



Association between C-reactive protein levels at hospital admission and long-term mortality in patients with acute decompensated heart failure

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Abstract

The C-reactive protein (CRP) levels obtained at hospital admission are associated with the prognosis of several cardiovascular diseases, including acute coronary syndrome. Although the admission CRP level is associated with in-hospital mortality in patients with acute decompensated heart failure (ADHF), there are limited data on the association between the admission CRP level and long-term mortality in patients with ADHF. This study included consecutive ADHF patients admitted to our institution from 2007 to 2011. Eligible patients were divided into four groups based on quartiles of admission CRP levels. The association between the admission CRP level and long-term mortality was assessed by multivariable Cox proportional analysis, including other independent variables with p values < 0.1 in the univariable analyses. Overall, 527 eligible patients were examined. There were 142 deaths (27%) during a median follow-up period of 2.0 years. In the multivariable analysis, the hazard ratio (HR) significantly increased with admission CRP levels in a dose-dependent manner for mortality (p for trend = 0.034). Multivariable analysis also showed a significant association between the admission CRP level, when treated as a natural logarithm-transformed continuous variable, and increased mortality (HR 1.16, $p = 0.030$). In patients with ADHF, the admission CRP level was associated with an increased risk of long-term mortality.

Keywords Heart failure · Biomarker · CRP · Mortality

Introduction

Heart failure (HF) remains one of the leading causes with increasing cardiovascular mortality despite the development of effective treatments [1]. When considering the long-term clinical course of HF patients, worsening episodes, which usually manifest as acute decompensated HF (ADHF), can

be key issues. These episodes can lead to the progression of HF itself [2], possibly through alterations in cardiovascular physiology and systemic or cardiac biomarkers [3]. Thus, in patients with ADHF, it is important to identify factors that show alterations in the acute phase which are associated with an increased long-term mortality, and more importantly, which are modifiable [4]. One such factor may be systemic inflammation, which has been recognized as an important aggravating factor in ADHF [5–7]. The acute-phase reactant against systemic inflammation, C-reactive protein (CRP) [8], is widely measured in daily clinical practice and routinely in almost all ADHF patients. Many studies suggest that CRP levels in patients with chronic HF have a prognostic value [9–13]. However, the prognostic value of CRP levels in patients with ADHF has not been fully elucidated. In particular, limited data are available regarding the association between CRP levels at hospital admission for ADHF and the long-term mortality risks. In the present study, we aimed to investigate the prognostic value of admission CRP levels on the long-term mortality of patients with ADHF.

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Materials and methods

Subjects

Patients who were admitted to the cardiac intensive care unit in the Juntendo University Hospital (Tokyo, Japan) with a diagnosis of ADHF between January 2007 and December 2011 were considered for the present study. ADHF was defined based on the modified Framingham criteria [14]. Patients who had acute coronary syndrome and/or had undergone cardiac surgery during the previous 4 weeks or during initial hospitalization, and those with life-threatening malignancies, were excluded. In addition, patients who died during their initial hospitalization, and those without documented admission CRP levels, were excluded.

The Institutional Review Board of the Juntendo University Hospital approved the study protocol, and the study complied with the Declaration of Helsinki. Informed consent was obtained from all patients.

Data collection

Baseline data were prospectively collected at the time of the initial hospital admission. Medical histories were obtained from the patients' clinical chart reviews. In the present study, a current smoker was defined as one who smoked at the time of admission or had quit smoking less than 1 year prior to admission. The estimated glomerular filtration rate (eGFR) was calculated from baseline serum creatinine levels using the Modification of Diet in Renal Disease equation with a Japanese coefficient [15]. The mean blood pressure (BP) was calculated using the following formula: mean BP = diastolic BP + $1/3 \times$ (systolic BP – diastolic BP). A complete 2-dimensional echocardiography was performed on each patient. The left ventricular ejection fraction (LVEF) was calculated according to the modified Simpson method. Given that there is no established cutoff value on which to define the admission CRP level in ADHF patients, all eligible patients were classified based on quintiles of the CRP value.

All patients were followed up from the date of index admission until June 2012; outcome data were obtained during a clinical visit or by reviewing the medical records for all recorded deaths. The endpoint of interest was the incidence of all-cause mortalities. An independent investigator who had no role in the patients' follow-up and treatment obtained information regarding the outcomes.

Statistical analysis

Continuous variables were expressed as mean \pm standard deviation (SD) or median (interquartile range). Categorical

data were tabulated as frequencies and ratios (%). The natural logarithm-transformed values were used for the statistical analyses of CRP and plasma B-type natriuretic peptide (BNP) levels as the original values were skewed. The baseline characteristics across the three groups were compared using the Cochran–Armitage test for categorical variables, the analysis of covariance for continuous variables, and the Kruskal–Wallis test for the New York Heart Association (NYHA) functional class.

Cumulative survival curves were plotted using Kaplan–Meier methods and the differences in CRP levels across quartiles were determined using log-rank tests. *p* values of the log-rank trend test were also estimated. Cox proportional hazard models were used to compute the hazard ratios (HR) and 95% confidence intervals (CI) for each CRP level quartile, using the lowest quartile as the reference group. The HR trend tests by the CRP quartiles were conducted by assigning an ordinal value to each quartile in separate models. The assumption of proportional hazards was assessed using a log-minus-log survival graph. A univariable Cox proportional hazard analysis was performed by considering the following as independent variables: age, sex, body mass index (BMI), current smoker, history of ADHF, ischemic heart disease, atrial fibrillation (AF), diabetes mellitus, chronic pulmonary disease, NYHA functional class, mean BP, heart rate, LVEF, hemoglobin level, eGFR, sodium and potassium serum levels, natural logarithm-transformed BNP levels, and medication use before admission, in addition to CRP quartiles. Variables with *p* values < 0.10 in the univariable analysis were included in a multivariable Cox proportional hazard regression analysis. To determine whether the results differed with the cutoff points, we performed secondary analyses in which CRP levels were treated as a natural logarithm-transformed continuous variable. A *p* value of < 0.05 was considered statistically significant. All analyses were performed using SPSS version 23 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

Overall, 751 ADHF patients were admitted to our institution between 2007 and 2011. Among them, 160 patients with concomitant acute coronary syndrome and/or those who had undergone cardiac surgery during the previous 4 weeks, or during initial hospitalization, as well as those who had life-threatening malignancies, were initially excluded. A further 52 patients who died during the initial hospitalization and 12 patients without a serum CRP value on admission were also excluded. Finally, 527 patients were targeted and divided into four groups based

on their CRP level quartiles: Quartile 1 (Q1), <0.3 mg/dL; Quartile 2 (Q2), ≥ 0.3 mg/dL and <1.0 mg/dL; Quartile 3 (Q3), ≥ 1.0 mg/dL and <3.9 mg/dL; and Quartile 4 (Q4), ≥ 3.9 mg/dL.

The baseline characteristics are shown in Table 1. Patients with higher CRP levels were more likely to have diabetes mellitus, a lower diastolic or mean BP, and a higher heart rate than those with lower CRP levels. Patients with higher CRP levels had lower levels of hemoglobin, sodium, and eGFR, but higher BNP levels than those with lower CRP levels. Furthermore, we found that patients with higher CRP levels were less likely to use beta blockers than those with lower CRP levels.

Outcomes

At a median follow-up of 2.0 years (interquartile range: 3.2 years), 142 patients had died (27%) including 19 (16.7%) in Q1, 31 (21.1%) in Q2, 49 (36.6%) in Q3, and 43 (32.6%) in Q4. The cumulative survival curves significantly differed across CRP quartiles (overall log-rank test, $p < 0.001$); the higher the CRP levels, the worse the survival (log-rank trend test, $p < 0.001$) (Fig. 1). Although patients in Q2 had a 1.4-times greater risk of mortality compared with those in Q1, the univariate analysis did not reach statistical significance (HR 1.40, 95% CI 0.79–2.47, $p = 0.251$). On the other hand, patients in Q3 and Q4 were at a significantly increased risk of mortality compared to those in Q1 (HR 2.69, 95% CI 1.59–4.58, $p < 0.001$, and HR 2.62, 95% CI

Table 1 Baseline characteristics

	CRP levels per quartile				<i>p</i>
	Q1 (<0.3 mg/dl) (<i>n</i> = 114)	Q2 (0.3–1.0 mg/dl) (<i>n</i> = 147)	Q3 (1.0–3.9 mg/dl) (<i>n</i> = 134)	Q4 (≥ 3.9 mg/dl) (<i>n</i> = 132)	
Age, years	69.7 \pm 12.3	70.5 \pm 13.6	71.0 \pm 14.7	71.0 \pm 14.2	0.877
Men, <i>n</i> (%)	69 (61)	100 (68)	81 (60)	87 (66)	0.462
BMI, kg/m ²	22.6 \pm 4.1	23.4 \pm 4.9	23.1 \pm 5.9	22.3 \pm 4.7	0.307
Current smokers, <i>n</i> (%)	53 (46)	67 (46)	61 (46)	55 (42)	0.869
History of ADHF, <i>n</i> (%)	59 (52)	68 (46)	74 (55)	72 (55)	0.418
NYHA class	3 (1)	3 (1)	4 (1)	4 (1)	0.002
Ischemic heart disease, <i>n</i> (%)	44 (39)	50 (34)	60 (45)	58 (44)	0.222
Atrial fibrillation, <i>n</i> (%)	47 (41)	57 (39)	46 (34)	46 (35)	0.630
Diabetes mellitus, <i>n</i> (%)	38 (33)	48 (33)	47 (35)	64 (48)	0.024
Chronic pulmonary disease, <i>n</i> (%)	6 (5)	5 (3)	10 (7)	8 (6)	0.507
Systolic BP, mmHg	142.1 \pm 31.0	139.8 \pm 37.5	134.1 \pm 32.5	131.4 \pm 28.5	0.056
Diastolic BP, mmHg	79.0 \pm 20.5	78.2 \pm 22.2	73.6 \pm 19.5	72.6 \pm 16.9	0.035
Mean BP, mmHg	99.8 \pm 21.4	98.6 \pm 25.3	93.9 \pm 22.2	92.2 \pm 18.4	0.028
Heart rate (per min)	89.4 \pm 28.1	89.6 \pm 30.0	94.5 \pm 29.9	98.7 \pm 27.1	0.042
LVEF, %	44.7 \pm 18.0	42.3 \pm 17.2	43.9 \pm 18.8	41.6 \pm 16.5	0.484
Hemoglobin, g/dl	12.7 \pm 2.9	12.6 \pm 2.6	11.7 \pm 2.5	11.5 \pm 2.5	<0.001
eGFR, ml/min/1.73 m ²	62.1 \pm 32.0	48.3 \pm 22.1	47.8 \pm 25.9	48.0 \pm 30.0	<0.001
Sodium, mmol/l	140.0 \pm 3.6	139.4 \pm 3.5	137.5 \pm 4.7	136.4 \pm 5.4	<0.001
Potassium, mmol/l	4.2 \pm 0.5	4.3 \pm 0.7	4.3 \pm 0.8	4.3 \pm 0.8	0.448
CRP, mg/dl	0.1 (0.1)	0.5 (0.3)	1.9 (1.3)	9.1 (8.5)	<0.001
BNP, pg/ml	480.5 (597.5)	613.4 (962.4)	864.3 (1205.3)	689.7 (998.9)	0.003
Medication before admission					
Beta blockers, <i>n</i> (%)	46 (40.4)	44 (29.9)	49 (36.6)	31 (23.5)	0.023
ACE-Is/ARBs, <i>n</i> (%)	47 (41.2)	28 (19.0)	59 (44.0)	41 (31.1)	0.159
Aldosterone blockers, <i>n</i> (%)	12 (10.5)	7 (10.4)	23 (17.2)	14 (10.6)	0.101
Diuretics, <i>n</i> (%)	42 (36.8)	67 (45.5)	65 (48.5)	46 (34.8)	0.068

Data are expressed as mean \pm standard deviation or median (interquartile range) for continuous variables, and numbers (%) for nominal variables. ADHF acute decompensated heart failure, ACE-Is angiotensin-converting enzyme inhibitors, ARBs angiotensin II receptor blockers, BMI body mass index, BNP B-type natriuretic peptide, BP blood pressure, CRP C-reactive protein, eGFR estimated glomerular filtration rate, LVEF left ventricular ejection fraction, NYHA New York Heart Association

1.53–4.50, $p < 0.001$, respectively). Among each serum CRP quartile, the HR for mortality significantly increased as the CRP level increased (p value for HR trend; < 0.001). In addition, the log-transformed CRP level was associated with an increased risk of mortality (HR 1.23, 95% CI 1.12–1.36, $p < 0.001$) suggesting that there is a dose-dependent relationship between CRP levels and long-term mortality. Other variables with p values < 0.1 in the univariate analyses were age, sex, BMI, history of ADHF, ischemic heart disease,

AF, diabetes mellitus, NYHA functional class, mean BP, hemoglobin, eGFR, serum sodium and potassium, and the use of diuretics.

Figure 2 shows the results of multivariable regression analyses. In terms of long-term mortality, even in the multivariable analysis, patients in Q4 were at an increased risk compared to those in Q1 (HR 2.20, 95% CI 1.10–4.38, $p = 0.026$), whereas the HRs of those in Q2 and Q3 were attenuated and either became, or remained, insignificant. The other variables in this multivariate analysis are summarized in Table 2. In multivariable analysis, the HR of each CRP quartile increased significantly as the CRP quartiles increased (p value for HR trend: 0.034, Fig. 2). Similarly, the results of multivariable analysis in which the CRP level was treated as a continuous variable indicated that the greater the CRP level, the greater the risk of all-cause mortality (HR 1.16, 95% CI 1.01–1.32, $p = 0.030$, Fig. 2).

Table 2 Variables in multivariate analysis other than CRP levels

	HR	95% CI		p
		Lower	Upper	
Age	1.026	1.003	1.049	0.024
Men	0.870	0.562	1.346	0.531
BMI	0.942	0.887	1.002	0.056
History of ADHF	1.529	0.972	2.405	0.066
NYHA class	0.979	0.726	1.321	0.892
Ischemic heart disease	1.022	0.638	1.639	0.927
Atrial fibrillation	1.552	0.958	2.513	0.074
Mean BP	0.992	0.981	1.003	0.157
Diabetes mellitus	1.404	0.881	2.238	0.154
Hemoglobin	0.846	0.763	0.938	0.002
Sodium	0.966	0.916	1.019	0.210
Potassium	1.097	0.833	1.446	0.510
eGFR	1.003	0.994	1.012	0.506
Diuretics	1.909	1.205	3.024	0.006

ADHF acute decompensated heart failure, BMI body mass index, BP blood pressure, CI confidence interval, CRP C-reactive protein, eGFR estimated glomerular filtration rate, HR hazard ratio

Discussion

The results of the present study provide several important insights into the association between CRP levels and clinical outcomes in patients with ADHF. First, ADHF patients in the highest admission CRP quartile (i.e., Q4: CRP ≥ 3.9 mg/dL) had a significantly greater risk of long-term mortality compared with those in the lowest CRP quartile (i.e., Q1: < 0.3 mg/dL), even after the adjustment of confounding factors. Second, in the multivariable analysis, the HR for mortality increased significantly as the admission CRP level increased (p value for HR trend: < 0.001). Third, there was a significant dose-dependent relationship between the

Fig. 1 Cumulative survival according to CRP quartiles. p values for overall log-rank tests indicate whether there is a difference in the four different survival curves ($p < 0.001$). p values for the log-rank trend test indicate whether increased levels of CRP are associated with increased cumulative mortality ($p < 0.001$). CRP C-reactive protein

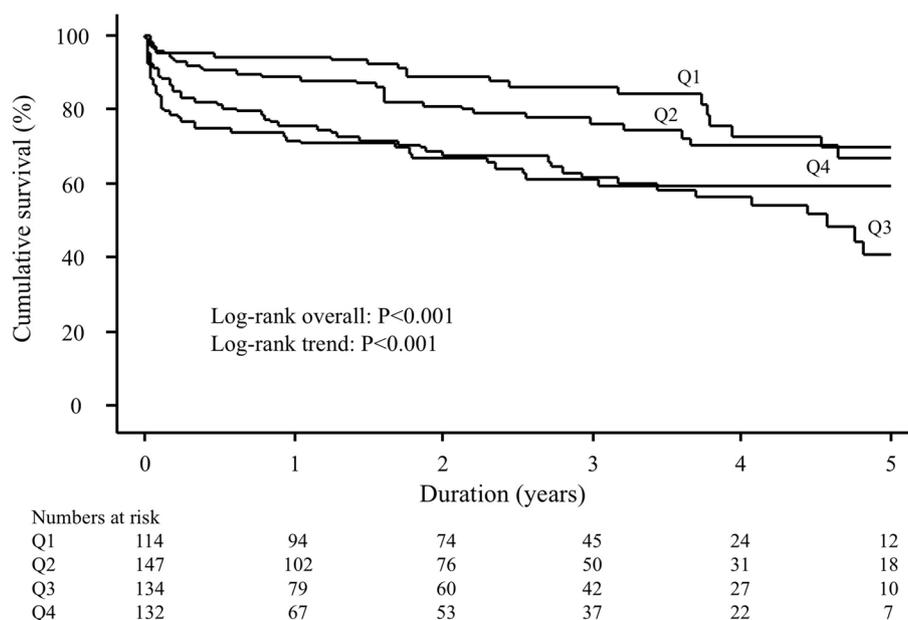
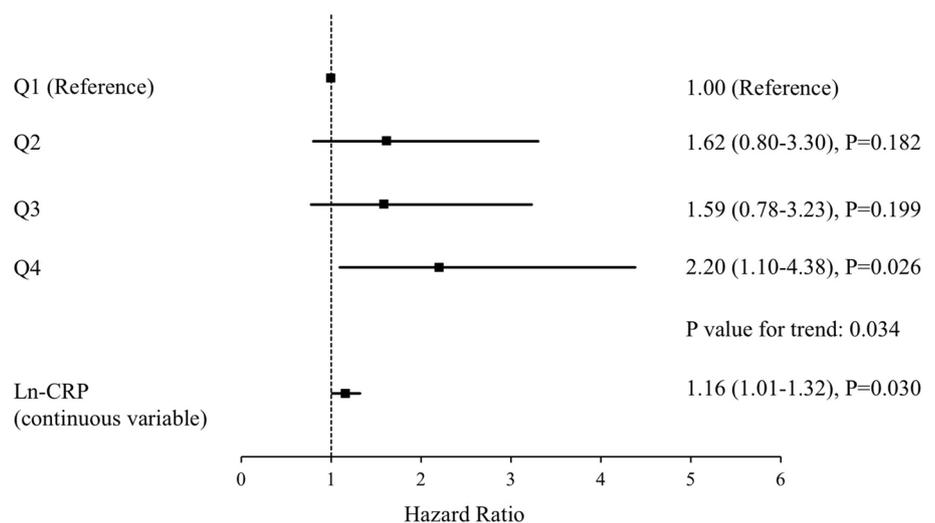


Fig. 2 Forest plots of multivariable analyses. In the multivariable analysis, patients in Q4 were at an increased risk for long-term mortality compared to those in Q1, and the HR of each CRP quartile significantly increased as the CRP quartiles increased. In multivariable analysis in which the CRP level was treated as a continuous variable, the greater the CRP level, the greater the risk of all-cause mortality. *CRP* C-reactive protein, *Ln* logarithm-transformed, *HR* hazard ratio



admission CRP level as a continuous variable and the risk of long-term mortality. These findings suggest that CRP levels on admission for ADHF can be a predictor of long-term mortality, and, therefore, increased levels of admission CRP have prognostic value for long-term outcomes in patients with ADHF.

In patients with ADHF, hemodynamic changes trigger neurohormonal activation, which has been considered a major cause of cardiac remodeling, consequently leading to the progression of HF [16]. Inflammation is thought to be an important contributor to the pathogenesis of ADHF and/or the progression of HF itself [17–22]. There are obvious associations between inflammatory mediators and various cardiovascular conditions such as coronary artery disease [23–25], AF [26], and valvular heart disease [27], which can play important roles in the onset of ADHF or the progression of HF. In these contexts, inflammation may simply be an indicator of alterations in the underlying cardiovascular condition in ADHF patients. However, several studies have shown that inflammatory cytokines, including tumor necrotic factor (TNF)- α and interleukin (IL)-1 β , have direct negative effects on cardiomyocytes by causing a Ca²⁺ imbalance following the suppression of Ca²⁺-regulating gene expression in the sarcoplasmic reticulum. This ultimately leads to cardiac dysfunction and the development of ADHF and/or the progression of HF [28–30]. Furthermore, these cytokines are known to increase angiotensin II type 1 receptors, tumor growth factor (TGF)- β , and lysyl oxidase, all of which stimulate cardiac fibroblasts leading to cardiac dysfunction and subsequent development of ADHF and/or the progression of HF [31–33]. Conversely, ADHF episodes may induce inflammation; indeed, TNF- α , IL-6, and IL-18 are secreted from the myocardium in response to mechanical stretch following hemodynamic overload [34]. In addition, increased monocyte differentiation is observed

in the bone marrow of patients with HF [35]. Mesenteric congestion causes bacterial translocation, and as a result, the serum endotoxin levels increase and activate the immune system [36].

In patients with ADHF, elevated admission CRP levels can be associated with concomitant infections. In terms of such concomitant infections, procalcitonin (PCT), a precursor peptide of calcitonin and a specific marker of bacterial infection, has become a recent focus in patients with HF. The response of PCT is both faster and greater than CRP [37], and PCT has a pivotal role in decision making for the prescription of antibiotics for patients with ADHF [38]. Furthermore, Meisel et al. [39] reported that patients with ADHF and high PCT levels had worse outcomes unless they received antibiotics [39], and the use of PCT in ADHF is recommended in the latest European Society of Cardiology (ESC) guidelines [40]. However, it is not conclusive whether PCT is a prognostic marker of ADHF patients without concomitant bacterial infections [38]. These results may imply that PCT is sensitive to bacterial infections, but not reflective of non-bacterial inflammation in patients with HF. Unlike PCT, CRP is a comprehensive downstream marker which represents systemic or cardiac (i.e., local) inflammation of a bacterial or non-bacterial nature which can be associated with the development or progression of HF in ADHF patients.

Alonso-Martinez et al. [41] reported that elevated CRP levels on admission (> 0.9 mg/dL) in ADHF patients was a risk factor for re-admission within 18 months [41]. Furthermore, Siirila-Waris et al. [42] reported that higher CRP levels (> 1.0 mg/dL) on admission were significantly associated with 12-month all-cause mortality following ADHF regardless of a diagnosis of concomitant infection [42]. Minami and colleagues [43] clearly showed that markedly elevated CRP levels on admission for ADHF (> 11.8 mg/

dL) were associated with all-cause mortality; however, in long-term follow-ups (> 120 days), the association between markedly elevated admission CRP levels and mortality was prominent in non-cardiac causes [43]. On the other hand, modestly elevated CRP levels on admission (2.9–11.8 mg/dL) were not associated with mortality within a 120-day follow-up period [43]. However, modestly elevated CRP levels on admission were associated with mortality in long-term follow-up (> 120 days). Taken together, modestly elevated admission CRP levels in ADHF patients may be a predictor for long-term mortality in association with chronic localized cardiac inflammation, compared with markedly elevated CRP levels which are reflective of systemic inflammation. Although admission CRP levels can indicate different etiologies for the elevation of CRP levels, it is clear that elevated CRP levels on admission for ADHF, even modest ones, can be a predictor of increased all-cause mortality. Thus, the results of the present study are in line with this context.

Whether elevated admission CRP levels in patients with ADHF are causes or consequences of HF remains unclear. In line with this, clinical studies to determine whether increased CRP levels are a promising therapeutic target in patients with ADHF are required. Aspirin and statin have anti-inflammatory effects [44, 45] and β -blockers, angiotensin-converting enzyme inhibitors (ACE-Is), and angiotensin II receptor blockers (ARBs) also modulate inflammation in patients with HF [9, 46, 47]. However, in some patients, inflammation is not sufficiently suppressed even with optimized medical therapy; possibly due to the multifactorial role of inflammation in ADHF as mentioned previously and might explain why anti-inflammatory strategies for HF have not yet achieved satisfactory results [48, 49]. On the other hand, canakinumab, a monoclonal antibody-targeting IL-1 β , has been shown to drastically reduce recurrent cardiovascular events in a pathway independent from lipid metabolism: Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) [50]. This sub-study revealed that canakinumab significantly improved the exercise capacity and LVEF in 30 patients with systolic HF (LVEF < 50%) and elevated CRP levels (> 2 mg/dL) [51]. In patients with increased CRP levels and ADHF, there are small randomized double-blind placebo controlled trials using anakinra, a recombinant IL-1 receptor antagonist. Van Tassel and colleagues [52] showed that anakinra reduced CRP by approximately 60% vs. baseline at 72 h, compared with a 6% reduction among patients who received a placebo. This was accompanied by a significant improvement in LVEF (+ 10% from baseline) by anakinra compared with a placebo (0%) at 2 weeks [52]. In the Recently Decompensated Heart Failure Anakinra Response Trial (REDHART), ADHF patients with increased CRP levels were randomly assigned to daily administration of anakinra for 2 weeks,

12 weeks, or a placebo to investigate whether anakinra could improve exercise capacity through the inhibition of inflammatory response. Although no change in exercise capacity occurred at 2 weeks in patients taking anakinra, an improvement was observed in patients when anakinra was continued for 12 weeks [53]. These findings at least partially suggested that increased CRP levels might be a promising therapeutic target in patients with ADHF.

Our study is subject to some limitations. First, it was limited to a single academic center and included only a Japanese patient population. Second, since the present study was observational in nature, even after the adjusted analysis, other confounders which might have affected the results cannot be ruled out. Despite these limitations, our study highlights that in ADHF patients, the greater the CRP level at admission is, the poorer the long-term outcome.

Conclusion

The admission CRP level was associated with an increased risk of long-term mortality in patients with ADHF. CRP was an independent prognostic factor, even following hospital discharge in patients with ADHF. Although a close association between inflammation and ADHF has been indicated for years, clinical evidence remains limited. Further investigations with a larger sample size are required to determine novel treatments which can modify CRP levels in patients with ADHF.

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Compliance with ethical standards

Conflict of interest Drs. Hiroki Matsumoto, Takatoshi Kasai, Akihiro Sato, Sayaki Ishiwata, and Yuya Matsue are affiliated with a department endowed by Philips Respirionics, ResMed, and Fukuda Denshi. Dr. Hiroyuki Daida received research grants from various pharmaceutical companies and payment for lectures, including service in speakers' bureaus from Medtronic Japan, AstraZeneca K.K., MSD K.K., Ono Pharmaceutical Co. Ltd, GlaxoSmithKline K.K., Shionogi & Co. Ltd, Daiichi Sankyo Company, Takeda Pharmaceutical Co. Ltd, Nippon Boehringer Ingelheim Co. Ltd, Bayer Yakuhin, Ltd, Terumo Corporation, and Astellas Pharma Inc. The other authors report no conflicts of interest.

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