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Original article

Utility of copeptin for predicting long-term clinical outcomes in patients with heart failure

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ABSTRACT

Background: Copeptin, a surrogate marker of pro-arginine vasopressin, is expected to be a marker in cardiovascular diseases. Its utility for predicting long-term clinical outcomes in heart failure (HF), however, has not been adequately evaluated in daily clinical practice in Japan.
Methods: To assess the relationship of serum copeptin at admission with long-term clinical outcomes, we evaluated serum copeptin at admission in consecutive 107 patients hospitalized for HF between April 2011 and July 2012. The primary outcome measure was defined as a composite of all-cause death and re-admission for HF (all-cause death/HF).
Results: In this study population, median serum copeptin at admission was 15.5 (6.7–32.0) pmol/L. As compared with the low-copeptin group (<18 pmol/L, $N = 60$), the high-copeptin group (≥18 pmol/L, $N = 47$) included more male patients and those with prior myocardial infarction, prior HF, low left ventricular ejection fraction, and chronic kidney disease. During median 4.5 (1.0–5.5) years of clinical follow-up, the cumulative incidence of all-cause death/HF was significantly higher in the high-copeptin than in the low-copeptin group (63.4% versus 33.0% at 1 year, and 85.2% versus 77.2% at 5 years, log-rank $p = 0.03$). After adjusting for confounders, high-copeptin was still an independent predictor for all-cause death/HF [hazard ratio (95% confidence interval): 1.77 (1.04–3.01), $p = 0.03$].
Conclusion: Copeptin was suggested as a useful marker for predicting long-term clinical outcomes in patients with HF.

Introduction

Arginine vasopressin (AVP) is released to regulate plasma osmolality and plays important roles in regulation of systemic vascular resistance and cardiac output [1,2]. Several previous studies showed that AVP was associated with the severity of heart failure (HF) [3–5]. However, its short half-life in circulation limits measurement of AVP as a biomarker in daily clinical practice [6].

Copeptin, the C-terminal part of pre-pro-vasopressin, is derived from the cleavage of the precursor of AVP [7]. Because copeptin is secreted in equimolar amounts to AVP and more stable than AVP, copeptin has been drawing attention as a useful surrogate biomarker for AVP in diagnosing HF and predicting prognosis of HF [2,8]. Several previous studies outside Japan reported that copeptin was significantly associated with clinical outcomes in patients with HF [9–13]. However, the usefulness of copeptin for predicting clinical outcomes has not been fully evaluated in HF patients in daily clinical practice in Japan. In addition, the utility of copeptin for predicting long-term (beyond 1 year) outcome has not been adequately evaluated. In this study, therefore, we sought to assess the usefulness of serum copeptin level at admission for predicting long-term clinical outcomes in patients hospitalized for HF.

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Methods

Study population

Among 120 consecutive patients who were hospitalized for HF and received blood examination for the cardiovascular biomarker study in Kyoto University Hospital between April 2011 and July 2012, the current study population consisted of 107 HF patients after excluding 1 patient whose blood sample amount was insufficient for assay and 12 patients with hemodialysis (Fig. 1). The cardiovascular biomarker study in Kyoto University Hospital was approved by the ethics committee in Kyoto University Hospital.

Data collection and outcome measures

We reviewed medical records to collect demographic data according to pre-specified definitions. HF with reduced ejection fraction (HFrEF) was defined as left ventricular ejection fraction (LVEF) less than 40% according to the current guidelines [14,15]. Etiology of HF was judged by an independent physician (Y.Y.) based on the information from medical records in a blinded fashion to the results of serum copeptin level.

The primary outcome measure was defined as a composite of all-cause death and re-admission for HF (all-cause death/HF). Secondary outcome measures included all-cause death, cardiac death, and re-admission for HF. Death was regarded as cardiac in origin unless obvious non-cardiac causes could be identified. Follow-up information was obtained by hospital-chart review and/or telephone contact with the patient, relatives, or referring practitioners. Written informed consent was obtained from the subjects.

Blood samples

At the time of admission, blood samples were obtained from a vein while the patients were in a supine or sitting position after informed consent was gained. The samples were obtained as soon after admission as possible. The serum samples were separated from blood samples and frozen at −80 °C until they were assayed. Copeptin was measured with a commercially available immunoluminometric assay (B.R.A.H.M.S. LUMItest CT-proAVP, B.R.A.H.M.S. AG, Hennigsdorf/Berlin, Germany) [7,9–13].

Statistical analyses

Categorical variables were presented as counts and percentages and were compared by the χ^2 test or Fisher's exact test. Continuous variables were presented as mean ± standard deviation or median with interquartile range (IQR). Continuous variables were compared using the Student t test or Wilcoxon rank-sum test depending on their distributions. Cumulative incidence of events was estimated by the Kaplan–Meier method, and the differences were assessed with the log-rank test. We estimated the risks of high-copeptin relative to low-copeptin for the outcome measures by the Cox's proportional hazard regression model, and expressed them as hazard ratios (HRs) and their 95% confidence intervals (CIs). According to the threshold of the previous report, we set the cut-off point of serum copeptin level as 18 pmol/L to discriminate high (≥18 pmol/L)- and low (<18 pmol/L)-copeptin groups [12]. We also estimated HR of high-copeptin level relative to low-copeptin level for the primary outcome measure by the multivariable Cox's proportional hazard regression model adjusted for 9 clinically relevant potential confounding factors (model 1). Continuous variables were dichotomized by clinically meaningful reference values. The proportional hazard assumption was tested by the plots of log (time) versus log [−log (survival)] and Schoenfeld's residuals, and the assumptions of all the variables were verified. To confirm the consistency in the results of multivariable analysis, we conducted an additional multivariable analysis in which B-type natriuretic peptide (BNP) was added as a risk adjusting factor (model 2).

Because the cut-off of 18 pmol/L was based on the previous report, we conducted the receiver operating characteristic (ROC) analysis and a sensitivity analysis stratified by the cut-off value by the ROC curve.

The statistical analyses were conducted by a physician (Y.Y.). All the analyses were performed with JMP version 13.2 (SAS Institute

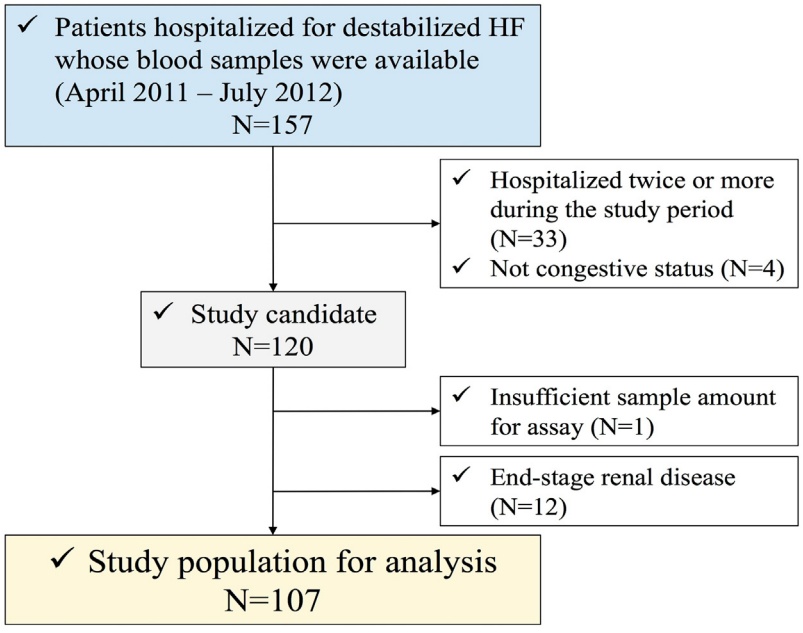


Fig. 1. Patient flow chart. HF, heart failure.

Table 1
Baseline patient characteristics of the study population.

	Study population ($N=107$)	Low-copeptin ($N=60$)	High-copeptin ($N=47$)	p-Value
Age in years	73.5 ± 13.3	72.0 ± 15.6	75.4 ± 9.3	0.16
Age ≥ 80	37 (35%)	23 (38%)	14 (30%)	0.36
Male sex	62 (58%)	29 (48%)	33 (70%)	0.02
Body mass index	23.0 ± 4.4	23.2 ± 4.8	22.7 ± 3.9	0.60
Smoking	61 (57%)	32 (53%)	29 (62%)	0.39
Current	8 (7%)	5 (8%)	3 (6%)	0.70
Vital signs				
Systolic BP [mmHg]	129.7 ± 29.2	130.3 ± 25.7	129.0 ± 33.5	0.83
Systolic BP <100 mmHg	11 (10%)	3 (5.0%)	8 (17%)	0.042
Diastolic BP [mmHg]	74.4 ± 18.3	73.7 ± 16.9	75.2 ± 20.1	0.68
Heart rate [/min]	85.7 ± 23.7	87.1 ± 26.7	83.9 ± 19.3	0.48
NYHA class				
NYHA II	33 (31%)	17 (28%)	16 (34%)	0.45
NYHA III	55 (51%)	34 (57%)	21 (45%)	
NYHA IV	19 (18%)	9 (15%)	10 (21%)	
Past history				
Hypertension	65 (61%)	37 (62%)	28 (60%)	0.83
Dyslipidemia	38 (36%)	23 (38%)	15 (32%)	0.49
Diabetes	37 (35%)	20 (33%)	17 (36%)	0.76
MI	28 (26%)	10 (17%)	18 (38%)	0.01
PAD	6 (6%)	1 (2%)	5 (11%)	0.045
Stroke	11 (10%)	4 (7%)	7 (15%)	0.16
Atrial fibrillation	31 (29%)	18 (30%)	13 (28%)	0.79
Liver cirrhosis	3 (3%)	1 (2%)	2 (4%)	0.42
Malignancy	8 (7%)	6 (10%)	2 (4%)	0.26
PCI	28 (26%)	9 (15%)	19 (40%)	0.003
CABG	10 (9%)	4 (7%)	6 (13%)	0.28
Device implantation	29 (27%)	14 (23%)	15 (32%)	0.32
CRT	12 (11%)	5 (8%)	7 (15%)	0.29
HF hospitalization	65 (61%)	30 (50%)	35 (75%)	0.01
Laboratory data				
Hemoglobin [g/dL]	11.4 ± 2.2	11.5 ± 2.2	11.2 ± 2.3	0.50
Osmolarity [mOsm/L]	296.0 ± 9.5	292.8 ± 8.8	300.1 ± 8.7	<0.001
Sodium [mEquiv./L]	139.4 ± 4.2	139.3 ± 4.3	139.4 ± 4.1	0.84
Potassium [mEquiv./L]	4.04 ± 0.61	4.03 ± 0.63	4.05 ± 0.58	0.86
Glucose [mg/dL]	126.4 ± 51.9	120.3 ± 40.0	134.1 ± 63.7	0.20
BUN [mg/dL]	28.8 ± 17.0	21.3 ± 11.6	38.5 ± 18.9	<0.001
Creatinine [mg/dL]	1.34 ± 0.85	1.01 ± 0.58	1.73 ± 0.95	<0.001
eGFR [mL/min/1.73 m^2]	50.0 ± 25.2	60.8 ± 24.7	36.9 ± 18.6	<0.001
eGFR <60	73 (68%)	30 (50%)	43 (91%)	<0.001
Copeptin	15.5 [6.7–32.0]	8.0 [5.1–12.1]	36.1 [26.6–71.3]	<0.001
BNP [pg/mL]	594.9 [254.9–988.0]	511.7 [250.7–867.0]	718.1 [254.9–1163.0]	0.15
Echocardiography				
LVDd [mm]	54.0 ± 13.8	51.7 ± 14.2	56.9 ± 12.6	0.051
LVDs [mm]	43.1 ± 16.5	39.7 ± 16.2	47.6 ± 16.0	0.01
LVEF [%]	44.6 ± 20.0	48.2 ± 19.7	40.0 ± 19.6	0.04
HFrEF (LVEF <40%)	50 (47%)	23 (38%)	27 (57%)	0.049
NIPPV	16 (15%)	4 (6.7%)	12 (26%)	0.007
Catecholamine use				
Dobutamine	15 (14%)	4 (6.7%)	11 (23%)	0.01
Dopamine	19 (18%)	8 (13%)	11 (23%)	0.18
Dobutamine/dopamine	22 (21%)	8 (13%)	14 (30%)	0.037
Medication on admission				
Loop diuretics	77 (72%)	38 (63%)	39 (83%)	0.02
Thiazide	12 (11%)	3 (5%)	9 (19%)	0.02
MRA	44 (41%)	22 (37%)	22 (47%)	0.29
ACE-I/ARB	59 (55%)	36 (60%)	23 (49%)	0.25
β-Blockers	51 (48%)	25 (42%)	26 (55%)	0.16
CCB	26 (24%)	15 (25%)	11 (23%)	0.85
Digitalis	11 (10%)	7 (12%)	4 (9%)	0.59
Nitrates	12 (11%)	7 (12%)	5 (11%)	0.87

Categorical variables were presented as number (percentage), and continuous variables were presented as mean ± SD.
*The estimated osmolarity was calculated by the following formula.

$$\text{Calculated osmolarity} = \text{Sodium[mEquiv./L]} \times 2 + \frac{\text{BUN[mg/dL]}}{2.8} + \frac{\text{Glucose[mg/dL]}}{18}$$

ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BNP, B-type natriuretic peptide; BP, blood pressure; BUN, blood urea nitrogen; CABG, coronary artery bypass grafting; CCB, calcium channel blockers; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; LVDd, left ventricular diameter at end-diastole; LVDs, left ventricular diameter at end-systole; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NIPPV, noninvasive positive pressure ventilation; NYHA, New York Heart Association; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; SD, standard deviation.

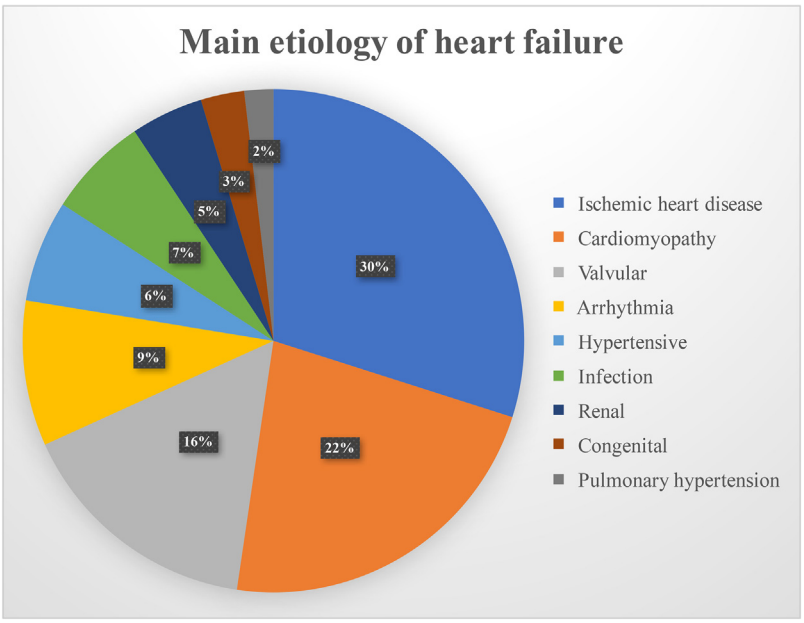


Fig. 2. Main etiologies of heart failure in the study population.

Inc., Cary, NC, USA) and R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). The reported *p*-values were 2-sided and *p*-values <0.05 were considered statistically significant.

Results

Baseline characteristics

This study population reflected real world clinical practice including a high proportion of older patients, prior myocardial infarction (MI), atrial fibrillation, and prior HF (Table 1). Regarding etiologies of HF, ischemic heart disease accounted for 30%, cardiomyopathy for 22%, and valvular heart disease for 16% (Fig. 2). The median serum copeptin level was 15.5 (6.7–32.0) pmol/L (Fig. 3).

As compared with the low-copeptin group, the high-copeptin group included more male patients, those with prior MI, peripheral artery disease, a history of percutaneous coronary intervention, and prior HF. Laboratory data showed that the high-copeptin group had significantly higher osmolarity and worse renal function than the low-copeptin group (Table 1). There was no statistically significant difference in serum sodium or BNP between the two groups.

Regarding cardiac function assessed by echocardiography, mean LVEF was significantly lower in the high-copeptin group than in the low-copeptin group. The high-copeptin group also had significantly more HFrEF patients than the low-copeptin group.

At initial treatment of HF, the high-copeptin group had higher prevalence of noninvasive positive pressure ventilation (NIPPV) use than the low-copeptin group (Table 1). The proportion of catecholamine use was also significantly higher in the high-copeptin group than in the low-copeptin group (Table 1).

Long-term clinical outcomes: high- versus low-copeptin group

During median 4.5 (IQR 1.0–5.5) years of clinical follow-up, the cumulative incidence of the primary outcome measure of all-cause death/HF was significantly higher in the high-copeptin group than in the low-copeptin group (63.4% versus 33.0% at 1 year, and 77.1% versus 62.2% at 3 years, respectively, log-rank $p = 0.03$) (Fig. 4A). The cumulative incidences of all-cause death and cardiac death were not significantly different between the high- and low-copeptin groups (53.8% versus 29.4% at 3 years, log-rank $p = 0.12$,

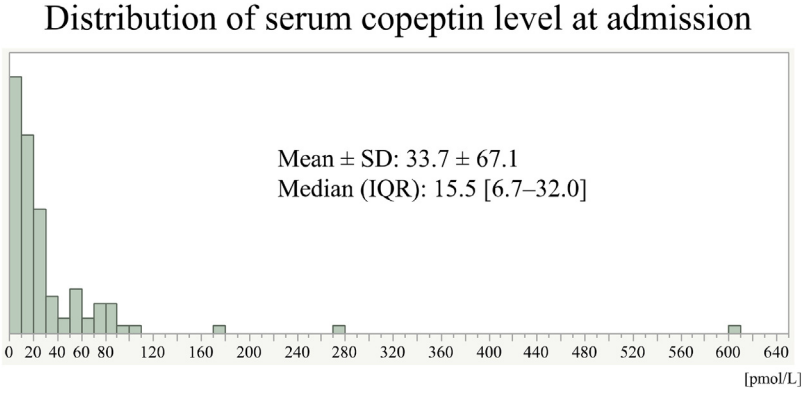
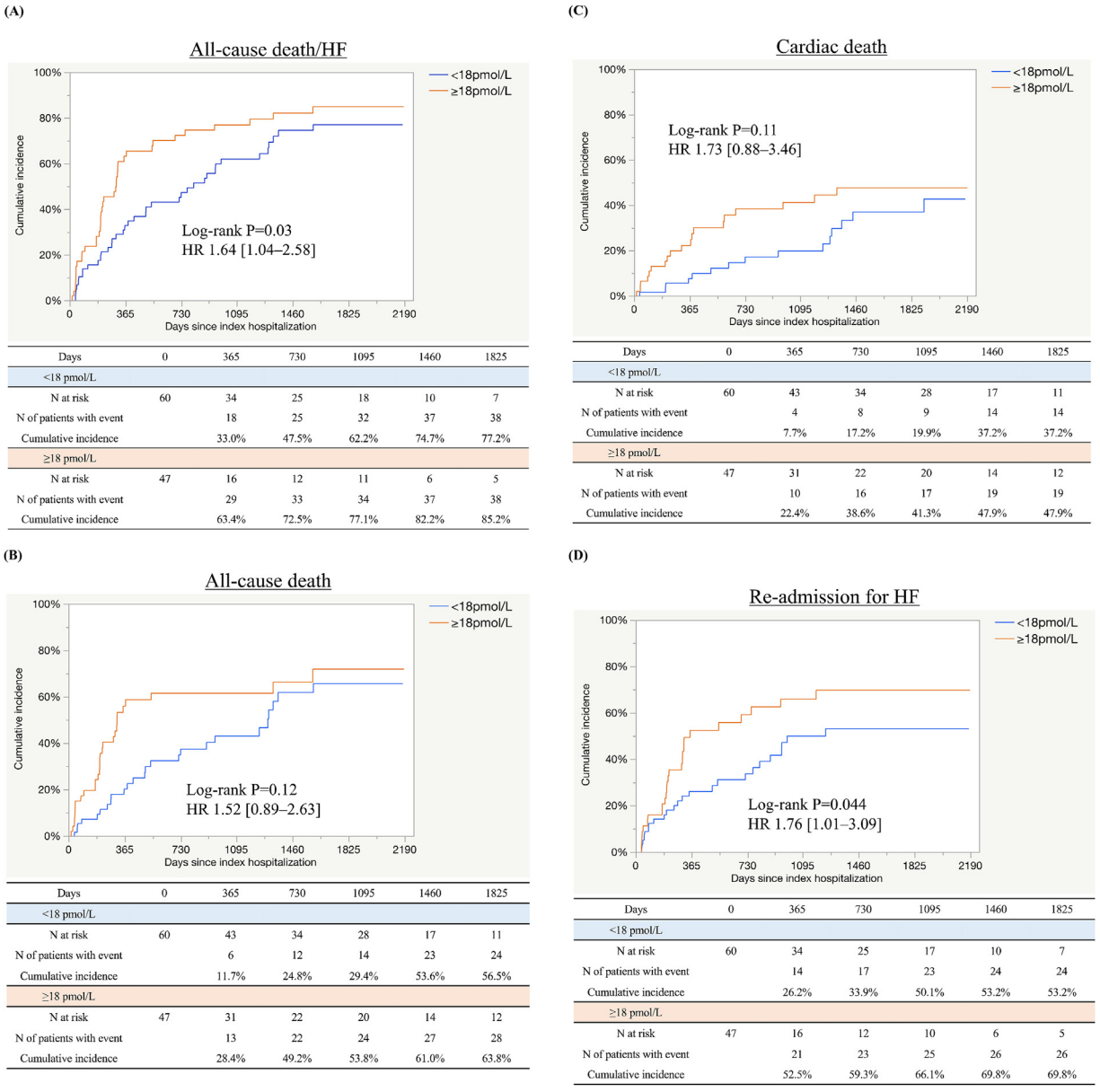


Fig. 3. Distribution of serum copeptin level at the time of admission. IQR, interquartile range; SD, standard deviation.



Days	0	365	730	1095	1460	1825
<18 pmol/L						
N at risk	60	34	25	18	10	7
N of patients with event		18	25	32	37	38
Cumulative incidence		33.0%	47.5%	62.2%	74.7%	77.2%
≥18 pmol/L						
N at risk	47	16	12	11	6	5
N of patients with event		29	33	34	37	38
Cumulative incidence		63.4%	72.5%	77.1%	82.2%	85.2%

Days	0	365	730	1095	1460	1825
<18 pmol/L						
N at risk	60	43	34	28	17	11
N of patients with event		6	12	14	23	24
Cumulative incidence		11.7%	24.8%	29.4%	53.6%	56.5%
≥18 pmol/L						
N at risk	47	31	22	20	14	12
N of patients with event		13	22	24	27	28
Cumulative incidence		28.4%	49.2%	53.8%	61.0%	63.8%

Days	0	365	730	1095	1460	1825
<18 pmol/L						
N at risk	60	43	34	28	17	11
N of patients with event		4	8	9	14	14
Cumulative incidence		7.7%	17.2%	19.9%	37.2%	37.2%
≥18 pmol/L						
N at risk	47	31	22	20	14	12
N of patients with event		10	16	17	19	19
Cumulative incidence		22.4%	38.6%	41.3%	47.9%	47.9%

Days	0	365	730	1095	1460	1825
<18 pmol/L						
N at risk	60	34	25	17	10	7
N of patients with event		14	17	23	24	24
Cumulative incidence		26.2%	33.9%	50.1%	53.2%	53.2%
≥18 pmol/L						
N at risk	47	16	12	10	6	5
N of patients with event		21	23	25	26	26
Cumulative incidence		52.5%	59.3%	66.1%	69.8%	69.8%

Fig. 4. Cumulative incidences of clinical outcomes in the high- and low-copeptin groups. (A) A composite of all-cause death and re-admission for HF; (B) all-cause death; (C) cardiac death; and (D) re-admission for HF. HF, heart failure.

and 41.3% versus 19.9% at 3 years, log-rank $p = 0.11$, respectively) (Fig. 4B and C). The cumulative incidence of re-admission for HF in the high-copeptin group was significantly higher than that in the low-copeptin group (66.1% versus 50.1% at 3 years, log-rank $p = 0.044$) (Fig. 4D).

After adjusting for the potential confounders listed in Table 2, the adjusted risk of high- relative to low-copeptin for the primary outcome measure of all-cause death/HF was still significant [HR (95% CI): 1.77 (95% CI 1.04–3.01), $p = 0.03$ in model 1 and HR: 1.82 (1.08–3.09), $p = 0.03$ in model 2] (Table 2).

The sensitivity analysis using the ROC curve showed consistent results. The detailed results are shown in Supplemental Material (Supplemental Figs. 1 and 2).

Discussion

The main finding of this study was the high serum copeptin at the time of admission was significantly associated with the higher long-term risk for all-cause death/HF in patients who were hospitalized for HF in real world clinical practice, suggesting the usefulness of copeptin as a biomarker in early risk stratification for long-term clinical outcomes in patients with HF.

This finding is in line with previous reports about the prognostic value of copeptin in HF patients. Alehagen et al. reported that elevated concentration of copeptin was associated with increased risk of all-cause mortality in elderly patients with symptoms of HF at a primary health care center [12]. Maisel et al. also reported that elevated copeptin predicted 90-day mortality in patients with HF [13]. This study demonstrated the utility of copeptin for predicting not only short-term prognosis but also long-term prognosis. To the best of our knowledge, this study is the first to examine very long-term follow-up and to demonstrate the utility of copeptin obtained at the time of admission for long-term prognosis in patients with HF in real world practice.

In recent years, the AVP system has been implicated in the stress response against disrupted homeostatic balance such as hemorrhagic and septic shock as well as cardiovascular diseases [16]. In this study, indeed, the patients in the high-copeptin group

Table 2
The unadjusted and adjusted risks of the high-copeptin relative to low-copeptin for a composite of all-cause death and re-admission for heart failure.

	Unadjusted HR		Model 1 Adjusted HR		Model 2 Adjusted HR	
	[95% CI]	*p*-value	[95% CI]	*p*-value	[95% CI]	*p*-value
Copeptin ≥18 pmol/L	1.64 [1.04–2.58]	0.03	1.77 [1.04–3.01]	0.03	1.82 [1.08–3.09]	0.03
BNP ≥1000 pg/mL	1.01 [0.59–1.66]	0.96			0.69 [0.38–1.22]	0.20
Age ≥80	1.34 [0.82–2.13]	0.23	1.75 [1.05–2.90]	0.03	1.92 [1.13–3.22]	0.02
Male sex	1.18 [0.75–1.90]	0.48	0.86 [0.53–1.46]	0.61	0.89 [0.54–1.50]	0.67
BMI ≥30	1.35 [0.52–2.88]	0.50				
Smoking	1.14 [0.72–1.81]	0.57				
History of hypertension	0.84 [0.54–1.35]	0.47				
History of diabetes	1.04 [0.65–1.65]	0.85	1.38 [0.81–2.32]	0.24	1.48 [0.86–2.51]	0.16
History of MI	1.19 [0.71–1.92]	0.51	0.68 [0.37–1.21]	0.19	0.67 [0.36–1.22]	0.19
History of PAD	0.73 [0.26–1.65]	0.49				
History of stroke	1.01 [0.42–2.05]	0.99				
History of atrial fibrillation	1.65 [1.01–2.62]	0.044	1.99 [1.17–3.35]	0.01	2.00 [1.17–3.38]	0.01
History of liver cirrhosis	0.80 [0.13–2.53]	0.75				
History of malignancy	0.59 [0.21–1.34]	0.23				
Prior HF hospitalization	2.43 [1.50–4.05]	<0.001	2.10 [1.25–3.62]	0.005	2.07 [1.23–3.57]	0.006
eGFR <60 mL/min/1.73 m^2	1.63 [1.001–2.77]	0.049	1.40 [0.81–2.48]	0.23	1.37 [0.80–2.43]	0.26
LVEF <40%	1.54 [0.98–2.44]	0.06	1.71 [1.00–2.88]	0.046	1.94 [1.11–3.38]	0.02

The hazard ratios indicate the risks of the high-copeptin relative to low-copeptin group for the primary outcome measure. In the model 1, clinically relevant and important factors were selected and incorporated into the Cox's proportional hazard regression model. In addition, BNP level at admission was also incorporated in the model 2. Copeptin level ≥18 pmol/L was an independent risk throughout these models.
BMI, body mass index; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PAD, peripheral artery disease.

required catecholamine support more than those in the low-copeptin group. This suggests that high copeptin level in HF patients might be an indicator of life-threatening severe HF with disrupted hemodynamic status. This would be the reason why serum high-copeptin levels predict worse clinical outcomes in patients with HF.

When compared with the previous reports [9–13], the overall copeptin level in the current population was relatively low. The time of blood sampling would be one of the reasons for relatively lower copeptin level. Although the samples were meant to be obtained as soon after admission as possible, some of them were obtained after initial treatment at emergency room. Another possible reason was the small sample size to compare the patients' characteristics in this study with those in other studies and to assess differences between Japanese patients and ones in other countries.

BNP is an established marker for diagnosing HF as well as predicting prognosis in patients with HF [14,15]. In this study, however, BNP at the time of admission was not significantly associated with clinical outcomes. For this unexpected result, the timing of evaluating BNP level may be a possible reason for non-significant association between BNP level and clinical outcomes in this study. It was reported that BNP/N-terminal proBNP at discharge predicted hospitalization-free survival better than BNP/N-terminal proBNP at the time of admission [17,18]. In contrast to BNP, copeptin at the time of admission was clearly associated with clinical outcomes in this study, suggesting that copeptin has the potential to be a more useful biomarker than BNP in risk stratification in patients with HF at the time of admission.

Limitations

This study has several limitations. First, this study has the inherent limitations of observational study design. Despite the statistical adjustment by the multivariable analyses, some potential confounding factors such as heart rate at discharge may affect the results of this study. Furthermore, during the long-term follow-up, the influence of confounders at baseline might have been attenuated. Second, because of the relatively small number of patients in this single center study, it was difficult to conduct more detailed sub-group analysis such as the relationship of copeptin with etiology of HF or cardiac function. In addition, due to the small sample size in this study, this study could not definitively conclude whether the predefined cut-off of 18 pmol/L based on the previous studies was optimal or not. Third, copeptin level was measured only once, and time course of copeptin level during HF treatment could not be evaluated in this study. Fourth, the time of blood sampling (before or after initial treatment) might have influenced the study results.

Conclusion

Copeptin was suggested as a potential useful marker for predicting long-term clinical outcomes in patients with HF.

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Conflict of interest

None of the authors have conflict of interest to disclose regarding this manuscript.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jjcc.2018.11.008.

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