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ORIGINAL ARTICLE

Type III procollagen peptide level can indicate liver dysfunction associated with volume overload in acute heart failure

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Abstract

Aim The role of serum type III procollagen peptide (P3P) level in the acute phase of acute heart failure (AHF) requires clarification. We hypothesized that serum P3P level is temporarily higher during the acute phase, reflecting liver dysfunction due to congestion.

Methods and results A total of 800 AHF patients were screened, and data from 643 patients were analysed. Heart failure was diagnosed by the treating physician according to the European Society of Cardiology (ESC) guidelines, and included patients being treated with high-concentration oxygen inhalation (including mechanical support) for orthopnea, inotrope administration, or mechanical support for low blood pressure, and various types of diuretics for peripheral or pulmonary oedema. In all cases, diuretics or vasodilators were administered to treat AHF. The patients were divided into three groups according to their quartile (Q) serum P3P level: low-P3P (Q1, P3P $\leq$ 0.6 U/mL), mid-P3P (Q2/Q3, 0.6 $<$ P3P $<$1.2 U/mL), and high-P3P (Q4, P3P $\geq$ 1.2 U/mL). The plasma volume status (PVS) was calculated using the following formula: ([actual PV $-$ ideal PV]/ideal PV) × 100 (%). The primary endpoint was 365 day mortality. A Kaplan–Meier curve analysis showed that prognoses, including all-cause mortality and heart failure events within 365 days, were significantly ($P < 0.001$) worse in the high-P3P group when compared with the mid-P3P and low-P3P groups. A multivariate logistic regression analysis showed that high PVS (Q4, odds ratio [OR]: 4.702, 95% CI: 2.012–20.989, $P < 0.001$), high fibrosis-4 index (Q4, OR: 2.627, 95% CI: 1.311–5.261, $P = 0.006$), and low estimated glomerular filtration rate per 10 mL/min/1.73 m^2 decrease (OR: 1.996, 95% CI: 1.718–2.326, $P < 0.001$) were associated with high P3P values. The Kaplan–Meier curve analysis demonstrated a significantly lower survival rate, as well as a higher rate of heart failure events, in the high-P3P and high-PVS groups when compared with the other groups. A multivariate Cox regression model identified high P3P level and high PVS as an independent predictor of 365 day all-cause mortality (hazard ratio [HR]: 2.249; 95% CI: 1.081–3.356; $P = 0.026$) and heart failure events (HR: 1.586, 95% CI: 1.005–2.503, $P = 0.048$).

Conclusion A high P3P level during the acute phase of AHF served as a comprehensive biomarker of liver dysfunction with volume overload (i.e. liver congestion) and renal dysfunction. A high P3P level at admission may be able to predict adverse outcomes in AHF patients.

Keywords Acute decompensated heart failure; Liver function; Haemodynamics; Plasma volume status; Mortality

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Introduction

The serum level of type III procollagen peptide (P3P) has been established as a marker for fibrosis in patients with hepatic disease.[1,2] P3P is released from fibroblasts during collagen synthesis and indicates rapid collagen turnover. The liver is one of the major organs that can contribute to an elevation in serum P3P level. Serum P3P has therefore been reported to be elevated in patients with viral hepatitis and alcoholic hepatitis.[2,3] It has also been suggested that serum P3P is elevated in patients with cardiovascular disease, such as acute myocardial infarction and atrial fibrillation. It has also been postulated to reflect myocardial fibrotic scar formation after acute myocardial infarction or atrial fibrosis due to atrial fibrillation.[4,5]

Acute heart failure (AHF) is becoming a more serious issue with an aging global population and is recognized as a fundamentally heterogeneous condition. Patients with AHF have many co-morbidities, including malnutrition, cachexia, anaemia, infection, and frailty. One of the major complications of AHF is liver dysfunction and damage, which may occur when the disease is at its most severe. The suggested pathophysiology of hepatic dysfunction during the acute phase of AHF is multifactorial, involving both liver hypoperfusion due to low cardiac output and liver congestion.[6,7] Although relationships have been reported between biomarkers, laboratory findings, and haemodynamic profiles in this acute phase,[8] a gold standard for the diagnosis of haemodynamic liver damage has not been established, so an accurate diagnosis based on biomarkers and laboratory findings is difficult. It would, however, be desirable to be able to diagnose acute liver damage due to haemodynamic changes, as well as to be able to predict the probability of an adverse outcome in patients with AHF based on their laboratory results.We hypothesized that serum P3P level might temporarily increase during the acute phase of AHF, resulting in liver dysfunction secondary to liver congestion. We therefore investigated the associated factors and prognostic impact of serum P3P level during this acute phase prior to initial treatment.

Methods

Subjects

A total of 800 AHF patients admitted to the intensive care unit (ICU) of Nippon Medical School at Chiba Hokusoh Hospital between March 2011 and December 2018 were screened. Analysis was performed on the data of 643 of these AHF patients whose serum P3P values had been evaluated.

Heart failure (HF) was diagnosed by the treating physician according to the European Society of Cardiology (ESC) guidelines.[9] Physicians first considered the patient's symptoms, medical history, physical findings, 12-lead electrocardiogram, and chest X-ray images, and then definitively diagnosed HF based on the N-terminal pro-brain natriuretic peptide (NT-proBNP)/BNP ratio, laboratory measurements [troponin, blood urea nitrogen (BUN), creatinine, sodium, potassium, glucose, liver function markers, and complete blood counts], and echocardiogram findings. All enrolled patients were diagnosed with AHF, either new-onset or decompensated chronic HF with symptoms sufficient to warrant hospitalization, by the treating physician of the emergency department.

Patients requiring any of the following were admitted to the ICU: (i) high-concentration oxygen inhalation (including mechanical support) to treat orthopnea; (ii) inotrope administration or mechanical support to treat low blood pressure; or (iii) various types of diuretics to treat peripheral or pulmonary oedema. The treatment strategy was chosen by each physician. In all cases, diuretics or vasodilators were administered to treat AHF. All patients had a New York Heart Association (NYHA) functional class of either III or IV.

Patient evaluation

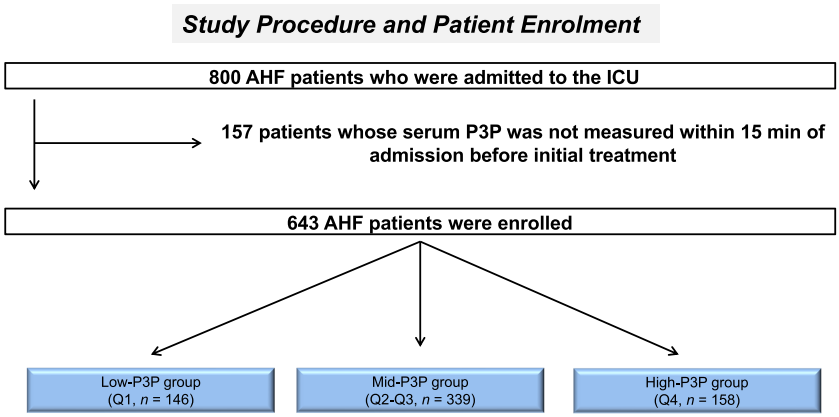
Acute heart failure patients were assigned to three groups according to the quartile (Q) of their serum P3P level: low-P3P (Q1, P3P $\leq$ 0.6 U/mL), mid-P3P (Q2/Q3, 0.6 $<$ P3P $<$ 1.2 U/mL), and high-P3P (Q4, P3P $\geq$ 1.2 U/mL) (*Figure 1*).

Patient characteristics included age; sex; presence of *de novo* or recurrent HF; aetiology of HF; risk factors for atherosclerosis (diabetes mellitus, hypertension, and dyslipidaemia); vital signs [systolic blood pressure (SBP) and heart rate]; disease status [left ventricular ejection fraction (LVEF) on echocardiogram, orthopnea, or presence of chronic kidney disease (CKD)], respiratory management status; arterial blood gas data, laboratory data [BUN, total bilirubin, haemoglobin, BNP, and C-reactive protein (CRP)]; diagnostic indices [plasma volume status (PVS) and fibrosis-4 (FIB4) index]; medications administered during ICU stay; duration of hospitalization (duration of ICU stay and hospital stay); and in-hospital mortality. Data from the low-P3P, mid-P3P, and high-P3P groups were compared.

Ischaemic aetiology was evaluated based on the findings of a coronary angiogram, an echocardiogram, a 12-lead electrocardiogram, and the patient's history. The primary aetiology of HF was decided by each treating physician.

The LVEF was calculated at admission using the Teicholz method or Simpson's method (Sonos 5500: Hewlett Packard, Palo Alto, CA, USA; or Vivid I: GE Yokogawa Medical, Tokyo, Japan). Because the LVEF was measured during the acute phase, it was not adequately evaluated in cases of severe orthopnea. The method of LVEF measurement (Teicholz method or Simpson's method) was decided on a case-by-case basis.

Figure 1 Study procedure and patient enrolment. A total of 800 AHF patients admitted to the ICU of Nippon Medical School at Chibah Hokusoh Hospital between March 2011 and December 2018 were screened. Among these, 157 patients were excluded whose serum P3P level was not measured within 15 min of admission before initial treatment. The analysis was thus conducted on data from 643 AHF patients whose serum P3P levels were recorded. Patients were assigned to three groups according to the quartile of their serum P3P level: low-P3P (Q1, P3P ≤ 0.6 U/mL), mid-P3P (Q2/Q3, 0.6 < P3P < 1.2 U/mL), and high-P3P (Q4, P3P ≥ 1.2 U/mL). AHF, acute heart failure; ICU, intensive care unit; P3P, type III procollagen peptide; Q, quartile.



Plasma volume status was assessed to evaluate fluid retention. PVS was calculated using the following formula: ([actual PV − ideal PV]/ideal PV) × 100 (%). Actual PV was defined as PV = (1 − haematocrit) × (a + [b × body weight]), where a = 1530 in men and 864 in women; b = 41.0 in men and 47.9 in women. Ideal PV was calculated as PV = c × body weight, where c = 39 in men and 40 in women.[10] Patients were divided into three groups according to the quartile of their PVS: low-PVS (PVS ≤ −6.37%; *n* = 364), mid-PVS (−6.37% < PVS < −16.09%; *n* = 728), and high-PVS (PVS ≥ 16.09%; *n* = 364).

The FIB4 index was originally established as a non-invasive index for hepatic disease staging in patients with viral infection.[11] It is calculated with the following formula: age × aspartate transaminase level (AST; U/L)/(platelet count [$10^3/\mu L$] × √alanine aminotransferase level [ALT; U/L]). The serum levels of AST and ALT, as well as the platelet count on the first day after admission, were included in the formula for the FIB4 index evaluation during the acute phase of AHF.

The factors significantly associated with a high serum P3P were determined using a multivariate logistic regression analysis.

Prognosis

Long-term prognosis, including all-cause death within 365 days (365 day mortality) and HF events, was also evaluated. An HF event was defined as readmission due to HF or death from any cause. The primary endpoint of the present study was 365 day mortality. The patients underwent routine clinical follow-up at an outpatient clinic. The prognoses of patients who had follow-ups at other institutes were determined by telephone contact. A Cox regression analysis was performed to obtain the hazard ratios (HRs) for 365 day mortality and HF events. For the sub-group analysis, the primary endpoint (365 day mortality) was evaluated in HF patients with a preserved ejection fraction (HFpEF) and HF patients with a reduced ejection fraction (HFrEF). In the present study, HFpEF was defined as LVEF ≥40% on an echocardiogram; HFrEF was defined as LVEF <40%.

Patients were further subdivided into four groups according to their serum P3P level and PVS, and their prognoses were evaluated using Kaplan–Meier curves. The patients were divided as follows: low-PVS/low-P3P (*n* = 384), high-PVS/low-P3P (*n* = 102), low-PVS/high-P3P (*n* = 98), and high-PVS/high-P3P (*n* = 60). The quartile values of P3P and PVS were used as cutoff values; for example, low P3P and PVS were defined as Q1 and high P3P and PVS were defined as Q4.

Statistical analyses

All data were statistically analysed using the SPSS 22.0 software program (SPSS Japan Institute, Tokyo, Japan). All numerical data were expressed as the median and range or interquartile range. The Kruskal–Wallis test was used for comparisons among the three groups. The χ^2 test was used to compare proportions. *P* values <0.05 were considered statistically significant.

All clinically relevant factors involved in high P3P levels, including PVS (Q2/Q3, and Q4 as the reference for Q1), FIB4 index (Q2/Q3, and Q4 as the reference for Q1), age (per year increase), sex (male), diabetes (yes), SBP (per 10 mmHg increase), heart rate (per 10 b.p.m. increase),

Table 1 Patient characteristics in the different serum P3P level groups

	Total (n = 643)	Low-P3P; Q1 (n = 146)	Middle-P3P; Q2/Q3 (n = 339)	High-P3P; Q4 (n = 158)	P
Characteristics					
Age (years)	76 (66–82)	71 (62–80)	77 (68–82)	77 (65–82)	0.006
Type (readmission, %)	221 (34.4%)	34 (23.1%)	115 (33.9%)	72 (45.6%)	<0.001
Sex (male, %)	425 (66.1%)	96 (65.3%)	224 (66.1%)	105 (66.5%)	0.992
Aetiology (ischaemia, %)	254 (39.5%)	53 (36.1%)	138 (40.7%)	63 (39.9%)	0.657
Atherosclerosis risk factors					
Hypertension (yes, %)	494 (76.8%)	94 (63.9%)	266 (78.5%)	134 (84.8%)	<0.001
Diabetes mellitus (yes, %)	312 (48.5%)	63 (42.9%)	166 (49.0%)	83 (52.5%)	0.255
Dyslipidaemia (yes, %)	334 (51.9%)	72 (49.0%)	176 (51.9%)	86 (54.4%)	0.672
Vital signs and status					
Systolic blood pressure (mmHg)	160 (130–188)	160 (135–188)	160 (131–186)	158 (120–190)	0.691
Heart rate (b.p.m.)	108 (90–127)	113 (98–133)	108 (91–129)	102 (84–116)	<0.001
LVEF (%)	38 (27–50)	34 (25–51)	37 (27–50)	40 (30–53)	0.143
Orthopnea (yes, %)	496 (77.1%)	111 (75.5%)	265 (78.2%)	120 (75.9%)	0.805
CKD (yes, %)	347 (54.0%)	41 (27.9%)	179 (52.8%)	127 (80.4%)	<0.001
Prescribed haemodialysis (yes, %)	29 (4.5%)	1 (0.7%)	0 (0.0%)	28 (17.7%)	<0.001
Respiratory management					
ETI (yes, %)	100 (15.6%)	20 (13.6%)	51 (15.0%)	29 (18.4%)	0.498
NPPV (yes, %)	437 (48.0%)	101 (68.7%)	236 (69.6%)	100 (63.3%)	0.348
Arterial blood gases					
pH	7.36 (7.23–7.43)	7.36 (7.26–7.43)	7.35 (7.21–7.44)	7.37 (7.29–7.42)	0.747
PCO_2 (mmHg)	39 (33–53)	42 (34–54)	39 (32–55)	37 (32–50)	0.041
PO_2 (mmHg)	97 (71–143)	90 (71–136)	94 (71–136)	106 (72–155)	0.279
HCO_3^- (mmol/L)	21.7 (19.1–24.3)	22.7 (20.3–25.2)	21.7 (19.2–24.2)	20.4 (17.7–23.9)	<0.001
SaO_2 (%)	97 (93–98)	96 (93–98)	96 (92–98)	97 (92–99)	0.263
Lactate (mmol/L)	1.8 (1.1–3.4)	1.8 (1.1–3.1)	1.8 (1.1–3.7)	1.7 (1.0–2.8)	0.054
Total bilirubin (mg/dL)	0.6 (0.4–0.9)	0.6 (0.5–0.9)	0.6 (0.4–0.9)	0.5 (0.5–1.0)	0.009
BUN (mg/dL)	25.4 (18.2–42.6)	18.8 (15.3–24.8)	24.8 (17.9–37.6)	45.8 (31.1–62.3)	<0.001
Creatinine (mg/dL)	1.20 (0.90–2.10)	0.93 (0.71–1.13)	1.18 (0.900–1.74)	2.78 (1.80–5.24)	<0.001
Sodium (mmol/L)	140 (137–142)	140 (138–142)	140 (137–142)	139 (136–142)	0.075
Potassium (mmol/L)	4.3 (3.9–4.8)	4.2 (3.8–4.5)	4.2 (3.8–4.7)	4.6 (4.3–5.1)	<0.001
Uric acid (mg/dL)	6.9 (5.5–8.2)	6.4 (5.1–7.7)	7.0 (5.6–8.2)	7.1 (5.7–8.6)	0.003
Haemoglobin (g/dL)	12.2 (10.2–13.9)	13.1 (11.8–14.9)	12.4 (10.6–13.8)	10.5 (9.1–12.1)	<0.001
CRP (mg/dL)	0.76 (0.22–3.44)	0.49 (0.16–1.73)	0.81 (0.24–3.11)	1.23 (0.28–5.47)	0.002
BNP (pg/dL)	836 (474–1518)	575 (334–965)	861 (469–1374)	1236 (704–1888)	<0.001
Indexes					
PVS	11.5 (−2.4–23.5)	2.6 (−8.7–15.1)	11.4 (−2.7–22.8)	19.8 (6.7–31.4)	<0.001
FIB4 index	2.77 (1.86–4.28)	2.53 (1.57–3.51)	2.83 (1.93–4.21)	3.19 (2.01–5.45)	<0.001

P values between the low-, mid- and high-P3P groups were determined by the Kruskal–Wallis test or χ^2 test. All numerical data are expressed as the median (25–75% interquartile range).
BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CKD, chronic kidney disease; CRP, C-reactive protein; ETI, endotracheal intubation; FIB4 index, fibrosis-4 index; LVEF, left ventricular ejection fraction measured by echocardiography; NPPV, non-invasive positive pressure ventilation; P3P, type III procollagen peptide; PVS, plasma volume status.

aetiology of ischaemic heart disease (yes), orthopnea (yes), estimated glomerular filtration rate (eGFR; per 10 mL/min/1.73 m^2 increase), LVEF (per 10% increase), readmission for HF (yes), and BNP (per 1 pg/mL increase) were included in the multivariate logistic regression model. Multivariate logistic regression analysis was performed using simultaneous forced entry.

We used a Cox regression analysis to determine the HRs for 365 day mortality and HF events. The cumulative survival rates and event rates in each of the groups were analysed using Kaplan–Meier curves, and a log-rank test was used to calculate the statistical significance of the differences.

Ethical review

The Research Ethics Committee of Nippon Medical School at Chiba Hokusoh Hospital approved the study protocol. The requirement for written informed consent was waived, in accordance with the advice given by the Ethics Committee, because of the study's retrospective design. We also described the content of the present study in a poster displayed at our institute and shared the content on our homepage, where it could be easily seen by anyone, following the advice of the ethics committee.

Results

Patient characteristics, prognoses, and differences in type III procollagen peptide level

The study population included 425 (66.1%) men (median age: 76 years), and 221 (34.4%) patients had been readmitted for HF. A total of 254 (39.5%) patients had ischaemic heart disease. In most cases, AHF was complicated by orthopnea at the emergency room (n = 496, 77.1%). The median LVEF on admission was 38.0% (*Table 1*).

The patients in the high-P3P group were significantly older, and their heart rates were significantly lower in comparison with the low-P3P group. Patients with CKD or patients who had been readmitted were more frequently in the high-P3P group compared with the low-P3P group. In terms of laboratory findings, in the high-P3P group, haemoglobin levels were significantly lower, and serum BUN, creatinine, CRP, and BNP levels were significantly higher compared with the low-P3P group (*Table 1*). Furthermore, in the high-P3P group, furosemide, angiotensin-converting enzyme (ACE) inhibitors (ACE-I), angiotensin receptor blockers (ARB), and spironolactone were less frequently administered when compared with the low-P3P group (*Table 2*). These findings might be associated with a significantly higher ratio of patients on haemodialysis (n = 28, 17.7%) and a higher ratio of patients with CKD

Table 2 ICU treatment in the different serum P3P level groups

	Total (N = 643)	Low-P3P; Q1 (n = 146)	Middle-P3P; Q2/Q3 (n = 339)	High-P3P; Q4 (n = 158)	P
Medication (cases) during ICU					
Furosemide (yes, %)	580 (90.2%)	132 (89.8%)	326 (96.2%)	122 (77.2%)	<0.001
Nitroglycerin (yes, %)	267 (41.5%)	63 (42.9%)	137 (40.4%)	67 (42.4%)	0.826
Nicorandil (yes, %)	94 (14.6%)	28 (19.0%)	45 (13.3%)	21 (13.3%)	0.207
Carperitide (yes, %)	224 (34.8%)	55 (37.4%)	119 (35.1%)	50 (31.6%)	0.539
Dopamine (yes, %)	33 (5.1%)	4 (2.7%)	17 (5.0%)	12 (7.6%)	0.158
Dobutamine (yes, %)	134 (20.8%)	25 (17.0%)	72 (21.2%)	37 (23.4%)	0.388
ACE-I/ARB (yes, %)	215 (33.4%)	62 (42.2%)	119 (35.1%)	34 (21.5%)	<0.001
Beta-blocker (yes, %)	182 (28.3%)	32 (21.8%)	109 (32.2%)	41 (25.9%)	0.054
Spironolactone (yes, %)	242 (37.6%)	68 (46.3%)	139 (41.0%)	35 (22.2%)	<0.001

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ICU, intensive-care unit; P3P, type III procollagen peptide.
P values between the low-P3P, mid-P3P, and high-P3P groups were determined by the Kruskal–Wallis test or χ^2 test. All numerical data are expressed as the median (25–75% interquartile range).

Table 3 Short-term outcomes in the different serum P3P level groups

	Total (N = 643)	Low-P3P; Q1 (n = 146)	Middle-P3P; Q2/Q3 (n = 339)	High-P3P; Q4 (n = 158)	P
Short-term outcome					
ICU hospitalization (days)	4 (3–6)	3 (3–5)	4 (3–6)	4 (3–7)	0.114
Total hospitalization (days)	24 (15–40)	20 (15–34)	25 (16–40)	27 (16–44)	0.102
In-hospital mortality (yes, %)	66 (10.3%)	8 (5.4%)	32 (9.4%)	26 (16.5%)	0.005

ICU, intensive-care unit; P3P, type III procollagen peptide.
P values between the low-P3P, mid-P3P, and high-P3P groups were determined by the Kruskal–Wallis test or χ^2 test. All numerical data are expressed as the median (25–75% interquartile range).

(*n* = 127, 80.4%) in the high-P3P group (*Table 1*). Compared with the low-P3P group, the length of ICU stay and total hospitalization time in the high-P3P group were not significantly different (*Table 3*).

The Kaplan–Meier survival curves of the three groups, including all-cause mortality and HF events within 365 days, are shown in *Figure 2*. In the high-P3P group, the survival rate and event-free rates were both significantly lower compared with the mid-P3P and low-P3P groups (*Figure 2A* and *2B*).

Interestingly, the findings from the sub-group analysis indicated that in the HFrEF cohort, the survival rate was significantly lower in the high-P3P group than in the mid-P3P and low-P3P groups, but no significant differences were observed in the HFpEF cohort (*Figure 3A* and *3B*). Although the statisti-

Figure 2 Kaplan–Meier survival curves for the three groups. (A) The prognosis for all-cause 365 day mortality was significantly worse in the high-P3P group than in the mid-P3P and low-P3P groups. (B) The prognosis for HF events within 365 days was significantly worse in the high-P3P group than in the mid-P3P and low-P3P groups. P3P, type III procollagen peptide; HF, heart failure; Q, quartile.

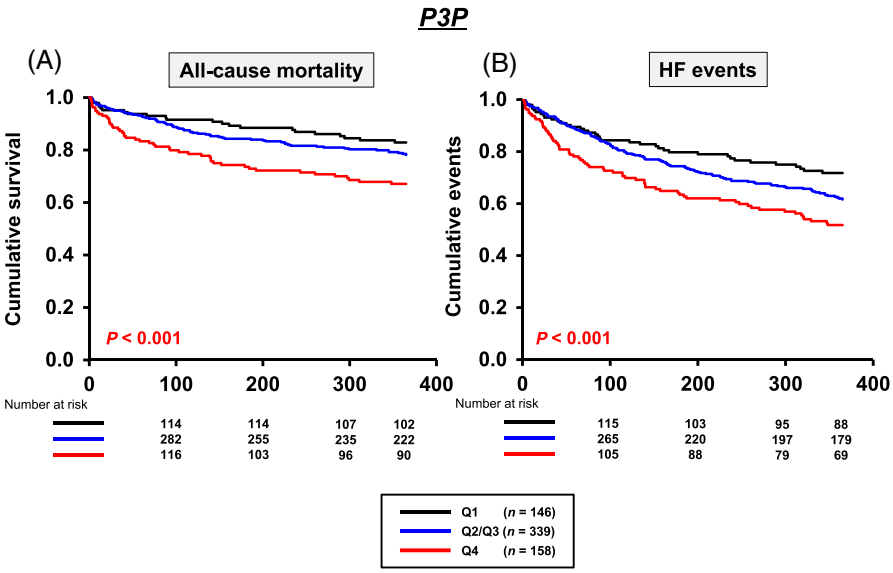
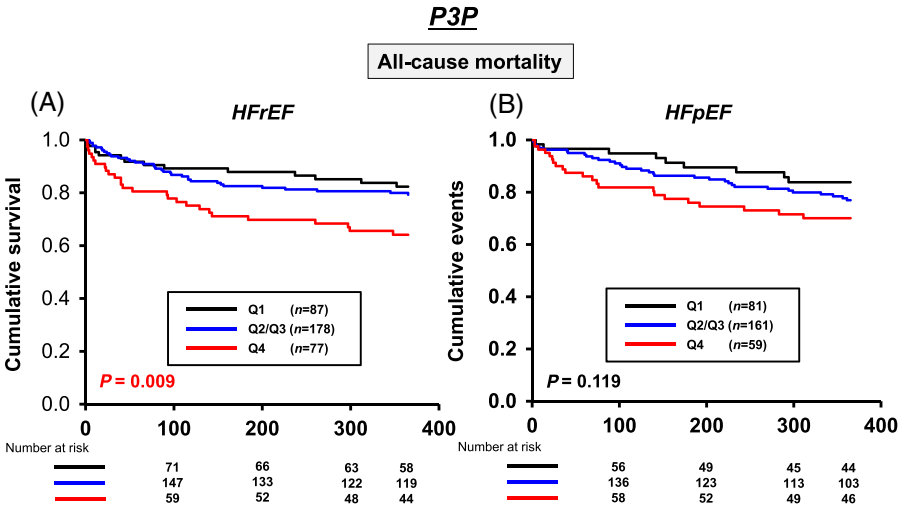


Figure 3 Kaplan–Meier survival curves for the sub-group analysis. (A) The prognosis for all-cause 365 day mortality in the HFrEF cohort was significantly worse in the high-P3P group than in the mid-P3P and low-P3P groups. (B) The prognosis for all-cause 365 day mortality in the HFpEF cohort was not significantly different between the low-P3P, mid-P3P, and high-P3P groups. P3P, type III procollagen peptide; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; Q, quartile.



cal difference was only apparent in the HFrEF cohort, there was still a strong trend in the HFpEF cohort.

Factors associated with high type III procollagen peptide levels and prognosis

The multivariate logistic regression analysis revealed that PVS [Q2/Q3, odds ratio (OR): 2.683, 95% CI: 1.291–5.575, $P = 0.008$; Q4, OR: 4.702, 95% CI: 2.012–20.989, $P < 0.001$], FIB4 index (Q4, OR: 2.627, 95% CI: 1.311–5.261, $P = 0.006$), and eGFR (per 0.1 mL/min/1.73 m^2 increase; OR: 1.996, 95% CI: 1.718–2.326, $P < 0.001$) were independently associated with high P3P levels at admission (*Table 4*), suggesting that high P3P is associated with a congested liver, as shown by high FIB4 index and high PVS, and renal dysfunction.

The Kaplan–Meier curves for the low-P3P/low-PVS and high-P3P/high-PVS groups are shown in *Figure 4*. The prognoses in both the high-P3P and low-P3P groups, including 365 day all-cause mortality and HF events, were significantly worse in patients with high PVS compared with those with low PVS (*Figure 4A* and *4B*). The multivariate Cox regression model identified high-PVS/high-P3P to be an independent predictor of 365 day all-cause mortality (HR: 2.249, 95% CI: 1.081–3.356, $P = 0.026$) and HF events (HR: 1.586, 95% CI: 1.005–2.503, $P = 0.048$; *Table 5*). These results suggest the importance of evaluating PVS in addition to P3P level to predict mortality and HF events caused by AHF; a high serum P3P level with a high PVS was clearly associated with adverse outcomes in patients with severely decompensated AHF.

Discussion

The present study revealed that a high P3P level was clearly associated with adverse outcomes. Furthermore, a high P3P level at admission was independently associated with high PVS, a high FIB4 index, and reduced eGFR.

There is already a great deal of evidence to support the hypothesis that the FIB4 index predicts cirrhosis risk and adverse outcomes in patients with various hepatic diseases.[12,13] The FIB4 index has also been recognized as a good predictor of adverse clinical outcomes in patients with compensated HF after admission for worsening HF[14,15] and could indicate haemodynamic liver damage, such as liver hypoperfusion as a result of low cardiac output or liver congestion, in the acute phase of AHF.[16] The clinical implications of the calculated or estimated PVS in patients with AHF and chronic HF were also explored in the 2010s.[10,17–19] High PVS was considered to be essentially indicative of volume overload during the acute phase of AHF.

As a result of these insights, it would be reasonable to suggest that AHF patients with a high FIB4 index and high PVS might have liver congestion. These findings underscore the fact that a high serum P3P level could indicate liver congestion during the acute phase of AHF.

Table 4 Multivariate analysis of factors associated with high serum P3P level

	Univariate			Multivariate		
	HR	95% CI	*P*	HR	95% CI	*P*
PVS						
Q1	1.000			1.000		
Q2/Q3	3.371	1.874–6.066	<0.001	2.683	1.291–5.575	0.008
Q4	5.686	3.059–10.569	<0.001	4.702	2.012–20.989	<0.001
FIB4 index						
Q1	1.000			1.000		
Q2/Q3	0.981	0.617–1.561	0.937	1.206	0.651–2.233	0.552
Q4	2.067	1.256–3.401	0.004	2.627	1.311–5.261	0.006
Other factors						
Age (per 1 year of increase)	1.001	0.987–1.016	0.847	0.984	0.962–1.006	0.153
Sex (male)	1.022	0.699–1.494	0.913	0.650	0.386–1.092	0.650
Diabetes mellitus (yes)	1.237	0.864–1.772	0.246	0.853	0.528–1.379	0.517
SBP (per 10 mmHg increase)	0.986	0.947–1.026	0.479	1.019	0.967–1.074	0.486
Heart rate (per 10 b.p.m. increase)	0.907	0.853–0.965	0.002	1.009	0.928–1.098	0.831
Ischaemic heart disease (yes)	1.021	0.707–1.473	0.913	0.798	0.486–1.311	0.373
Orthopnea (yes)	0.915	0.600–1.397	0.682	0.649	0.380–1.109	0.113
eGFR (per 10 mL/min/1.62 m^2 decrease)	2.041	1.783–2.342	<0.001	1.996	1.718–2.326	<0.001
LVEF (per 10% increase)	1.085	0.978–1.203	0.124	1.069	0.924–1.237	0.367
Re-admission (yes)	1.882	1.303–2.719	0.001	1.109	0.689–1.787	0.670
BNP (per 1 pg/mL increase)	1.000	1.000–1.000	0.007	1.000	1.000–1.000	0.334

BNP, brain natriuretic peptide; CI, confidence interval; eGFR, estimated glomerular filtration rate; FIB4 index, fibrosis-4 index; HR, hazard ratio; LVEF, left ventricular ejection fraction measured by echocardiography; P3P, type III procollagen peptide; PVS, plasma volume status; SBP, systolic blood pressure.

Figure 4 Kaplan–Meier survival curves for serum P3P level and PVS. (A) The prognosis for all-cause mortality was significantly worse in the high-P3P/high-PVS group compared with the low-P3P/low-PVS group. (B) The prognosis for HF events was significantly worse in the high-P3P/high-PVS group than in the low-P3P/low-PVS group. P3P, type III procollagen peptide; PVS, plasma volume status; HF, heart failure; Q, quartile.

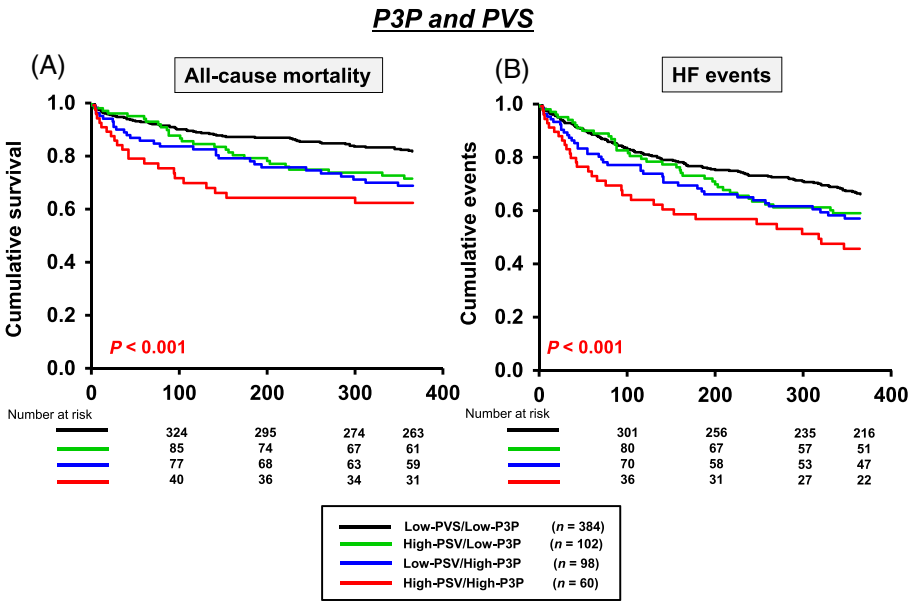


Table 5 Multivariate analysis of factors associated with 365 day all-cause mortality

	Multivariate					
	All-cause mortality			HF event		
All-cause mortality	HR	95% CI	*P*	HR	95% CI	*P*
PVS						
Low-PVS/low-P3P	1.000			1.000		
High-PVS/low-P3P	1.305	0.793–2.147	0.294	1.081	0.725–1.611	0.702
Low-PVS/high-P3P	1.559	0.690–1.934	0.583	1.029	0.675–1.468	0.894
High-PVS/high-P3P	2.249	1.081–3.356	0.026	1.586	1.005–2.503	0.048
Other factors						
Age (>75 years)	1.412	0.977–2.039	0.066	1.555	1.168–2.070	0.002
Sex (male)	1.063	0.725–1.559	0.754	0.989	0.732–1.335	0.940
Ischaemic heart disease (yes)	0.852	0.593–1.225	0.388	0.976	0.741–1.286	0.861
SBP (<100 mmHg)	3.188	2.074–4.900	<0.001	2.025	1.376–2.981	<0.001
Heart rate (per 10 b.p.m. increase)	0.958	0.903–1.016	0.155	0.979	0.935–1.026	0.385
Creatinine (per 0.1 mg/dL increase)	1.003	0.994–1.012	0.530	1.004	0.997–1.012	0.254
Sodium (per 1.0 mEq/L increase)	0.967	0.937–0.998	0.040	0.973	0.946–1.000	0.051
Potassium (per 1.0 mEq/L increase)	1.211	0.969–1.514	0.092	1.180	0.984–1.414	0.074
CRP (per 1.0 mg/dL increase)	1.000	0.985–1.016	0.981	0.994	0.978–1.011	0.504
LVEF (<40%)	1.083	0.745–1.573	0.677	1.229	0.918–1.647	0.166

CI, confidence interval; CRP, C-reactive protein; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction measured by echocardiography; P3P, type III procollagen peptide; PVS, plasma volume status; SBP, systolic blood pressure.

Haemodynamic liver damage in acute heart failure

The ESC guidelines propose several phenotypes for AHF and classify patients across several clinical conditions.[9] Patients with pulmonary oedema could be divided into two categories: those with vascular failure and those with cardiac failure.[9,20,21] Cardiac failure is defined as the deterioration of cardiac performance over days to weeks, leading to decompensation.[22] Patients with cardiac failure present with pulmonary congestion caused by ventricular output failure, which is often accompanied by systemic fluid retention. Meanwhile, vascular failure is defined as acute hypertension and increased vascular stiffness.[22] Vascular failure is characterized by a transient volume shift from the peripheral veins to pulmonary circulation, leading to fluid accumulation. This

concept is described as fluid redistribution, which was found to be generally associated with a more urgent presentation. The volume status therefore varies for each AHF patient, and it is necessary to comprehend volume status appropriately on a case-by-case basis.

Liver function test abnormalities (e.g. abnormal AST, ALT, total bilirubin, gamma-glutamyl transpeptidase, and alkaline phosphatases) during the acute phase of AHF are usually complicated by cardiac failure and are reported to occur in approximately 30% of AHF patients.[6] Two mechanisms for acute liver dysfunction in the acute phase of AHF were suggested based on the observed haemodynamic changes.[6,7] In patients with liver hypoperfusion, reduced cardiac output induces acute centrilobular hepatocellular damage, ischaemic hepatic injury, and hepatic necrosis. Meanwhile, congestive hepatic damage is induced in patients with systemic congestion by right atrial pressure elevation. When we discuss the exacerbation of liver function test parameters, the degree of systemic volume retention and the haemodynamic profile are important factors to consider.

In the 1970s, haemodynamic profiles were evaluated using pulmonary artery catheters (PACs). The risks and benefits of continuous monitoring using PACs in the ICU were carefully discussed in the 1990s.[23] Although the prognostic importance of using a PAC in patients with cardiogenic shock has been recently reported,[24,25] it was still found to be rather difficult to perform the PAC procedure on patients who were supported by non-invasive positive pressure ventilation. Because the use of non-invasive positive pressure ventilation is recommended without sedation, the use of PAC monitoring in the ICU has decreased dramatically since the 2000s.[26] Liver congestion during the most severe stages of an AHF presentation may therefore be very difficult to strictly define. Although the present study was performed retrospectively, PAC data in the acute phase were lacking in almost every case. We therefore used PVS instead of a haemodynamic profile in the present study. Research into the PVS of AHF patients was discussed in the 2010s,[10,17–19] so plasma volume can be easily estimated with a formula. High PVS with a high FIB4 index may indicate liver congestion. This investigation into the relationship between biomarkers and liver congestion using PVS and FIB4 index in the acute phase of AHF can thus offer new insights.

Type III procollagen peptide in hepatic disease and cardiovascular disease

Hepatic cell injury is generally determined based on elevated transaminase level. Meanwhile, cholestasis is determined based on elevated bilirubin or alkaline phosphatase. A low cardiac index (i.e. liver hypoperfusion) and a high central venous pressure (i.e. liver congestion) were correlated with total bilirubin level in patients with chronic HF.[27,28] Previous studies have indicated that reduced perfusion and venous congestion were the main causes of elevated total serum bilirubin. However, it is still difficult to accurately indicate liver congestion based on laboratory examinations and biomarkers. It remains unclear whether there is a definitive connection between haemodynamic profile and specific liver function test results.[8]

Type III procollagen peptide is the N-terminal propeptide of type III procollagen, which is liberated during the biosynthesis of collagen III. It is upregulated during normal tissue repair and is used as a marker of fibrogenesis and scar formation. It has been thus reported to be elevated in various diseases, such as sclerosis and lung fibrosis.[29,30] Because the liver is the heaviest organ in the body, and because a large amount of extracellular matrix is produced by the liver, P3P level has mainly been established as a marker of fibrosis in patients with hepatic disease.[1–3] In the present study, serum P3P levels were independently associated with high FIB4 index and PVS values, suggesting that liver congestion occurs as a result of acute haemodynamic changes. Tissue remodelling, which is the normal process of tissue repair via collagen III biosynthesis, progresses gradually over several months. Thus, the hypothesis that serum P3P level reflects acute haemodynamic changes might not be consistent with this process. However, acute remodelling has been reported during the acute phase of AHF.[31] Time-dependent changes in matrix metalloproteinase-2 (MMP-2) levels during the treatment of AHF have also been documented.[31] Serum MMP-2 levels were found to be above the normal range in the decompensated state and thereafter rapidly decreased throughout compensation in patients with AHF. Therefore, MMP-2 levels reached a plateau 3 days after admission. Although MMPs were found to be a representative biomarker of cardiac remodelling, our previous study demonstrated that MMP production is also altered by changes in haemodynamic, neurohormonal, and inflammatory factors in patients with AHF. Biolo *et al*. reported that some markers of extracellular matrix turnover (MMP-2, tissue inhibitors of MMP-1, and P3P) were elevated in AHF patients and concluded that the increase in extracellular matrix turnover may be associated with an acceleration in pathological myocardial remodelling.[32] The same pathological changes might occur in the liver during the most severe stages of AHF. Volume overload due to AHF can easily induce organ dysfunction of the liver, kidneys, and heart. The present study indicated that high P3P levels were independently associated with increased serum ALT levels and high PVS. Liver congestion might induce temporal pathological liver remodelling during the acute phase of AHF.

Volume expansion through systemic venous congestion sometimes leads to adverse outcomes in HF patients, perhaps due to vital organ congestion.[33] Furthermore, renal insufficiency, such as acute kidney injury and CKD, show an ob-

vious independent association with the prognoses.[34] P3P level at admission is a comprehensive biomarker that reflects these findings surrounding liver congestion and renal dysfunction, suggesting its potential for application as a prognostic marker of AHF.

Study limitations

The present study has several limitations. First, enrolled patients were limited to patients who were admitted to the ICU, which excluded AHF patients who were admitted to general wards. At our institute, patients are treated in a closed ICU, in which all physicians are cardiologists; the majority of patients with severely decompensated AHF were thus admitted to the ICU. However, in some cases, increasing competition for a limited number of available ICU beds may force physicians to send a greater number of severe AHF cases to general wards. The best strategy for presenting our data and analysis to the broader medical community would have been to include all patients with AHF that were admitted to the emergency department. Therefore, the exclusion of HF patients admitted to general wards may reduce the generalizability of the study results. Second, this study was performed at a single center and was not a prospective randomized controlled trial. We did not evaluate key factors associated with the main results. It is therefore possible that unmeasured variables may have affected the results. Third, other estimates of patients' volume status (e.g. PAC data, BNP level, or chest X-ray results for congestion) were not quantitatively evaluated in the present study. Of note, the prognostic utility of PAC in patients with cardiogenic shock has recently been suggested.[24,25] We found that PVS, FIB4 index, and BNP were correlated with each other (data not shown), and PVS was able to precisely evaluate patients' volume status. However, the lack of data from additional clinical investigations may have weakened our findings. Fourth, the prevalence of pharmacological treatment with furosemide, ACE-I/ARB, and spironolactone was significantly lower in the high-P3P group. Low administration rates of prognostically beneficial drugs may have been associated with worse outcomes in the high-P3P group. Fifth, we only measured serum P3P level once at admission, so time-dependent changes in P3P level induced by AHF treatment were not evaluated in the present study. Further studies are required to address this issue. Finally, 157 of 800 patients were excluded due to missing P3P data at admission. Although the prognoses, including all-cause mortality and HF events, did not significantly differ between included and excluded patients, this may be a source of selection bias.

Conclusions

A high P3P level in the acute phase of AHF was independently associated with high PVS, a high FIB4 index, and reduced eGFR. High FIB4 index values during the acute phase of AHF could indicate haemodynamic liver damage, and high PVS was considered to be essentially indicative of volume overload. Accordingly, AHF patients with a high FIB4 index and high PVS were considered to have liver congestion. A high serum P3P level at admission was thus a comprehensive biomarker that could indicate liver congestion and renal dysfunction during the acute phase of AHF. It was therefore independently associated with adverse outcomes in AHF patients.

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Conflict of interest

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

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