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Original Article

Hypocapnia and its relationship with in-hospital mortality in acute heart failure patients: Insights from the Indonesian multicenter ICCU registry

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Abstract

Acute heart failure (AHF) presents serious risks for hospitalized patients. The aim of this study was to explore the relationship between arterial partial pressure of carbon dioxide ($PaCO_2$) levels and outcomes in AHF patients admitted to the intensive cardiovascular care unit (ICCU), utilizing data from the IndONEsia ICCU Registry (One ICCU Registry). A multicenter retrospective observational study was performed covering data between August 2021–2023. Participants were categorized by $PaCO_2$ levels: hypocapnia (<35 mmHg), normocapnia (35–45 mmHg), and hypercapnia (>45 mmHg). The primary outcomes included ICCU mortality, in-hospital mortality, and 30-day mortality, whereas the length of the stays in the ICCU or hospital and ventilation requirement were set as the secondary outcomes. Mortality risks were assessed using Cox proportional hazards models. Of the 1,870 patients, 1,102 (58.96%) had hypocapnia, 645 (34.5%) had normocapnia, and 123 (6.5%) had hypercapnia. Hypocapnia patients had significantly higher ICCU, in-hospital, and at 30-day mortality rates compared to normocapnic patients (all $p<0.001$), along with longer lengths of stay in ICCU and in hospital ($p<0.001$). Hypocapnia significantly increased noninvasive and mechanical ventilation requirement compared to normocapnia patients. Multivariate analysis identified factors impacting patients' survival, including age, treatment with angiotensin-converting enzyme inhibitors (ACEi)/angiotensin II receptor blockers (ARBs) drugs, and severity scores such as the quick sequential organ failure assessment (qSOFA) and simplified acute physiology score II (SAPS II). In conclusion, hypocapnia in AHF patients could increase in-hospital, ICU and 30-days mortality rates and length of hospital stays, as well as noninvasive and mechanical ventilation requirements.

Keywords: Hypocapnia, acute heart failure, in-hospital mortality, length of stay, ICCU

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Introduction

Acute heart failure (AHF) is a critical clinical condition characterized by the sudden or progressive onset of symptoms resulting from impaired cardiac function [1,2]. This dysfunction leads to decreased cardiac output, increased ventricular filling pressures, and subsequent peripheral organ hypoperfusion, manifesting as pulmonary and/or systemic congestion [3,4]. Globally, over 26 million patients are hospitalized annually due to AHF [5]. Particularly among individuals aged 65 and older, AHF is a leading cause of sudden hospital admissions, associated with elevated morbidity, mortality, and significant healthcare costs [6]. The in-hospital mortality rate following an AHF diagnosis is approximately 10%, with one-year mortality reaching around 30% [6]. Alarmingly, 20–30% of these patients are readmitted within the first 90 days post-discharge [6].

Dyspnea emerges as the most prevalent symptom in patients hospitalized for AHF [7]. These individuals frequently experience pulmonary edema and decreased tissue perfusion, which can lead to disruptions in acid-base balance [8]. A critical factor influencing the prognosis of AHF patients is the level of arterial blood carbon dioxide (CO_2). Fluctuations in arterial blood gas (ABG) measurements, particularly the partial pressure of carbon dioxide ($PaCO_2$), have been associated with adverse clinical outcomes in various patients [9]. Indeed, ABG analysis has proven instrumental in enhancing the quality of prehospital treatment and about one-third of patients with AHF present with either hypercapnia or hypocapnia [10]. Hypercapnia, commonly observed in intensive care unit (ICU)-admitted patients experiencing AHF, is indicated when $PaCO_2$ exceeds 45 mmHg. This condition not only signifies respiratory failure but also correlates with poor prognoses across multiple clinical scenarios, including AHF [11]. Recent studies have highlighted that hypocapnia ($PaCO_2$<35 mmHg) is significantly associated with increased mortality following cardiac arrest [12,13]. A previous study demonstrated that hypocapnia serves as an independent predictor of all-cause in-hospital mortality among patients with AHF [14]. Given the clinical implications of these findings, comprehensive study on assessing the role of $PaCO_2$ on mortality rate of AHF patients in Indonesia is limited. The aim of this study was to examine the relationship between hypocapnia and mortality in AHF patients admitted to the intensive cardiovascular care unit (ICCU).

Methods

Study design, setting, sampling

A multicenter retrospective observational study was conducted on patients that were admitted to the ICCU of ten hospitals in Indonesia, which participating in the IndONEsia ICCU Registry (One ICCU Registry). The hospitals involved were National Cardiovascular Center Harapan Kita (Jakarta), Saiful Anwar General Hospital (Malang), Dr. Sardjito General Hospital (Yogyakarta), Dr. Wahidin Sudirohusodo General Hospital (Makassar), Haji Adam Malik General Hospital (Medan), Prof. Dr. I.G.N.G. Ngoerah Central General Hospital (Denpasar), Dr. M. Djamil General Hospital (Padang), Prof. Dr. R. D. Kandou General Hospital (Manado), Dr. Iskak General Hospital (Tulungagung), and Dr. Kariadi General Hospital (Semarang). Data were collected over a two-year period from August 2021–2023. The One ICCU Registry is Indonesia's first multicenter observational cohort dedicated to cardiac critical care. This registry was established to compile an epidemiological database and support a collaborative network for research into ICCU patients' outcomes. The study focused on patient demographics, clinical diagnoses, and in-hospital outcomes to assess variations and trends within critical cardiac care.

Consecutive sampling was used to enroll all ICCU admissions meeting the inclusion criteria during the study period. Patients were categorized based on arterial $PaCO_2$ levels into three groups: hypocapnia, normocapnia, and hypercapnia. Mortality during hospitalization was analyzed across these groups to evaluate the prognostic relevance of $PaCO_2$ levels in ICCU settings.

Patients

This study included patients aged over 18 years from the One ICCU Registry with a confirmed diagnosis of AHF, diagnosed using the European Society of Cardiology guidelines (2016 and

2021) [15,16]. AHF was defined by a rapid onset or worsening of heart failure, triggered by underlying cardiac issues or external factors, presenting as either a first event or an acute decompensation of chronic heart failure. Clinically, AHF was categorized as "wet" or "dry" based on fluid congestion status and as "cold" or "warm" depending on blood flow adequacy [15].

Patients with missing blood gas analysis data, renal impairment, malignancies, ventilator dependency at admission, or chronic lung diseases (e.g., emphysema, chronic bronchitis) or other acute respiratory distress conditions (e.g., pulmonary embolism, pneumothorax, COPD exacerbations, asthma, or bronchitis) were excluded from the study. To prevent bias in arterial $PaCO_2$ measurements, those requiring ventilator support at admission were excluded, although patients who required ventilator support later during hospitalization were included. Arterial $PaCO_2$ levels for the assessment of hypocapnia were collected within the first 24 hours of ICCU admission.

Data collection and variables

Data collection was conducted systematically within the first 24 hours of ICCU admission to ensure consistency and accuracy in initial assessments. To conduct a detailed and structured analysis, primary data were sourced from the One ICCU Registry in Indonesia, encompassing patient demographics, comorbid conditions, physical examinations, any other clinical diagnoses, echocardiography, laboratory indicators, treatment history, disease severity, and outcomes. Data on demographic factors included age, weight, height, gender, and body mass index (BMI). Comorbidities data included ischemic heart disease, hypertensive heart disease, pulmonary hypertension, peripheral artery disease, hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, smoking status, and cardiomyopathy.

Physical examination data included Glasgow coma scale, systolic and diastolic blood pressure, pulse rate, temperature, respiratory rate, peripheral oxygen saturation (SpO_2), fraction of inspired oxygen (FiO_2), cold acral, oliguria, and congestion. Clinical diagnoses were documented, covering acute coronary syndrome, arrhythmia, vascular and aortic emergencies, obstructive and congenital heart diseases, hemodynamic disorders, respiratory failure, post-cardiac arrest with return of spontaneous circulation (ROSC), chronic kidney disease, sepsis, shock, and various categories of ejection fraction. Transthoracic echocardiography measured the ejection fraction (EF), calculated as continuous data, utilizing the biplane Simpson's method. EF was also categorized into <40% and ≥40%.

Laboratory data comprised of hemoglobin, hematocrit, creatinine, blood creatinine levels, estimated glomerular filtration rate (eGFR), HbA1c, sodium, potassium, chloride, pH, bicarbonate, anion gap, partial pressure of oxygen (PaO_2), arterial oxygen saturation (SaO_2), arterial $PaCO_2$, and lactate levels. Based on arterial $PaCO_2$, the patients were into three groups: hypocapnia ($PaCO_2$ <35 mmHg), normocapnia ($PaCO_2$: 35–45 mmHg), and hypercapnia ($PaCO_2$ >45 mmHg). Medication usage was recorded, noting administration of angiotensin-converting enzyme inhibitors (ACEi)/angiotensin II receptor blockers (ARBs), calcium channel blockers (CCBs), beta-blockers, diuretics, nitrates, statins, aldosterone antagonists, tolvaptan, ivabradine, and insulin.

Diseases severity was measured using the quick sequential organ failure assessment (qSOFA) score, simplified acute physiology score II (SAPS II), and Glasgow coma scale (GCS). The qSOFA score, ranging from 0–3, identifies patients at high risk for adverse outcomes with scores of ≥2. The SAPS II scoring system was used to estimate mortality risk, with higher scores indicating greater predicted mortality, while the GCS score was used to assess the neurological status, with scores from 3 to 15 indicating levels of consciousness. Clinical outcomes were assessed using qSOFA score, ICCU and in-hospital mortality rates, 30-day mortality, the length of the stays in the ICCU, the length of the stays in the hospital, and the requirement for non-invasive or mechanical ventilation.

Endpoints

The study endpoints were the clinical outcomes of the patients, focusing on both primary and secondary measures. The primary outcomes were ICCU mortality, in-hospital mortality, and 30-day mortality. The secondary outcomes were the length of the stays in the ICCU, the length of the stays in the hospital, and the requirement for non-invasive or mechanical ventilation.

Statistical analysis

Categorical variables were summarized as frequencies and percentages, with group comparisons performed using the Chi-squared test or Fisher's exact test as appropriate. Continuous variables with normal distribution were reported as means ± standard deviations (SD) and analyzed using one-way analysis of variance (ANOVA).

To assess mortality differences among the three groups, the Chi-squared test was employed. The relationship between arterial $PaCO_2$ levels and in-hospital and 30-day mortality as well as length of hospital stay was analyzed using the Cox proportional hazards regression model. Significant differences among groups in survival rate were evaluated with the log-rank test. All statistical analyses were performed using SPSS Statistics version 26.0 (IBM Corporation, Armonk, USA) and STATA version 16.0 (StataCorp LLC, College Station, USA), with a significance threshold set at $p<0.05$.

Results

Characteristics of the patients

A total of 10,454 patients were admitted to the ICCU between August 2021 and August 2023, according to the One ICCU Registry (**Figure 1**). Of these, 6,823 patients were excluded due to the absence of AHF, which left 3,631 patients diagnosed with AHF. Subsequent exclusions included 1,161 patients that had no arterial $PaCO_2$ data, 134 with chronic kidney disease, 403 required mechanical ventilation at admission, three with malignancies, 32 with chronic lung disease, and 28 with other lung diseases, yielding 1,870 patients included in the final analysis. These patients were further categorized according to $PaCO_2$ levels: 645 with normocapnia, 1,102 with hypocapnia, and 123 with hypercapnia. In total, 1,461 AHF patients survived, while 409 succumbed to the condition. The final cohort consisted of 1,461 surviving patients and 409 who died (**Figure 1**).

Patients' characteristics and factors associated with arterial partial pressure of carbon dioxide ($PaCO_2$)

Demographics

The patients' characteristics of the included 1870 patients are presented in **Table 1**. Out of total patients, the median age was 58.17±12.87 years and most them were male (68.90%). The mean body weight was 58.47±10.83 kg and the average height was 161.87±6.43 cm. Most patients had a normal body mass index (60.50%), while a smaller portion were classified as obese (7.30%). The mean age, weight, height, and gender distribution were similar across the groups ($p>0.05$). However, the proportion of underweight patients was significantly higher in the hypercapnic group (12.2%) compared to the hypocapnia (3.9%) and normocapnic (4.3%) groups ($p=0.001$) (**Table 1**).

Comorbidities

Common comorbidities included hypertension (51.60%), smoker/ex-smoker (48.40%), diabetes mellitus (26.10%), and dyslipidemia (11.50%). Significant differences in comorbidities were observed between groups. Hypertensive heart disease was the most prevalent in the hypercapnic group (27.6%, $p<0.001$), as was hypertension (57.7%, $p<0.001$). Pulmonary hypertension was also more frequent in hypercapnic patients (5.7%, $p=0.016$). Diabetes mellitus occurred more commonly in the hypocapnia group (31.6%) compared to the normocapnic (25.0%) and hypercapnic groups (23.6%, $p=0.005$) (**Table 1**).

Physical examination

Key differences in clinical parameters were evident between groups. Systolic and diastolic blood pressures were significantly higher in hypercapnic patients compared to the other groups ($p<0.001$). Hypercapnic patients also had the highest respiratory rate ($p<0.001$) and required greater oxygen supplementation, as indicated by their higher FiO_2 ($p<0.001$) (**Table 1**).

Clinical conditions

Differences in clinical conditions included a higher prevalence of respiratory failure in the hypercapnic group (14.6%, $p<0.001$) and a greater incidence of acute coronary syndrome in the

normocapnic group (61.4%, p<0.001). Arrhythmia was more common in the hypocapnia and hypercapnic groups (p=0.021) and hemodynamic disorders were more prevalent in hypercapnic patients (17.1%, p=0.007) (**Table 1**).

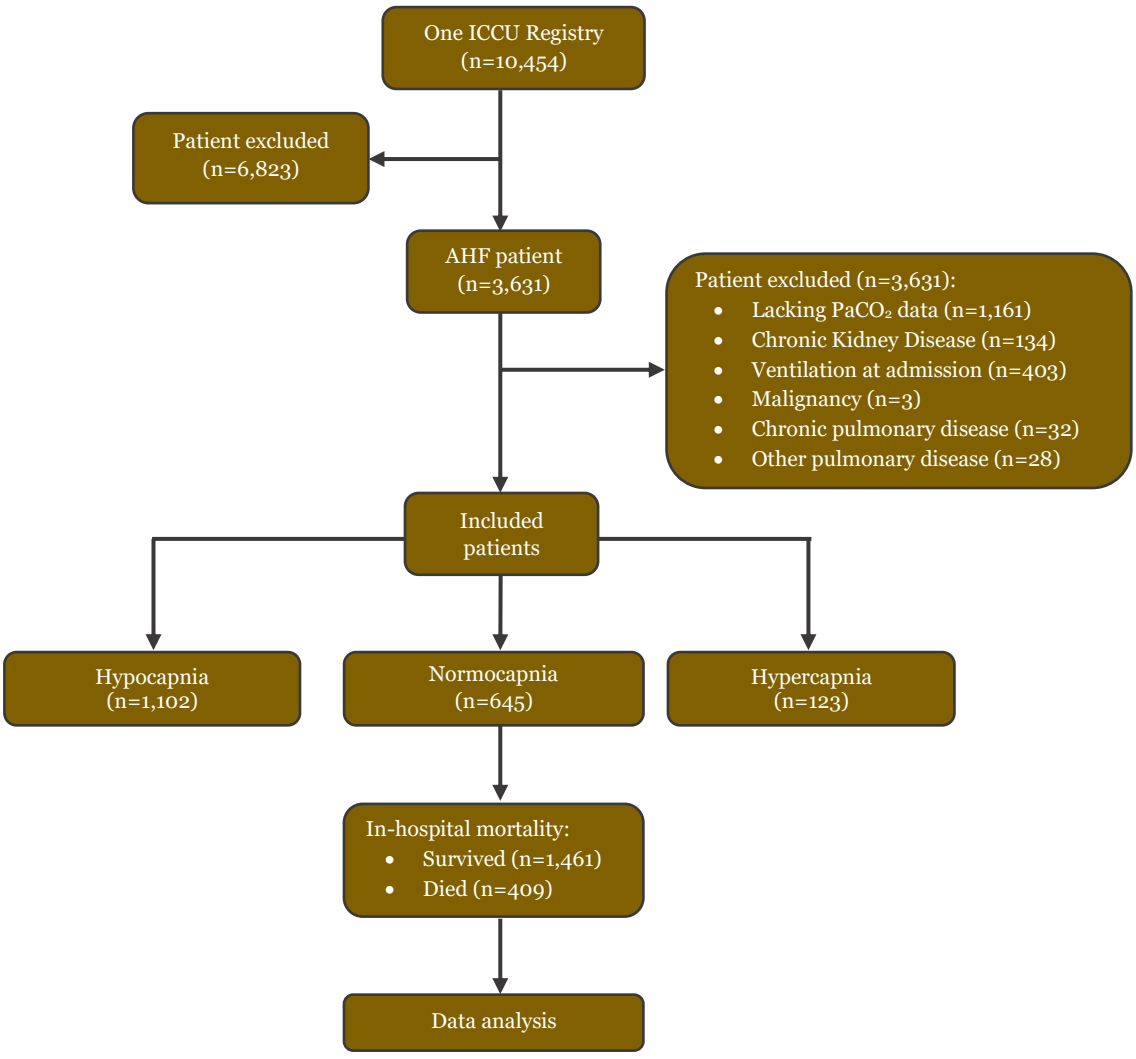

Figure 1. Flowchart of the acute heart failure (AHF) patients' selection process.

Laboratory findings

Hypercapnic patients had notable laboratory abnormalities, including elevated bicarbonate levels (p<0.001) and reduced arterial oxygen saturation (p<0.001). The mean of potassium level was lower in the hypercapnic group (p<0.001), while the mean of sodium level was highest in the normocapnic and hypercapnic groups (p<0.001). The eGFR was significantly higher in hypercapnic patients (p<0.001) (**Table 1**).

Treatments

Therapeutic strategies varied significantly between groups. Statin use was least common in the hypercapnic group (59.3%) compared to the hypocapnia group (p<0.001), while beta blocker therapy was most frequent in the normocapnic group (p<0.001). Diuretic therapy with continuous intravenous administration was most commonly used in hypercapnic patients (p<0.001). Aldosterone antagonist use was higher in normocapnic (40.0%) and hypercapnic (40.7%) groups compared to the hypocapnia group (32.3%, p=0.002) (**Table 1**).

Disease severity

Patients in the hypercapnic group were more likely to have a qSOFA score ≥2 (p<0.001), while the hypocapnia group demonstrated significantly higher SAPS II scores (p<0.001), reflecting greater disease severity in these groups (**Table 1**).

Table 1. Comparison of acute heart failure (AHF) patients' characteristics with hypocapnia vs normocapnia vs hypercapnia

Domain	Variables	Total (n=1,870)	$PaCO_2$ status, n (%)			*p*-value
			$PaCO_2$ <35 mmHg (n=1,102)	$PaCO_2$ 35–45 mmHg (n=645)	$PaCO_2$ >45 mmHg (n=123)	
Demographic	Age (years), mean±SD	58.17±12.87	58.21±12.56	57.71±13.42	60.24±12.56	0.134
	Weight (kg), mean±SD	63.58±12.77	63.48±12.44	63.79±12.79	63.48±15.40	0.885
	Height (cm), mean±SD	161.83±7.21	161.76±7.25	162.13±7.07	160.85±7.50	0.175
	Gender					0.110
	Male	1,289 (68.90)	759 (68.90)	455 (70.50)	75 (61.00)	
	Female	581 (31.10)	343 (31.10)	190 (29.50)	48 (39.00)	
	Body mass index					0.001**
	Underweight	86 (4.60)	43 (3.90)	28 (4.30)	15 (12.20)	
	Normal	1,132 (60.50)	683 (62.00)	390 (60.50)	59 (48.00)	
	Overweight	516 (27.60)	303 (27.50)	178 (27.60)	35 (28.50)	
	Obese	136 (7.30)	73 (6.60)	49 (7.60)	14 (11.40)	
Comorbidities	Ischemic heart disease	121 (6.50)	81 (7.40)	29 (4.50)	11 (8.90)	0.033*
	Hypertensive heart disease	277 (14.80)	167 (15.20)	76 (11.80)	34 (27.60)	<0.001**
	Pulmonary hypertension	41 (2.20)	24 (2.20)	10 (1.60)	7 (5.70)	0.016*
	Peripheral artery disease	15 (0.80)	11 (1.00)	2 (0.30)	2 (1.60)	0.170
	Hypertension	964 (51.60)	523 (47.50)	370 (57.40)	71 (57.70)	<0.001**
	Diabetes mellitus	538 (28.80)	348 (31.60)	161 (25.00)	29 (23.60)	0.005**
	Dyslipidaemia	215 (11.50)	140 (12.70)	62 (9.60)	13 (10.60)	0.140
	Chronic kidney disease	185 (9.90)	100 (9.10)	76 (11.80)	9 (7.30)	0.115
	Smokers/ex-smoker	906 (48.40)	536 (48.60)	320 (49.60)	50 (40.70)	0.186
	Cardiomyopathy	42 (2.20)	28 (2.50)	12 (1.90)	2 (1.60)	0.580
Physical examination	Glasgow coma scale, mean±SD	14.89±0.784	14.88±0.841	14.93±0.545	14.74±1.200	0.033*
	Systolic blood pressure (mmHg), mean±SD	122.62±32.87	118.08±31.41	128.27±32.96	133.59±37.83	<0.001**
	Diastolic blood pressure (mmHg), mean±SD	75.85±18.74	73.38±18.37	79.08±18.11	80.98±21.54	<0.001**
	Pulse rate (bpm), mean±SD	97.68±25.48	97.72±26.73	97.30±23.88	99.41±22.03	0.700
	Temperature (Celsius), mean±SD	36.49±0.38	36.48±0.40	36.50±0.34	36.54±0.43	0.129
	Respiratory rate (tpm), mean±SD	24.29±4.92	24.44±5.02	23.76±4.61	25.64±5.30	<0.001**
	Oxygen peripheral saturation (SpO_2) (%), mean±SD	97.47±4.05	97.61±3.55	97.33±4.58	96.92±5.11	0.112
	Fraction of oxygen (FiO_2) (%), mean±SD	43.20±24.54	44.01±24.71	39.48±22.69	55.48±27.75	<0.001**
	Cold acral	144 (7.70)	102 (9.30)	34 (5.30)	8 (6.50)	0.009**
	Oliguria	157 (8.40)	84 (7.60)	61 (9.50)	12 (9.80)	0.350
	Congestion	1,253 (67.00)	731 (66.30)	426 (66.00)	96 (78.00)	0.026*
Clinical condition	Acute coronary syndrome	1,054 (56.40)	616 (55.90)	396 (61.40)	42 (34.10)	<0.001**
	Arrhythmia	539 (28.80)	341 (30.90)	160 (24.80)	38 (30.90)	0.021*
	Vascular emergency	63 (3.40)	46 (4.20)	12 (1.90)	5 (4.10)	0.032*

Domain	Variables	Total (n=1,870)	$PaCO_2$ status, n (%)			*p*-value
			$PaCO_2$ <35 mmHg (n=1,102)	$PaCO_2$ 35–45 mmHg (n=645)	$PaCO_2$ >45 mmHg (n=123)	
	Aortic emergency	27 (1.40)	8 (0.70)	19 (2.90)	0 0.00	0.716
	Obstructive heart disease	52 (2.80)	32 (2.90)	18 (2.80)	2 (1.60)	0.010*
	Congenital heart Disease	26 (1.40)	8 (0.70)	16 (2.50)	2 (1.60)	0.007**
	Hemodynamic disorders	255 (13.60)	168 (15.20)	66 (10.20)	21 (17.10)	0.007**
	Respiratory failure	81 (4.30)	43 (3.90)	20 (3.10)	18 (14.60)	<0.001**
	ROSC after cardiac arrest	66 (3.50)	44 (4.00)	18 (2.80)	4 (3.30)	0.416
	Chronic kidney disease	341 (18.20)	226 (20.50)	107 (16.60)	8 (6.50)	<0.001**
	Sepsis	416 (22.20)	301 (27.30)	86 (13.30)	29 (23.60)	<0.001**
	Shock	882 (47.20)	604 (54.80)	226 (35.00)	52 (42.30)	<0.001**
Echocardiography	Ejection fraction (%), mean±SD	33.54±17.32	33.18±17.21	33.90±17.49	34.85±17.35	0.483
	Ejection fraction (category)					0.723
	EF <40%	1,199 (64.10)	714 (64.80)	409 (63.40)	76 (61.80)	
	EF ≥40%	671 (35.90)	388 (35.20)	236 (36.60)	47 (38.20)	
Laboratory findings	Haemoglobin (g/dL), mean±SD	12.56±2.43	12.54±2.43	12.53±2.45	12.92±2.26	0.225
	Haematocrit (%), mean±SD	38.00±7.16	37.80±7.25	37.98±6.99	39.94±7.10	0.007**
	Creatinine (mg/dL), mean±SD	30.83±35.78	29.87±33.36	32.50±39.07	30.67±38.60	0.335
	eGFR (mL/min), mean±SD	54.47±30.75	50.15±28.30	59.98±32.77	64.26±34.13	<0.001**
	HbA1c (%), mean±SD	6.28±0.61	6.27±0.55	6.27±0.69	6.29±0.71	0.951
	Natrium (Na^+) (mEq/L), mean±SD	134.59±6.30	133.93±6.26	135.47±6.22	135.84±6.42	<0.001**
	Potassium (K^+) (mEq/L), mean±SD	4.27±0.84	4.35±0.85	4.18±0.79	3.98±0.84	<0.001**
	Chloride (Cl) (mEq/L), mean±SD	101.11±6.91	101.48±6.68	101.06±6.86	98.07±8.28	<0.001**
	pH, mean±SD	7.31±0.69	7.37±0.39	7.22±1.05	7.29±0.23	<0.001**
	Bicarbonate (mEq/L), mean±SD	23.30±8.39	21.89±8.47	24.52±7.32	29.51±9.10	<0.001**
	Anion gap (mEq/L), mean±SD	19.47±18.42	16.13±12.05	27.60±24.63	6.67±8.34	<0.001**
	Partial pressure of oxygen (PaO_2) (mmHg), mean±SD	128.82±51.98	130.83±50.52	129.01±52.46	109.89±58.56	<0.001**
	Oxygen saturation in the arteries (SaO_2) (%), mean±SD	96.47±7.72	97.27±5.38	96.42±7.67	89.61±16.96	<0.001**
	Lactate (mmol/L), mean±SD	4.42±3.60	4.51±3.90	4.33±2.98	4.18±3.76	0.028*
Treatment	ACEi/ARB	1,197 (64.00)	662 (60.10)	452 (70.10)	83 (67.50)	<0.001**
	CCB					<0.001**
	Continuous intravenous	5 (0.30)	2 (0.20)	3 (0.50)	0 (0.00)	
	Continuous intravenous and oral	6 (0.30)	2 (0.20)	4 (0.60)	0 (0.00)	
	Oral	177 (9.50)	74 (6.70)	79 (12.20)	24 (19.50)	
	Beta blocker	574 (30.70)	258 (23.40)	292 (45.30)	24 (19.50)	<0.001**
	Diuretic					<0.001**
	Intravenous (periodic bolus)	686 (36.70)	431 (39.10)	214 (33.20)	41 (33.30)	
	Intravenous (continuous)	638 (34.10)	390 (35.40)	186 (28.80)	62 (50.40)	
	Oral	63 (3.40)	26 (2.40)	36 (5.60)	1 (0.80)	

Domain	Variables	Total (n=1,870)	$PaCO_2$ status, n (%)			*p*-value
			$PaCO_2$ <35 mmHg (n=1,102)	$PaCO_2$ 35–45 mmHg (n=645)	$PaCO_2$ >45 mmHg (n=123)	
	Nitrate					<0.001**
	Continuous intravenous	304 (16.30)	167 (15.20)	101 (15.70)	36 (29.30)	
	Continuous intravenous and oral	77 (4.10)	46 (4.20)	26 (4.00)	5 (4.10)	
	Oral	369 (19.70)	174 (15.80)	181 (28.10)	14 (11.40)	
	Statin	1,436 (76.80)	875 (79.40)	488 (75.70)	73 (59.30)	<0.001**
	Aldosterone antagonist	664 (35.50)	356 (32.30)	258 (40.00)	50 (40.70)	0.002**
	Tolvaptan	9 (0.50)	4 (0.40)	3 (0.50)	2 (1.60)	0.158
	Ivabradine	16 (0.90)	14 (1.30)	0 0.00	2 (1.60)	0.013*
	Insulin					<0.001**
	Intravenous	172 (9.20)	134 (12.20)	30 (4.70)	8 (6.50)	
	Subcutaneous	218 (11.70)	124 (11.30)	76 (11.80)	18 (14.60)	
Severity	qSOFA ≥2	145 (7.80)	91 (8.30)	34 (5.30)	20 (16.30)	<0.001**
	SAPS II, mean±SD	47.63±9.14	48.80±9.42	45.70±7.95	47.21±10.70	<0.001**
Primary outcomes	ICCU mortality					<0.001**
	Alive	1,551 (82.90)	881 (79.90)	573 (88.80)	97 (78.90)	
	Passed away	319 (17.10)	221 (20.10)	72 (11.20)	26 (21.10)	
	In-hospital mortality					<0.001**
	Alive	1,461 (78.10)	811 (73.60)	556 (86.20)	94 (76.40)	
	Passed away	409 (21.90)	291 (26.40)	89 (13.80)	29 (23.60)	
	30-day mortality					<0.001**
	Alive	1,139 (60.90)	632 (57.40)	444 (68.80)	63 (51.20)	
	Passed away	731 (39.10)	470 (42.60)	201 (31.20)	60 (48.80)	
Secondary outcomes	Length of stay ICCU (days), mean±SD	4.52±3.71	4.79±4.02	4.04±2.97	4.64±4.04	<0.001**
	Length of stay in-hospital (days), mean±SD	8.15±6.49	8.60±6.46	7.29±6.51	8.63±6.20	<0.001**
	Non-invasive ventilation	29 (1.60)	22 (2.00)	5 (0.80)	2 (1.60)	0.137
	Mechanical ventilation	142 (7.60)	101 (9.20)	34 (5.30)	7 (5.70)	0.001**

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; CCB: calcium channel blocker; EF: ejection fraction; eGFR: estimated glomerular filtration rate; ICCU: intensive cardiovascular care unit; $PaCO_2$: partial pressure of carbon dioxide; qSOFA: quick sequential organ failure assessment; ROSC: return of spontaneous circulation; SAPS II: simplified acute physiology score II; SD: standard deviation

*Statistically significant at p=0.05

**Statistically significant at p=0.01

Primary outcomes

The mortality outcomes in AHF patients significantly varied across the three $PaCO_2$ categories. Patients with hypocapnia had the high mortality rates across all three primary outcomes, including ICCU mortality (20.1%), in-hospital mortality (26.4%), and 30-day mortality (42.6%). Hypercapnic patients had similar mortality rates, with ICCU, in-hospital, and 30-day mortality at 21.1%, 23.6%, and 48.8%, respectively. In contrast, normocapnic patients had the lowest mortality rates, with 11.2% for ICCU mortality, 13.8% for in-hospital mortality, and 31.2% for 30-day mortality. Chi-squared test for the ICCU, in-hospital, and 30-day mortality showed mortality differences between the three groups in (p<0.001) (**Table 1**).

The pairwise Chi-squared analysis confirmed that hypocapnia had significantly higher ICCU, in-hospital, and 30-day mortality compared to normocapnic patients (all had p<0.001) (**Figure 2**). Hypercapnic patients also had significantly higher ICCU, in-hospital, and 30-day mortality rates compared normocapnic patients (p=0.002, p=0.006, and p<0.001, respectively). However, the difference between hypocapnia and hypercapnic patients was not significant for ICCU, in-hospital, and 30-day mortality outcomes (**Figure 2**).

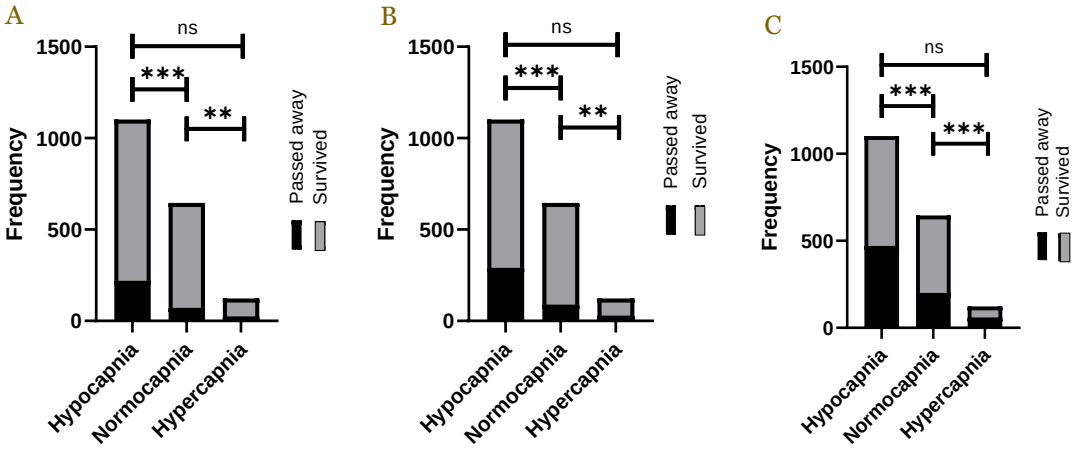

Figure 2. Comparisons of mortality rate between different arterial partial pressure of carbon dioxide ($PaCO_2$) groups: (A) intensive cardiovascular care unit (ICCU) mortality; (B) in-hospital mortality; (C) 30-day mortality. Ns: not significant; **significant at p<0.01; ***significant p<0.001.

Multivariate analysis factor associated with ICCU mortality

The results of a multivariate regression analysis, examining risk factors associated with ICCU mortality, are presented in **Table 2**. Ischemic heart disease showed a significant association with increased mortality (hazard ratio (HR): 2.198, p=0.022), as well as obstructive heart disease (HR: 5.606, p<0.001) and respiratory failure (HR: 3.537, p=0.003). Acute coronary syndrome (HR: 1.880, p=0.007) and shock (HR: 3.236, p<0.001) were also strongly linked to higher mortality risk.

Protective factors included smoking history (HR: 0.485, p=0.001) and beta-blocker treatment (HR: 0.566, p=0.029). Laboratory values revealed significant associations, with higher creatinine levels (HR: 0.989, p=0.002) and PaO_2 (HR: 0.996, p=0.045) indicating reduced risk. Conversely, anion gap (HR: 1.019, p=0.005) was associated with increased mortality.

Interventions such as non-invasive ventilation (HR: 8.241, p=0.002) and mechanical ventilation (HR: 22.407, p<0.001) were linked to highly increased mortality. Disease severity scores, including qSOFA ≥2 (HR: 0.0247, p<0.001) and SAPS II (HR: 1.087, p<0.001) were associated with decreased and increased ICCU mortality, respectively. $PaCO_2$ levels between 35–45 mmHg showed a protective effect (HR: 0.245, p=0.004).

Table 2. Multivariate regression analysis of risk factors associated with ICCU mortality

Variables	β	HR	Wald	p-value
Ischemic heart disease	0.788	2.198	5.246	0.022
Smoker/ex-smoker	-0.724	0.485	10.315	0.001
Acute coronary syndrome	0.631	1.880	7.271	0.007

Variables	β	HR	Wald	*p*-value
Aortic emergency	-3.271	0.038	5.538	0.019
Obstructive heart disease	1.724	5.606	13.316	<0.001
Respiratory failure	1.263	3.537	8.906	0.003
Shock	1.174	3.236	31.879	<0.001
Systolic blood pressure	-0.012	0.988	4.459	0.035
Diastolic blood pressure	0.023	1.023	5.413	0.020
Oliguria	0.648	1.912	4.542	0.033
Ejection fraction <40%	1.102	3.011	7.419	0.006
Creatinine	-0.011	0.989	9.699	0.002
Anion gap	0.019	1.019	7.837	0.005
PaO2	-0.004	0.996	4.023	0.045
ACEi/ARB treatment	-0.792	0.453	13.047	<0.001
Beta-blocker treatment	-0.570	0.566	4.782	0.029
Continuous intravenous and oral CCB	3.694	40.207	7.918	0.005
Length of stay in ICCU	0.175	1.192	25.774	<0.001
Length of stay in hospital	-0.255	0.775	81.758	<0.001
Non-invasive ventilation	2.109	8.241	9.659	0.002
Mechanical ventilation	3.109	22.407	67.839	<0.001
qSOFA ≥2	-1.397	0.247	14.630	<0.001
SAPS II	0.084	1.087	40.676	<0.001

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; CCB: calcium channel blocker; ICCU: intensive cardiovascular care unit; HR: hazard ratio; qSOFA: quick sequential organ failure assessment; SAPS II: simplified acute physiology score II

Multivariate analysis factor associated with in-hospital mortality

In the multivariate Cox regression analysis that is presented in **Table 3**, several variables demonstrated significant associations with in-hospital mortality among patients. Age was inversely associated with mortality (HR: 0.921, $p<0.001$), indicating a slight decrease in risk per year increase. In terms of disease history, obstructive heart disease presented a protective effect (HR: 0.444, $p<0.001$), as well as the presence of shock (HR: 0.532, $p<0.001$). Among laboratory values, higher creatinine levels showed a marginal decrease in mortality risk (HR: 0.994, $p<0.001$), while chloride levels were also inversely associated with mortality (HR: 0.978, $p=0.001$).

The use of ACEi/ARB medications showed a stronger association with increased mortality risk (HR: 1.716, $p<0.001$). Interventions, including non-invasive ventilation (HR: 0.266, $p<0.001$) and mechanical ventilation (HR: 0.268, $p<0.001$), were all significantly associated with decreased mortality. Lastly, higher scores on the qSOFA ≥2 (HR: 1.958, $p<0.001$) and SAPS II (HR: 1.045, $p<0.001$) scales were associated with increased in-hospital mortality risk, underscoring the impact of disease severity on outcomes (**Table 4**).

Table 3. Multivariate Cox regression analysis of risk factors associated with in-hospital mortality

Variables	β	HR	Wald	*p*-value
Age	-0.082	0.921	321.697	<0.001
Obstructive heart disease	-0.811	0.444	12.806	<0.001
Shock	-0.631	0.532	33.009	<0.001
Creatinine	-0.006	0.994	14.113	<0.001
Chloride	-0.022	0.978	11.300	0.001
ACEi/ARB treatment	0.540	1.716	25.055	<0.001
Non-invasive ventilation	-1.323	0.266	39.240	<0.001
Mechanical ventilation	-1.315	0.268	95.180	<0.001
qSOFA ≥2	0.672	1.958	24.036	<0.001
SAPS II	0.044	1.045	58.516	<0.001

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; HR: hazard ratio; qSOFA: quick sequential organ failure assessment; SAPS II: simplified acute physiology score II

Multivariate analysis factor associated with 30-day mortality

In the multivariate Cox regression analysis examining risk factors for 30-day mortality, presented in **Table 5**, several significant associations were identified. Age showed an inverse relationship with mortality (HR: 0.927, $p<0.001$), suggesting a reduced risk per year increase. Peripheral artery disease also had a protective effect (HR: 0.497, $p=0.025$), while pulmonary hypertension (HR: 1.908, $p=0.014$) and rheumatic heart disease (HR: 2.132, $p=0.005$) were associated with higher mortality risk. Sepsis was associated with a modestly increased mortality risk (HR: 1.228,

p=0.046), whereas shock showed a protective effect (HR: 0.708, p<0.001). Among laboratory values, elevated creatinine (HR: 0.994, p<0.001), chloride (HR: 0.966, p<0.001), anion gap (HR: 0.988, p<0.001), and lactate (HR: 0.973, p=0.032) were associated with reduced mortality risk, while higher sodium levels increased mortality risk (HR: 1.024, p=0.002).

Regarding medications, beta-blocker use (HR: 1.731, p<0.001) and aldosterone antagonists (HR: 1.753, p<0.001) were associated with higher mortality. Supportive interventions, including non-invasive ventilation (HR: 0.502, p=0.001) and mechanical ventilation (HR: 0.388, p<0.001), were strongly associated with lower mortality risk. Lastly, qSOFA scores (HR: 0.651, p=0.002) were protective, whereas higher SAPS II scores (HR: 1.028, p<0.001) indicated an increased mortality risk, highlighting the impact of clinical severity on patient outcomes (**Table 5**).

Table 4. Multivariate Cox regression analysis of risk factors associated with 30-day mortality

Variable	β	HR	Wald	*p*-value
Age	-0.075	0.927	448.773	<0.001
Peripheral artery disease	-0.699	0.497	4.994	0.025
Pulmonary hypertension	0.646	1.908	6.011	0.014
Rheumatic heart disease	0.757	2.132	7.840	0.005
Sepsis	0.205	1.228	3.985	0.046
Shock	-0.346	0.708	19.044	<0.001
Creatinine	-0.006	0.994	21.661	<0.001
Sodium (Na^+)	0.024	1.024	9.969	0.002
Chloride (Cl^-)	-0.034	0.966	25.906	<0.001
Anion gap	-0.012	0.988	18.750	<0.001
Lactate	-0.028	0.973	4.601	0.032
Beta-blocker	0.549	1.731	27.192	<0.001
Antagonist aldosterone	0.562	1.753	36.090	<0.001
Non-invasive ventilation	-0.690	0.502	11.719	0.001
Mechanical ventilation	-0.947	0.388	78.675	<0.001
qSOFA ≥2	-0.429	0.651	9.567	0.002
SAPS II	0.027	1.028	36.282	<0.001

HR: hazard ratio; qSOFA: quick sequential organ failure assessment; SAPS II: simplified acute physiology score II

Secondary outcomes

Secondary outcomes included length of stay and ventilation requirement outcomes. The results of the post-hoc analysis showed that AHF patients with hypocapnia had a significantly longer length of stay in both ICCU and the hospital compared to those with normocapnia (p<0.001). However, no significant differences for ICCU and in-hospital length of stay were observed between the normocapnic and hypercapnic groups (p=0.224 and p=0.088, respectively) or hypocapnia and hypercapnic groups (p=0.904 and p=0.999, respectively) (**Figure 3**). In addition, the hypocapnia group had significantly higher non-invasive and mechanical ventilation compared to normocapnic group (p=0.046 and p=0.003, respectively).

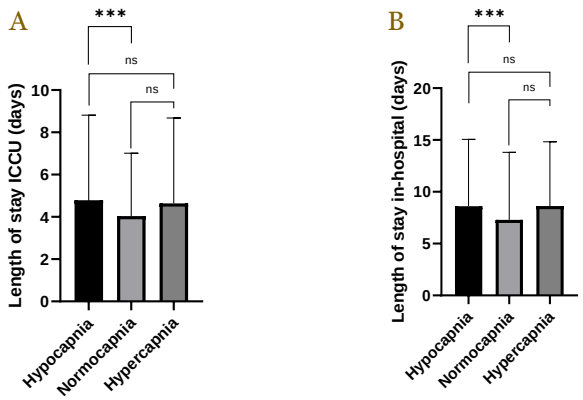

Figure 3. Comparisons of length of stay in (A) intensive cardiovascular care unit (ICCU) and (B) hospital outcomes among acute heart failure (AHF) patients with different arterial partial pressure of carbon dioxide ($PaCO_2$) groups. Ns: not significant; ***significant at p<0.001.

Discussion

The aim of this study was to investigate the relationship between $PaCO_2$ levels and mortality outcomes in patients with AHF admitted to ICCU in Indonesia. The main findings revealed that patients with hypocapnia ($PaCO_2$ <35 mmHg) experienced significantly higher rates of ICCU, in-hospital, and 30-day mortality compared to those with normocapnia ($PaCO_2$ 35–45 mmHg) or hypercapnia ($PaCO_2$ >45 mmHg). Additionally, hypocapnia patients had longer lengths of stay in both the ICCU and the hospital. Multivariate analysis identified several factors independently associated with mortality, including age, qSOFA and SAPS II scores, and specific treatments and clinical conditions.

AHF is frequently the result of a considerable reduction in tissue perfusion. This can lead to tissue hypoxia, which in turn triggers hyperventilation to increase oxygenation. Hyperventilation can cause a reduction in blood CO_2 levels, known as hypocapnia [14]. Hypocapnia can lead to changes in acid-base balance because CO_2 plays a key role as a primary buffer in regulating blood pH [17].

Analysis of patient profiles by $PaCO_2$ revealed no significant differences in gender, age, weight, or height across the $PaCO_2$ groups, indicating similar demographics regardless of $PaCO_2$ variations. However, BMI significantly differed among groups (p=0.001), with patients having $PaCO_2$ >45 mmHg tend to have poorer nutritional statis, specifically overweight and obesity. Higher BMI is often associated with CO_2 retention (hypercapnia), while lower BMI correlated with reduced CO_2 levels (hypocapnia) [18].

A previous study identified hypocapnia as an independent predictor of in-hospital mortality in AHF patients, associating lower $PaCO_2$ levels with deteriorating heart and kidney function. Correcting hypocapnia promptly may improve short-term outcomes for these patients, highlighting the need for continuous monitoring during hospitalization [14]. Established risk scores like MEESSI, ADHERE, and GWTG-HF focus on predicting in-hospital mortality and long-term prognosis in AHF patients, emphasizing factors like age, hyponatremia, tissue hypoperfusion, and low SBP [19]. However, the role of hypocapnia remains less understood, though it is linked to poor outcomes in mechanically ventilated patients, increasing risks such as impaired tissue perfusion and peripheral vasoconstriction [20-22]. $PaCO_2$ below 35 mmHg is also associated with poorer outcomes with in cardiogenic pulmonary edema patients. Factors like acute comorbidities, multi-organ dysfunction, and pulmonary congestion contribute to hypocapnia in AHF, correlating with worse kidney function and potentially exacerbating myocardial stiffness and dysfunction [23,24].

Several factors contribute to the development of hypocapnia in patients with AHF. First, acute comorbidities like pulmonary embolism, pneumothorax, pneumonia, and asthma can lead to tachypnea and reduced carbon dioxide levels. Second, multi-organ dysfunction in AHF, characterized by increased heart filling pressures and pulmonary congestion, stimulates the vagus nerve, resulting in hyperventilation and hypocapnia. Additionally, conditions such as pleural effusion, vascular disease, and chronic kidney failure can contribute to hypocapnia due to impaired tissue perfusion, compensatory carbon dioxide reduction, and restricted lung expansion [12]. This study specifically excluded patients with active lung diseases. Findings revealed that patients with lower $PaCO_2$ levels had a higher prevalence of chronic kidney disease, with no significant differences in pulmonary embolism or pleural effusion among the $PaCO_2$ level groups. The analysis showed that lower $PaCO_2$ levels were linked to worse kidney function (20.50%, p<0.000), suggesting an association between lower $PaCO_2$ and poorer kidney and heart function in AHF patients. Moreover, lower $PaCO_2$ can lead to adverse effects, including increased coronary flow resistance, metabolic remodeling, and deterioration of myocardial energy homeostasis, contributing to myocardial stiffness and a detrimental cycle of myocardial dysfunction [14].

This study identifies several independent predictors of in-hospital mortality in AHF patients, including older age, increased heart rate, reduced SBP, prolonged disease duration, lower serum sodium, and elevated BNP and lactate levels. However, eGFR was not an independent predictor, diverging from prior research—a difference possibly due to eGFR categorization at a threshold of 60 mL/min/1.73 m^2, as highlighted by studies reported that heart failure patients with hypocapnia have poor long-term outcomes, with hypoperfusion being a key factor [19,25]. Dyspnea, a common symptom in AHF, complicates diagnosis due to its complex causes and the

lack of objective metrics. In AHF, dyspnea may be linked to hyperventilation, marked by increased respiratory rate or tidal volume, but also influenced by the subjective sense of poor inspiration, often due to respiratory muscle weakness or lung hyperinflation. Clinicians often fail to measure respiratory rate and tidal volume accurately in AHF patients, underlining the need for objective ventilation assessment. Hyperventilation is thought to worsen heart failure by causing further physiological disruptions [26-28]. Notably, patients with low $PaCO_2$ had significantly higher lactate levels (p=0.028), suggesting tissue hypoperfusion and anaerobic metabolism [17].

This study suggested that patients with abnormal $PaCO_2$ levels, either hypocapnia or hypercapnia, tend to have longer ICCU and hospital stays, likely due to more severe illness and tissue hypoperfusion. In contrast, patients with normal $PaCO_2$ (35–45 mmHg) have shorter stays, indicating a more stable condition and quicker recovery. These results supported that hypocapnia is linked to longer ICU stays and higher mortality rates compared to normocapnia and hypercapnia. Hypocapnia, often linked to respiratory alkalosis, can cause cerebral vasoconstriction and ischemia, worsening ICU outcomes, while normal $PaCO_2$ levels appear to support more stable clinical outcomes and reduced complication risks [12,29]. Although mild hypercapnia did not significantly affect mortality, hypocapnia was associated with a longer ICU stay and increased risk of complications, especially in patients with chronic heart disease [30]. Abnormal $PaCO_2$ disrupts oxygen transport and can lead to complications, including prolonged ventilator use [31]. Based on this study, patients with hypocapnia ($PaCO_2$ <35 mmHg) showed higher mortality rates both during and after hospitalization due to associations with hypoxia and metabolic disorders. In contrast, hypercapnia ($PaCO_2$ >45 mmHg) may indicate better compensatory responses, especially in acute respiratory acidosis, resulting in lower ICCU mortality.

Additionally, higher values in the qSOFA and SAPS II scores were linked to a higher risk of mortality [32]. Furthermore, elevated qSOFA and SAPS II scores correlated with higher mortality rates in the intensive care unit, supporting other studies that highlighted the impact of these predictive scores on ICU patient mortality [12]. High qSOFA scores upon hospital admission were also associated with poorer clinical outcomes, including death or re-hospitalization due to heart failure symptoms [30]. These findings underscore the utility of qSOFA as a tool for identifying heart failure patients at high risk for adverse clinical outcomes, reaffirming its effectiveness as a mortality predictor in AHF patients in this study.

This study found that hypocapnia, characterized by low $PaCO_2$, was strongly linked to mortality in AHF patients in the ICCU. Although the ROC curve showed limited predictive ability of $PaCO_2$ for mortality, these results emphasize the importance of $PaCO_2$ monitoring as an additional indicator in patient management. The clinical implication is that close monitoring of $PaCO_2$ may aid in risk stratification and therapeutic decision-making, allowing for more timely interventions and tailored management strategies to reduce mortality. Application of these results may increase attention to correction of ventilatory disorders and better respiratory management in patients with AHF.

This study has several key strengths, notably its use of data from a large multicenter registry, which boosts statistical power and enables a comprehensive analysis of various clinical and laboratory factors associated with mortality in patients with AHF. The analysis includes a broad range of variables, including $PaCO_2$ levels, qSOFA, and SAPS II, providing valuable insights into the predictors of mortality. However, there are several limitations to consider. First, the exclusion of AHF patients without ABG analysis or $PaCO_2$ data may have led to selection bias. Second, although ABG records were collected within 24 hours of ICU admission, the timing of these analyses varied among individuals, and there was no information on the duration of abnormal $PaCO_2$ levels. This lack of data prevents an assessment of whether extended periods of abnormal levels impact mortality in AHF patients. Third, despite the application of multivariate regression analysis to adjust for confounding variables, considerable heterogeneity was observed among critically ill patients, indicating the potential influence of unrecognized factors on the outcomes. Finally, all area under the curve (AUC) values were below 0.5, suggesting that $PaCO_2$ has limited predictive power for predicting in-hospital and 30-day mortality. This underscores the necessity for additional research aimed at improving the sensitivity and specificity of mortality prediction tools for AHF patients.

Conclusion

Abnormal arterial $PaCO_2$ levels, particularly hypocapnia, are linked to longer ICCU and hospital stays and higher mortality in AHF patients, likely due to the severity of underlying conditions and issues like tissue hypoperfusion. Patients with normal arterial $PaCO_2$ levels tend to show more stable clinical outcomes, suggesting that maintaining a balanced $PaCO_2$ is critical for improving prognosis and reducing complications. Continuous monitoring and targeted interventions for patients with hypocapnia or hypercapnia may enhance treatment effectiveness and patient recovery.

Ethics approval

This study was conducted in accordance with the ethical standards of the institutional and national research committees, as well as the 1964 Helsinki Declaration and its subsequent amendments. Ethical approval was obtained from the Ethics Committee of National Cardiovascular Center Harapan Kita, Jakarta.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

Declaration of artificial intelligence use

We hereby confirm that no artificial intelligence (AI) tools or methodologies were utilized at any stage of this study, including during data collection, analysis, visualization, or manuscript preparation. All work presented in this study was conducted manually by the authors without the assistance of AI-based tools or systems.

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References

1. Falco L, Martucci ML, Valente F, *et al.* Pathophysiology-based management of acute heart failure. Clin Pract 2023;13(1):206-218.
2. Khaidirman SK, Hasan H, Andra CA, *et al.* Relationship of left ventricular diastolic dysfunction with quality of life in heart failure patients with reduced ejection fraction (HFrEF). Narra J 2024;4(2):e707.
3. Takagi K, Kimmoun A, Sato N, Mebazaa A. Management of acute heart failure during an early phase. Int J Heart Fail 2020;2(2):91-110.
4. Kamran H, Tang WHW. Medical management of acute heart failure. Fac Rev 2021;10:82.
5. Chapman B, DeVore AD, Mentz RJ, Metra M. Clinical profiles in acute heart failure: An urgent need for a new approach. ESC Heart Fail 2019;6(3):464-474.
6. Mauro C, Chianese S, Cocchia R, *et al.* Acute heart failure: Diagnostic-therapeutic pathways and preventive strategies-a real-world clinician's guide. J Clin Med 2023;12(3):846.
7. Zhang X, Zhao C, Zhang H, *et al.* Dyspnea measurement in acute heart failure: A systematic review and evidence map of randomized controlled trials. Front Med 2021;8:728772.

8. Park JJ, Choi DJ, Yoo BS, *et al.* The prognostic value of arterial blood gas analysis in acute heart failure patients. J Card Fail 2014;20(10):S169.
9. McGuigan PJ, Shankar-Hari M, Harrison DA, *et al.* The interaction between arterial oxygenation and carbon dioxide and hospital mortality following out of hospital cardiac arrest: A cohort study. Crit Care 2020;24(1):336.
10. Kato T, Kasai T, Suda S, *et al.* Prognostic effects of arterial carbon dioxide levels in patients hospitalized into the cardiac intensive care unit for acute heart failure. Eur Heart J Acute Cardiovasc Care 2021;10(5):497-502.
11. Fabre M, Fehlmann CA, Gartner B, *et al.* Prehospital arterial hypercapnia in acute heart failure is associated with admission to acute care units and emergency room length of stay: A retrospective cohort study. BMC Emerg Med 2021;21(1):14.
12. Zhang L, Sun Y, Sui X, *et al.* Hypocapnia is associated with increased in-hospital mortality and 1 year mortality in acute heart failure patients. ESC Heart Fail 2024;11(4):2138-2147.
13. Arrigo M, Jessup M, Mullens W, *et al.* Acute heart failure. Nat Rev Dis Prim 2020;6(1):16.
14. Tang WJ, Xie BK, Liang W, *et al.* Hypocapnia is an independent predictor of in-hospital mortality in acute heart failure. ESC Heart Fail 2023;10(2):1385-1400.
15. Ponikowski P, Voors AA, Anker SD, *et al.* 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37(27):2129-2200.
16. McDonagh TA, Metra M, Adamo M, *et al.* 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021;42(36):3599-3726.
17. Garus M, Zdanowicz A, Fudim M, *et al.* Clinical determinants and prognostic significance of hypocapnia in acute heart failure. Sci Rep 2022;12(1):16889.
18. Kaw R, Hernandez AV, Walker E, *et al.* Determinants of hypercapnia in obese patients with obstructive sleep apnea: A systematic review and metaanalysis of cohort studies. Chest 2009;136(3):787-796.
19. Miro O, Rossello X, Gil V, *et al.* Predicting 30-day mortality for patients with acute heart failure in the emergency department. Ann Intern Med 2017;167(10):698-705.
20. Peterson PN, Rumsfeld JS, Liang L, *et al.* A validated risk score for in-hospital mortality in patients with heart failure from the American heart association get with the guidelines program. Circ Cardiovasc Qual Outcomes 2010;3(1):25-32.
21. Fonarow GC, Adams KF Jr, Abraham WT, *et al.* Risk stratification for in-hospital mortality in acutely decompensated heart failure: Classification and regression tree analysis. JAMA 2005;293(5):572-580.
22. Gheorghiade M, Abraham WT, Albert NM, *et al.* Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. JAMA 2006;296(18):2217-2226.
23. Citerio G, Robba C, Rebora P, *et al.* Management of arterial partial pressure of carbon dioxide in the first week after traumatic brain injury: Results from the CENTER-TBI study. Intensive Care Med 2021;47(9):961-973.
24. Madotto F, Rezoagli E, McNicholas BA, *et al.* Patterns and impact of arterial CO_2 management in patients with acute respiratory distress syndrome: Insights from the LUNG SAFE Study. Chest 2020;158(5):1967-1982.
25. Kajimoto K, Sato N, Takano T. Association of anemia and renal dysfunction with in-hospital mortality among patients hospitalized for acute heart failure syndromes with preserved or reduced ejection fraction. Eur Heart J Acute Cardiovasc Care 2016;5(7):89-99.
26. Dubé BP, Agostoni P, Laveneziana P. Exertional dyspnoea in chronic heart failure: The role of the lung and respiratory mechanical factors. Eur Respir Rev 2016;25(141):317-332.
27. Hawkins SM, Guensch DP, Friedrich MG, *et al.* Hyperventilation-induced heart rate response as a potential marker for cardiovascular disease. Sci Rep 2019;9(1):17887.
28. Van Iterson EH, Johnson BD, Borlaug BA, *et al.* Physiological dead space and arterial carbon dioxide contributions to exercise ventilatory inefficiency in patients with reduced or preserved ejection fraction heart failure. Eur J Heart Fail 2017;19(12):1675-1685.
29. Kaydu A, Orhun G, Çakar N. Relationship between arterial oxygen tension and mortality of patients in intensive care unit on mechanical ventilation support. Ulus Travma Acil Cerrahi Derg 2019;25(4):331-337.
30. Chan MJ, Lucchetta L, Cutuli S, *et al.* A pilot randomized controlled study of mild hypercapnia during cardiac surgery with cardiopulmonary bypass. J Cardiothorac Vasc Anesth 2019;33(11):2968-2978.
31. John S, Ozanne R, Ho KM. Pathophysiological determinants of arterial carbon dioxide tension ($PaCO_2$) in spontaneously breathing and mechanically ventilated patients. J Emerg Crit Care Med 2021;5:30.
32. Wagner T, Sinning C, Haumann J, *et al.* qSOFA score is useful to assess disease severity in patients with heart failure in the setting of a heart failure unit (HFU). Front Cardiovasc Med 2020;7:574768.