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ORIGINAL SCIENTIFIC PAPER

Prognostic effects of arterial carbon dioxide levels in patients hospitalized into the cardiac intensive care unit for acute heart failure

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Aims Although both hypercapnia and hypocapnia are common in acute heart failure (AHF) patients, routine assessment of arterial blood gas is not recommended. Additionally, no association between hypercapnia and increased mortality has been found, and the prognostic value of hypocapnia in AHF patients remains to be elucidated. In this observational study, we aimed to investigate the relationship between partial pressure of arterial carbon dioxide ($PaCO_2$), especially low $PaCO_2$, and long-term mortality in AHF patients.

Methods and results Acute heart failure patients hospitalized in the cardiac intensive care unit of our institution between 2007 and 2011 were screened. All eligible patients were divided into two groups based on the inflection point (i.e. 31.0 mmHg) of the 3-knot cubic spline curve of the hazard ratio (HR), with a $PaCO_2$ of 40 mmHg as a reference. The association between $PaCO_2$ levels and all-cause mortality was assessed using Cox proportional hazards regression models. Among 435 patients with a median follow-up of 1.8 years, 115 (26.4%) died. Adjusted analysis with relevant variables as confounders indicated that $PaCO_2$ <31 mmHg was significantly associated with increased all-cause mortality [HR 1.71, 95% confidence interval (CI) 1.05–2.79; $P = 0.032$]. When $PaCO_2$ was considered as a continuous variable, the lower was the log-transformed $PaCO_2$, the greater was the increased risk of mortality (HR 0.71, 95% CI 0.52–0.96; $P = 0.024$).

Conclusions In AHF patients, lower $PaCO_2$ at admission was associated with increased long-term mortality risk.

Keywords Arterial blood gas • Hypercapnia • Hypocapnia • Outcome

Introduction

Considering the long-term clinical course of heart failure (HF) patients, a focus should be on the management of acute HF (AHF) because AHF affects HF illness trajectory.[1] The most frequent complaint of AHF patients is dyspnoea.[2,3] Although arterial blood gas (ABG) analysis is a primary tool for establishing the diagnosis, decision-making, and guiding the therapy in patients with other diseases who complain of dyspnoea,[4,5] the role of ABG analysis in AHF patients remains unknown. Alterations in ABG, the especially arterial partial pressure of CO_2 ($PaCO_2$), have been previously demonstrated to result in worse clinical outcomes in several patient populations.[6–8] Among AHF patients, one-third have hypercapnia and another third have hypocapnia.[9] In a previous study, no association

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was observed between hypercapnia and increased mortality;[10] however, the prognostic value of hypocapnia in AHF patients remains unknown. Therefore, the purpose of this study was to investigate the relationship between hypocapnia and long-term mortality in AHF patients. We hypothesized that the lower the $PaCO_2$, the worse the long-term mortality in AHF patients.

Methods

Subjects

This observational study was performed using a prospectively collected database that included AHF patients hospitalized to the cardiac intensive care unit at the Juntendo University Hospital, Tokyo, Japan between 2007 and 2011. The diagnosis of AHF was made clinically according to the attending cardiologists. We excluded patients with acute coronary syndrome and/or those who had undergone cardiac surgery during the previous 4 weeks or during initial hospitalization, those with an end-stage renal disease requiring dialysis, and those with life-threatening malignancies. Additionally, patients with invasive or non-invasive ventilation, those with shock [defined as a systolic blood pressure (BP) <90 mmHg or a reduction in BP of ≥30 mmHg from the normal pressure with signs of tissue hypoperfusion] at the time of ABG analysis, and those in whom ABG analysis was not performed at admission were excluded. The Institutional Review Board of the Juntendo University Hospital approved the study protocol, and the study conformed to the principles outlined in the *Declaration of Helsinki*. Informed consent was obtained from all patients.

Data collection

Baseline data, including ABG findings, were collected prospectively at the time of initial hospitalization. ABGArterial blood gas analysis was performed routinely during the study period according to the Guidelines for Treatment of Acute Heart Failure. Medical histories were obtained from clinical records. A current smoker was defined as an individual who smoked at the time of admission or had quit smoking less than 1 year prior to admission. Renal function was assessed using the estimated glomerular filtration rate (eGFR), which was calculated based on the baseline serum creatinine levels using the Modification of Diet in Renal Disease equation with Japanese coefficient.[11] Two-dimensional echocardiography was performed for each patient, and the left ventricular ejection fraction (LVEF) was calculated according to the modified Simpson method. All patients were followed up from the date of index admission until July 2013. Outcome data were obtained by reviewing medical records for all deaths recorded following discharge.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) or median and interquartile range. Categorical variables are presented as numbers and percentages. To compare baseline characteristics between the two groups, the χ^2 test or Fisher's exact test was used for categorical variables and the unpaired Student's *t*-test or Mann–Whitney *U*-test for continuous variables. The patients were divided into two groups based on the inflection point of the 3-knot cubic spline curve of the hazard ratio (HR), with $PaCO_2$ of 40 mmHg as a reference.

Cumulative survival curves were plotted using the Kaplan–Meier method and compared using the log-rank test. Cox proportional hazards models were used to identify the association between all-cause mortality and $PaCO_2$. In addition to the unadjusted model, the adjusted model was constructed including relevant variables as confounders, such as age, sex, body mass index, systolic BP, eGFR, plasma B-type natriuretic peptide (BNP) level, pH, and PaO_2. To determine whether the results differed with the cut-off points, we performed secondary analyses in which $PaCO_2$ levels were treated as a natural logarithm-transformed continuous variable. In addition, serum BNP level was naturally log-transformed owing to their non-normal distributions. The assumption of proportional hazards was assessed using a log-minus-log survival graph. A *P*-value <0.05 was considered statistically significant. All analyses were performed using SPSS v23 (IBM Inc., Armonk, NY, USA).

Results

Baseline characteristics of patients

Overall, 751 AHF patients were admitted to our institution between 2007 and 2011. Of those patients, 190 with concomitant acute coronary syndrome, an end-stage renal disease requiring dialysis, and life-threatening malignancy and those who underwent cardiac surgery within the previous 4 weeks were excluded. Additionally, 105 patients with invasive or non-invasive ventilation, those with shock at the time of ABG analysis, and 21 patients in whom ABG analysis was not performed at admission were excluded (*Figure 1*). Consequently, 435 patients were included and then divided into two groups based on the $PaCO_2$ value at the inflection point of the cubic spline curve of the HR for all-cause mortality (i.e. $PaCO_2$, 31 mmHg) (*Figure 2*).

The baseline characteristics of patients with $PaCO_2$ ≥31 or <31 mmHg are summarized in *Table 1*. Patients with $PaCO_2$ <31 mmHg were more likely to have lower LVEF and greater heart rates than those with $PaCO_2$ ≥31 mmHg. Patients with $PaCO_2$ <31 mmHg had lower eGFR and serum sodium levels and higher potassium, C-reactive protein, and BNP levels than those with $PaCO_2$ ≥31 mmHg. Patients with $PaCO_2$ <31 mmHg had a higher pH and lower $PaCO_2$ (by definition) and HCO_3^- than those with $PaCO_2$ ≥31 mmHg, whereas no significant difference in PaO_2 was observed between the two groups. Thirty-four patients whose $PaCO_2$ was <31 mmHg (29.8%) and 76 patients whose $PaCO_2$ was ≥31 mmHg (23.7%) were treated with invasive or non-invasive ventilation after baseline assessment; however, there was no significant difference between the two groups ($P = 0.211$).

Outcomes

The median follow-up period was 1.8 years. During the follow-up, all-cause mortality was observed in 115/435 (26.4%) patients; 70 (21.8%) and 45 (39.5%) patients with $PaCO_2$ ≥31 and <31 mmHg, respectively, died. There was a significant difference in the cumulative survival curves between the two groups (log-rank test, $P < 0.001$) (*Figure 3*). As summarized in Table 2, various forms of death were observed in patients with $PaCO_2$ <31 mmHg. The results of the Cox proportional hazards regression analysis of $PaCO_2$ for all-cause mortality are summarized in *Table 3*. In addition to the unadjusted model, the adjusted model indicated that $PaCO_2$ <31 mmHg was significantly associated with increased all-cause mortality. When $PaCO_2$ was considered a continuous variable, the lower the log-transformed $PaCO_2$, the greater the increased risk of mortality in the adjusted model [HR for mortality according to increasing $PaCO_2$, 0.71; 95% confidence interval (CI) 0.52–0.96; $P = 0.024$].

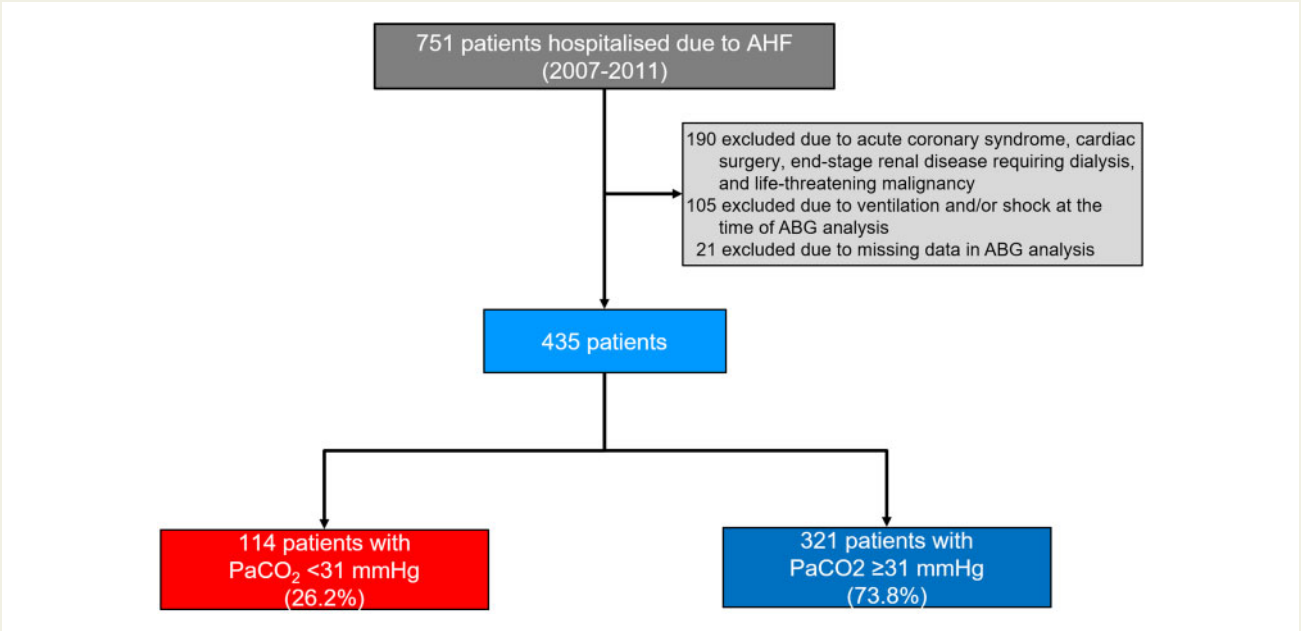

Figure 1 Flowchart of the study. Overall, 751 patients were admitted to the cardiac intensive care unit due to acute heart failure between 2007 and 2011. Among those patients, 190 who had acute coronary syndrome and/or had undergone cardiac surgery, who had had malignancy, and who were on haemodialysis were initially excluded. Furthermore, 105 patients with invasive or non-invasive ventilation, those with shock at the time of arterial blood gas analysis, and 21 patients in whom arterial blood gas analysis was not performed at admission were excluded. Finally, 435 acute heart failure patients were included and divided into two groups based on $PaCO_2$ of 31 mmHg. ABG, arterial blood gas; AHF, acute heart failure; $PaCO_2$, arterial partial pressure of carbon dioxide

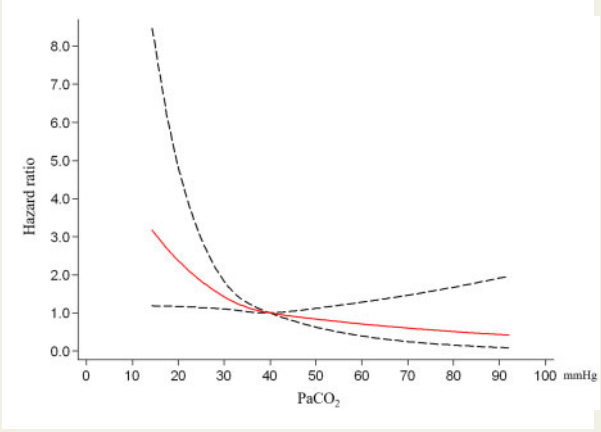

Figure 2 Three-knot cubic spline curve of hazard ratio for all-cause mortality. A three-knot cubic spline curve of the hazard ratio with $PaCO_2$ of 40 mmHg as a reference was drawn. The inflection point of this three-knot cubic spline curve was determined at $PaCO_2$ of 31 mmHg. HR, hazard ratio; $PaCO_2$, arterial partial pressure of carbon dioxide

Discussion

The findings of the present study provide several important insights into the association between ABG parameters and clinical outcomes in AHF patients. First, in our AHF patients, $PaCO_2$ of 31 mmHg was identified as a cut-off point based on the three-knot cubic spline curve of the HR. Second, the mortality risk of patients with $PaCO_2$ <31 mmHg was significantly greater than that of patients with $PaCO_2$ ≥31 mmHg, even after adjustments for confounding factors. Finally, when $PaCO_2$ was considered a continuous variable, the lower the $PaCO_2$, the greater the risk of mortality; this relationship persisted even after adjustments for confounding factors. These findings suggest that low $PaCO_2$ on admission in AHF patients can be a predictor of long-term mortality; therefore, $PaCO_2$ at admission has a prognostic value in predicting long-term outcomes in AHF patients.

Heart failure patients may have restrictive ventilatory defects that area characterized by reductions in the vital capacity resulting from the replacement of air in the lungs with blood or interstitial fluid,[12] leading to hypercapnia. Additionally, AHF patients with disturbances of consciousness are likely to have hypercapnia.[9] Exposure to high $PaCO_2$ can induce acidaemia and result in the release of endogenous catecholamines.[13] Consequently, hypercapnia induces vasoconstriction of the pulmonary arteries, which leads to impairment of the right ventricle, tachycardia, and systemic hypertension. Therefore, hypercapnia is generally avoided and has been reported to be a strong predictor of immediate airway intervention in AHF patients.[9] In contrast, hypercapnia may have beneficial roles in the pathogenesis of inflammation and tissue injury and in increasing cerebral blood flow. However, it should be noted that these may hinder the host's response to sepsis, reduce the ability to repair, and may adversely affect intracranial pressure in patients with brain injury. Additionally, differences in the cut-off point of $PaCO_2$ may have affected the results. Miñana *et al.*[10] demonstrated that hypercapnia ($PaCO_2$ >50 mmHg)

Table 1 Baseline characteristics of the patients

	$PaCO_2$		P
	≥31.0 mmHg *n* = 321	<31.0 mmHg *n* = 114	
Age (years)	70.5 ± 13.8	68.7 ± 15.1	0.255
Women, *n* (%)	109 (34.0)	40 (35.1)	0.917
BMI (kg/m^2)	23.1 ± 4.6	22.4 ± 4.2	0.170
Current smokers, *n* (%)	152 (47.4)	47 (41.2)	0.309
History of HF, *n* (%)	168 (52.3)	59 (51.8)	0.999
NYHA Class II, *n* (%)	45 (14.0)	16 (14.0)	0.405
III, *n* (%)	108 (33.6)	46 (40.4)	
IV, *n* (%)	168 (52.3)	52 (45.6)	
Ischaemic aetiology, *n* (%)	129 (40.2)	39 (34.2)	0.311
AF, *n* (%)	116 (36.1)	41 (36.0)	0.999
Diabetes, *n* (%)	130 (40.5)	40 (35.1)	0.365
Chronic pulmonary disease, *n* (%)	18 (5.6)	2 (1.8)	0.153
Systolic BP (mmHg)	137.6 ± 32.0	130.5 ± 30.0	0.050
Diastolic BP (mmHg)	76.1 ± 20.4	74.3 ± 18.7	0.428
HR (/min)	90.9 ± 26.3	99.8 ± 28.7	0.011
LVEF (%)	44.0 ± 17.2	39.5 ± 18.5	0.020
Haemoglobin (g/dL)	12.1 ± 2.5	12.2 ± 2.7	0.716
eGFR ($mL/min/1.73\ m^2$)	52.5 ± 28.6	45.2 ± 27.5	0.019
Sodium (mmol/L)	138.9 ± 4.1	136.3 ± 5.0	<0.001
Potassium (mmol/L)	4.2 ± 0.7	4.4 ± 0.8	0.026
CRP (mg/dL)	0.7 [2.5]	2.6 [6.2]	<0.001
BNP (pg/mL)	598.5 [753.5]	1065.9 [1205.8]	<0.001
Arterial blood gas			
pH	7.41 ± 0.08	7.45 ± 0.05	<0.001
PaO_2 (mmHg)	99.1 ± 42.2	93.4 ± 36.6	0.201
$PaCO_2$ (mmHg)	39.4 ± 10.6	27.4 ± 3.3	<0.001
HCO_3^- (mEq/L)	24.2 ± 3.7	19.1 ± 3.0	<0.001
Oxygen inhalation, *n* (%)	269 (83.8)	89 (78.1)	0.217
Beta-blockers, *n* (%)	99 (30.8)	31 (27.2)	0.540
ACE-Is/ARBs, *n* (%)	127 (39.6)	38 (33.3)	0.287
Aldosterone blockers, *n* (%)	47 (14.6)	15 (13.2)	0.815
Diuretics, *n* (%)	124 (38.6)	52 (45.6)	0.232

Variables are expressed as mean ± standard deviation, median [interquartile range], or *n* (%).
AF, atrial fibrillation; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; BP, blood pressure; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HCO_3^-, bicarbonate; HF, heart failure; HR, heart rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2, arterial partial pressure of oxygen.

was not associated with increased mortality in AHF patients. Thus, the prognostic importance of high $PaCO_2$ remains unclear.

The pathogenesis of low $PaCO_2$ on admission in AHF patients may vary. Anxiety, fear, and panic against symptoms related to AHF may induce hyperventilation and reduce $PaCO_2$.[14] In AHF patients, low $PaCO_2$ might be due to an increased respiratory rate in response to comorbid hypoxia, compensation for metabolic acidosis secondary to renal dysfunction, and hypoperfusion related to increased lactate levels.[15] Furthermore, it has been demonstrated that HF patients with elevated pulmonary capillary wedge pressure (PCWP), such as those with AHF, have significantly lower $PaCO_2$ than those with normal PCWP.[16] This is explained by the fact that elevated PCWP and/or pulmonary congestion induces hyperventilation and consequently, reduces $PaCO_2$[17] by stimulating pulmonary vagal afferents.[18] Irrespective of the pathogenesis, low $PaCO_2$ can result in multiple adverse effects, such as systemic arterial vasoconstriction,[14,19] cerebral vasoconstriction/hypoperfusion,[13] alterations in coronary blood flow,[20] imbalance of cellular oxygen supply and demand,[21] and pulmonary dysfunction,[13] all of which may increase all-cause mortality. It should be noted that even in AHF patients, alterations in one of the ABG parameters, low $PaCO_2$, can provide prognostic information. Indeed, this is consistent with the relationship between low $PaCO_2$ levels and poor clinical outcomes that has been demonstrated in several patient populations, such as those with brain injury,[6] those who were resuscitated from cardiac arrest,[7] and those with community-acquired pneumonia.[8] Nevertheless, to the best of our knowledge,

this study is the first to demonstrate the prognostic effects of low $PaCO_2$ on admission in AHF patients. Furthermore, the prognostic effects of low $PaCO_2$ were demonstrated in relation to all-cause mortality, including not only cardiovascular causes but also non-cardiovascular causes. This may be further proof of the idea that hypocapnia can result in multiple adverse effects and consequently be associated with various causes of death.

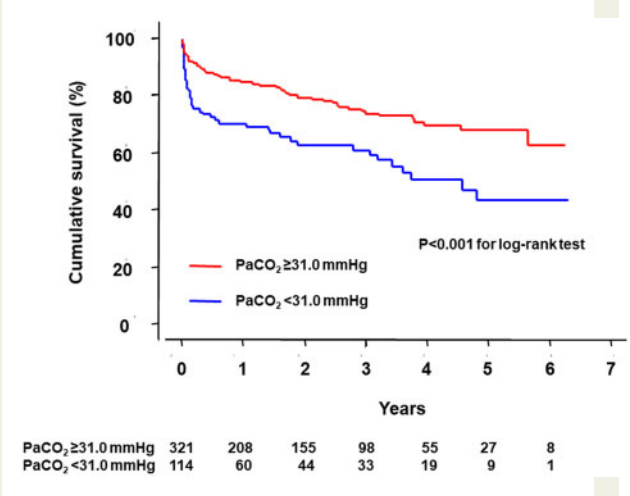

Figure 3 Cumulative survival curves for all-cause mortality. The cumulative survival curves for all-cause mortality showed significantly worse survival of patients with $PaCO_2$ <31 mmHg than that of those with $PaCO_2$ ≥31 mmHg (log-rank test: $P = 0.001$).

The findings of the present study indicate the importance of measuring CO_2 levels during the acute phase in AHF patients, even in those who do not have indications for invasive or non-invasive ventilation and who are not in shock. Therefore, since ABG analysis is an invasive procedure, less or non-invasive alternatives to measure CO_2 levels, such as venous blood gas analysis, end-tidal CO_2, or transcutaneous CO_2, should be considered. Further studies are warranted to elucidate the association between such alternative measures of CO_2 and clinical outcomes in AHF patients.

Our study had some limitations. First, it was an observational study performed at a single academic centre with a limited number of patients. Second, since the present study was observational in nature, unknown confounders may have affected the results, even after adjustments were made. Third, we did not consider the timing and duration of the changes in $PaCO_2$ because of a lack of multiple measurements of ABG analyses in most patients. Finally, relatively few patients had high $PaCO_2$ levels; indeed, the mean $PaCO_2$ in patients with $PaCO_2$ ≥31 mmHg was 39.4 mmHg. This is probably due to the exclusion of patients on invasive or non-invasive ventilation at the time of ABG assessment, which indicates that ventilation may be required immediately before ABG analysis; such patients are

Table 2 Causes of death

	$PaCO_2$	
	≥31.0 mmHg *n* = 321	<31.0 mmHg *n* = 114
All-cause death	70 (21.8)	45 (39.5)
Cardiovascular death[a]	35 (10.9)	19 (16.7)
Stroke death	1 (0.3)	2 (1.8)
Kidney disease death	1 (0.3)	5 (4.4)
Infection-related death	17 (5.3)	7 (6.1)
Cancer-related death	2 (0.6)	5 (4.4)
Miscellaneous/unknown	14 (4.4)	7 (6.1)

[a]Cardiovascular death includes death related to cardiac and aortic causes and peripheral artery disease.
$PaCO_2$, arterial partial pressure of carbon dioxide.

Table 3 Cox proportional hazard analysis of the association between $PaCO_2$ and all-cause death

	Unadjusted			Adjusted		
	HR	95% CI	*P*	HR	95% CI	*P*
$PaCO_2$ <31 mmHg	2.04	1.40–2.96	<0.001	1.71	1.05–2.79	0.032
Log-transformed $PaCO_2$	0.72	0.59–0.89	0.002	0.71	0.52–0.96	0.024

In adjusted analyses, age, sex, BMI, systolic BP, LVEF, eGFR, BNP, pH, and PaO_2 were included in addition to $PaCO_2$ <31 mmHg or log-transformed $PaCO_2$.
BMI, body mass index; BNP, B-type natriuretic peptide; BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LVEF, left ventricular ejection fraction; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2, arterial partial pressure of oxygen.

likely to have high $PaCO_2$. In addition, it should be noted that differences in the timing and duration of high $PaCO_2$ may play some roles. In the present study, there was an obvious selection bias caused by the exclusion of patients with invasive or non-invasive ventilation and those with shock at the time of ABG analysis. However, we believe that the dose–response relationship between $PaCO_2$, considered a continuous variable, and increased mortality warrants further investigation into the prognostic effects of estimating $PaCO_2$ at admission.

In conclusion, we found that the lower the $PaCO_2$ level at admission, the greater the risk of long-term all-cause mortality in AHF patients. These findings highlight the clinical importance of ABG analysis at admission in these patients. Further investigations are required to determine the effects of the timing or duration of low $PaCO_2$, and the effects of interventions to normalize $PaCO_2$ in AHF patients.

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