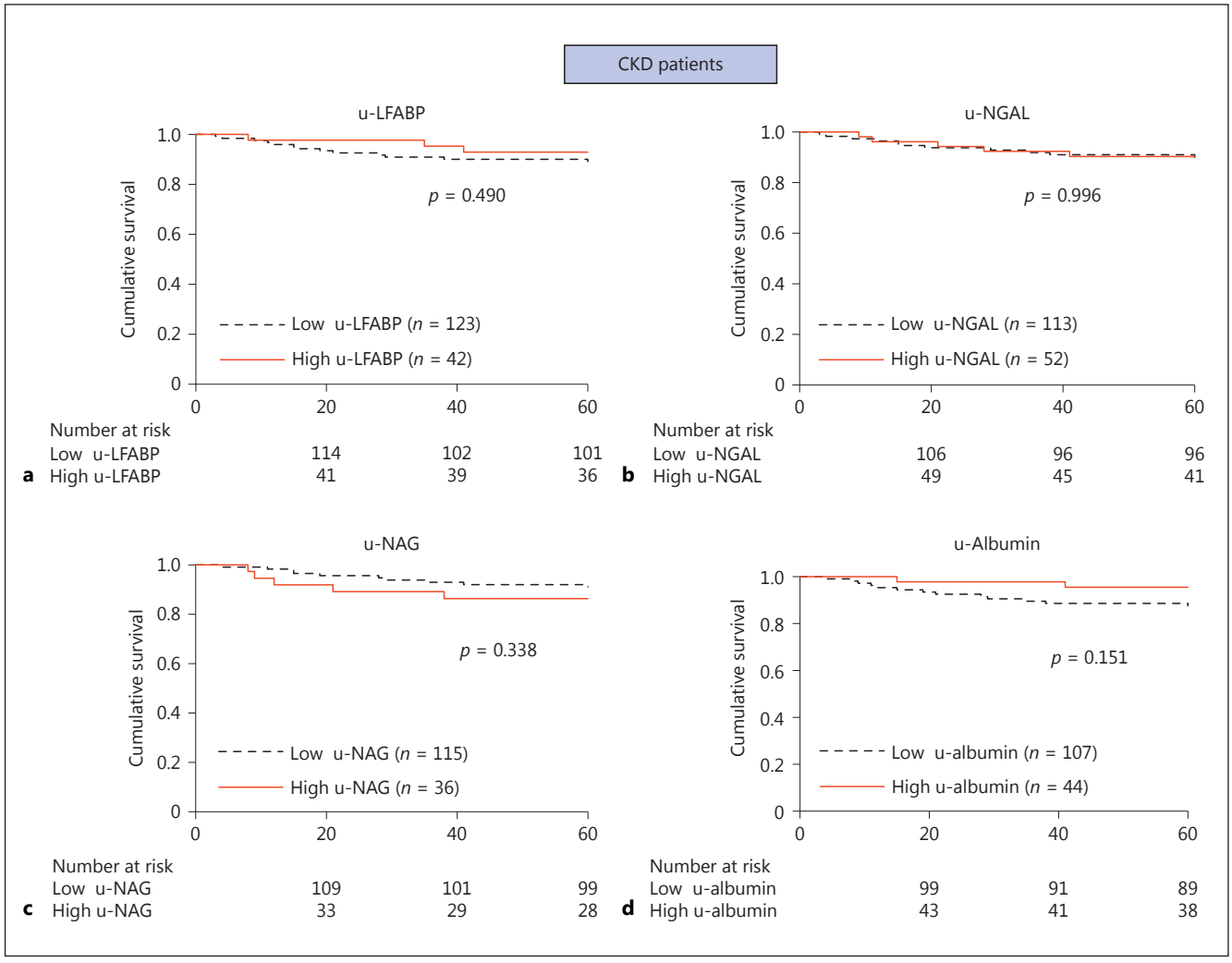

Fig. 3. Kaplan-Meier curves based on the differences in each biomarker in CKD patients. **a** The all-cause death rate was not markedly different between the high urinary liver fatty acid-binding protein (u-LFABP) group and the low u-LFABP group. **b** The all-cause death rate was not markedly different between the high urinary neutrophil gelatinase-associated lipocalin (u-NGAL) group and the low u-NGAL group. **c** The all-cause death rate was not markedly different between the high urinary N-acetyl-β-D-glucosaminidase (u-NAG) group and the low u-NAG group. **d** The all-cause death rate was not markedly different between the high u-albumin group and the low u-albumin group.

phobic character and cytotoxicity. Overloading of free fatty acid has been reported in the proximal tubule under various conditions, such as massive proteinuria, ischemia and toxic insight. Furthermore, free fatty acids and their transformations accumulate easily under conditions of proteinuria and other stressors, including ischemia or the presence of toxins [19]. The overproduction of free fatty acids induces oxidative stress and the production of inflammatory cytokines by increasing mitochondrial reactive oxygen species, subsequently leading to tubulointerstitial damage [20]. Fatty acids also become cytotoxic because of peroxidation and induce the expression of chemo-attractants in the proximal tubules, leading to tubulointerstitial damage [21].

Under such cytotoxic conditions with overproduction of free fatty acid, free fatty acid induces LFABP gene expression, and LFABP is thought to be a regulator of free fatty acid homeostasis in the cytoplasm. LFABP levels have also been found to be activated in the proximal tubule, triggered not only by the overproduction of free fatty acids, but also by tubular ischemia; u-LFABP therefore binds the free fatty acids produced by oxidative stress and toxic insults [19]. After binding strongly to free fatty acids, LFABP is then excreted from the cytoplasm of proximal tubular cells into the urine in response to hypoxic stress, independent of the serum LFABP levels. u-LFABP may therefore help prevent free fatty acid-induced tubulointerstitial damage and might reflect various kinds of stress that cause such damage, making it a potentially useful clinical marker for the progression of kidney damage. Measuring u-LFABP may therefore enable us to monitor renal tubulointerstitial damage [19, 22], with kidney injury assessed by directly measuring protein levels [23].

The u-LFABP level might increase before the occurrence of tubular structural damage; therefore, it might be a real-time indicator of tubulointerstitial damage and become a useful biomarker for the early detection of AKI. u-LFABP was identified as a useful marker for the diagnosis of AKI in patients in the intensive care unit after cardiac surgery [7, 24] and for predicting the onset of contrast-induced AKI before contrast medium exposure [8]. Matsui et al. [7] reported that the u-LFABP level before a cardiac operation and within the first 6 h after surgery was associated with the onset of AKI. In the AKI setting, various stresses, especially oxidative stress, the presence of tissue hypoxia and tubule ischemia upregulate the renal LFABP expression, with increased secretion of LFABP from damaged proximal tubular cells into the luminal space of proximal tubules [22, 25, 26]. Therefore, the measurement of LFABP in urine also might be a suitable biomarker for the early detection of AKI in patients with severely decompensated HF.

We were only able to detect AKI in patients with non-CKD in the present study. Chronic hypoxia is recognized as an aggravating factor of CKD. In the early phase of diabetic nephropathy without glomerular dysfunction, chronic hyperglycemia causes oxidative stress and sympathetic denervation of the kidney because of autonomic neuropathy, which provokes microvasculature damage and leads to tubulointerstitial hypoxia. Therefore, chronic hypoxia appears to play a dominant pathogenic role both in triggering early-stage diabetic nephropathy and in promoting the progression of diabetic nephropathy. Kamijyo-Ikemori et al. [27] reported that the measurement of LFABP in urine provides a suitable biomarker for the early detection and monitoring of progression of diabetic nephropathy in clinical practice. Therefore, u-LFABP would likely be elevated even in early-stage CKD patients complicated with AHF. Given that both AKI and CKD can induce elevations in u-LFABP, it might be difficult to distinguish between AKI and CKD as the cause of the elevated LFABP value in the acute phase of AHF. It would be approximate to limit the non-CKD patients for the evaluation of AKI using u-LFBP excretion in severely decompensated AHF patients. In this setting, the quartiles of LFABP might be valuable, thus; only Q4 status (definition of high u-LFABP) is an independent predictor of AKI during the first 7 days and adverse outcome within 60 days in present study.

In contrast to LFABP, other urinary markers such as β_2-microglobulin, NAG, albuminuria, and creatinine clearance only increase after cellular structural damage [28]. Therefore, these traditional markers of kidney dysfunction might reflect the distant production of an endogenous marker and its subsequent filtration, secretion and reabsorption by the kidney. Thus, all of these conventional markers indirectly estimate the kidney function. The u-LFABP level was superior to urinary microalbumin excretion, urinary NAG, and urinary α-microglobulin in detecting the progression of chronic glomerular disease [19].

Given that the major urinary biomarker for the detection of AKI in AHF patients was NGAL in a European cohort [5, 6, 29], urinary NGAL was recognized as the gold-standard

urinary biomarker for detecting AKI. However, NGAL may be associated with several issues. Under normal conditions, NGAL is filtered by the glomeruli and reabsorbed by the proximal tubules, leaving only 0.1–0.2% in the urine. However, under AKI conditions, various stresses increase the serum NGAL in the circulation, which induces the activation of neutrophils, and an increased amount of NGAL is filtered from the glomerular filtrate. Some NGAL molecules are reabsorbed by the damaged proximal tubules, while others are excreted. Therefore, the increased urinary NGAL level is mainly attributed to impaired renal absorption, and it takes a longer period of time for the urinary NGAL level to increase than the u-LFABP level. Urinary NGAL is also readily influenced by preoperative comorbidities such as diabetes, hypertension, hyperlipidemia, and cardiovascular disease.

Study Limitations

Several limitations associated with the present study warrant mention. First, diagnosing CKD based on the lowest value recorded within 1 year before admission was important, but it was difficult to accomplish in all patients in the present study. Second, the present study was a single-center study, and a small number of patients were included in each of the groups used to evaluate the prognosis, so patient bias might exist. Third, no urine volume criteria were used for the definition of AKI in the present study. The definition of AKI used in the present study included the presence of AKI on admission; therefore, it was impossible to include urinary criteria. Fourth, the relationship between the classification of AKI and the u-LFABP level was not discussed in the present paper. The median (range) u-LFABP levels were 31.2 (9.7–120.1) ng/mg × cre in no-AKI patients, 72.7 (21.7–334.2) ng/mg × cre in class R patients, 99.1 (39.3–350.1) ng/mg × cre in class I patients, and 59.9 (14.2–183.4) ng/mg × cre in class F patients among non-CKD patients. The classification could not be determined using u-LFABP level in the present study. This result might have been affected by the definition of class F which included patients who had undergone CRRT. We sometimes might perform the CRRT in mild AKI patients. Further studies will be required to resolve this issue. Finally, 26 patients with missing data for β_2-microglobulin, NAG, and albumin excretion were included in the present study. Furthermore, a substantial amount of u-LFABP and u-NGAL data was missed on day 4 and before discharge.

Conclusions

The u-LFABP level was the most readily available marker for predicting the presence of AKI during the first 7 days after admission and produced the optimum balance between sensitivity and specificity in AHF patients with non-CKD. Furthermore, high levels of u-LFABP were able to predict a poor short-term prognosis, including all-cause death within 60 days, in AHF patients with non-CKD.

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Statement of Ethics

The research ethics committee at Nippon Medical School Chiba Hokusoh Hospital approved the study protocol, and subjects have given their informed written consent.

Disclosure Statement

The authors declare no conflicts of interest in association with the present study.

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