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Prognostic value of carbohydrate antigen 125 combined with N-terminal pro B-type natriuretic peptide in patients with acute heart failure: a prospective cohort study in Vietnam

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Abstract

Background Carbohydrate antigen 125 (CA125) is an emerging prognostic biomarker for acute heart failure (AHF). This study aimed to evaluate the prognostic utility of CA125 in combination with N-terminal pro–B-type natriuretic peptide (NT-proBNP) for predicting cardiovascular mortality, all-cause mortality, and a composite outcome of all-cause mortality or rehospitalization due to heart failure in patients with AHF.

Methods This prospective observational study included 316 patients with AHF. Both CA125 and NT-proBNP levels were measured at the time of first admission. Mortality and rehospitalization due to heart failure were recorded over a 12-month follow-up period.

Results During the follow-up period, 38 patients (12.0%) died from cardiovascular disease, 81 patients (25.6%) died from any cause, and 145 patients (45.9%) experienced either all-cause mortality or rehospitalization due to heart failure. In multivariate Cox regression analyses, the combination of high CA125 and high NT-proBNP levels was associated with increased risks of cardiovascular mortality (adjusted Hazard Ratio [aHR] = 11.77, 95% Confidence Interval [CI]: 3.73–37.09, $p < 0.001$), all-cause mortality (aHR = 4.53, 95% CI: 1.99–10.28, $p < 0.001$), and the composite outcome (aHR = 6.02, 95% CI: 2.75–13.24, $p < 0.001$). The addition of CA125 significantly improved prognostic performance when combined with NT-proBNP.

Conclusions Both CA125 and NT-proBNP are significant prognostic biomarkers in patients with AHF. The combination of CA125 and NT-proBNP significantly enhances the prediction of cardiovascular mortality, all-cause mortality and the composite outcome of all-cause mortality or rehospitalization due to heart failure in patients with AHF.

Keywords Prognostic value, Carbohydrate antigen 125, N-terminal pro B-type natriuretic peptide, Acute heart failure, Vietnam

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Background

Heart failure has emerged as a global pandemic, with its prevalence steadily increasing [1]. Currently, approximately 64.3 million patients worldwide live with heart failure [2]. Patients with heart failure have a poor prognosis, with a 5-year mortality rate of 44.2–50.5%, which is higher than the mortality rates of prostate and bladder cancers in men and breast cancer in women [3]. Notably, the mortality risk increases significantly in patients with acute heart failure (AHF) with a 1-year mortality risk four times higher than that of chronic heart failure (23.6% vs. 6.4%, respectively) [4]. Therefore, the role of prognostic assessment in patients with AHF is critically important.

To date, there are two main tools for prognostic assessment in heart failure patients: prognostic models and cardiac biomarkers. Prognostic models for heart failure patients exhibit moderate accuracy. A meta-analysis by Ouwerkerk W [5] analyzed 117 prognostic models for heart failure patients and found that these models demonstrated a moderate discriminative ability for predicting mortality outcomes. For the composite outcome (mortality or rehospitalization) or rehospitalization alone, the predictive capability was lower [5]. The main reason for this limitation lies in the diversity of causes and phenotypes of heart failure patients. The latest guidelines from the American College of Cardiology recommend the use of heart failure prognostic models with a class IIa, level B evidence rating [6]. Biomarkers are widely used in cardiology [7, 8], with natriuretic peptides, including B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) being the most applied in heart failure. These biomarkers reflect hemodynamic stress, systolic dysfunction, and diastolic dysfunction [9]. Natriuretic peptides are widely applied in clinical practice and are considered standard biomarkers for heart failure prognosis, with a class I, level A evidence rating as recommended [6]. However, their levels can be influenced by non-heart failure conditions such as advanced age, renal impairment, and obesity, limiting their specificity in certain clinical contexts [6]. Therefore, combining natriuretic peptides with other biomarkers is essential to improve the prognosis of heart failure patients [10].

Carbohydrate antigen 125 (CA125), also known as cancer antigen 125, is a complex glycoprotein encoded by the MUC16 gene. It is primarily synthesized by mesothelial cells in the pericardium, pleura, and peritoneum. While its exact biological function is not fully understood, studies have shown that CA125 is involved in several biological pathways, including immune responses [11]. CA125 has been extensively studied as a circulating biomarker for monitoring ovarian cancer [12]. Recently, increasing evidence has supported the use of CA125 in cardiovascular diseases, particularly in AHF [13]. High CA125 levels have been observed in almost two-thirds of patients with AHF and have been strongly correlated with the severity of congestion [11] and with the prediction of adverse outcomes [14, 15]. However, most studies on the prognostic role of CA125 in AHF patients have been conducted in Europe [14–16], and evidence indicates racial differences in CA125 levels, with lower CA125 levels observed in non-White populations [17].

In Vietnam, AHF patients have a poor prognosis, with a 1-year mortality rate of 25.8%, higher than the global average of 20% [18]. However, evidence on the prognosis of AHF patients in Vietnam remains limited. This study aimed to evaluate the prognostic value of combining CA125 with NT-proBNP in patients with AHF. Specifically, we assessed whether the combination of these two biomarkers was associated with cardiovascular mortality, all-cause mortality, and a composite outcome of all-cause mortality or rehospitalization due to heart failure, and whether it enhanced the predictive performance of risk models for these outcomes. Our findings may assist clinicians in optimizing prognostic assessment and management strategies for AHF patients.

Methods

Study design and participants

This prospective cohort study was conducted at the General Cardiology Department of Nhan Dan Gia Dinh Hospital, a tertiary hospital in Ho Chi Minh City, Vietnam, from February 2022 to November 2023. The Cardiology Department admits an average of 5,475–7,300 patients annually, including 730–1,460 patients hospitalized for AHF. The sample size calculation was based on findings from Núñez J [19] where the 6-month mortality rates of patients with AHF were 25.2% for those with high CA125 (CA125 ≥ 60 U/mL) and 10.8% for those with low CA125. We estimated a loss to follow-up rate of 10% during the 12-month follow-up. With a statistical power of 0.8 for detecting a significant difference ($p = 0.05$, two-sided), at least 256 patients were required for this study.

Adult patients aged 18 years or older admitted to the hospital with AHF, regardless of ejection fraction (acute de novo heart failure or acute decompensated heart failure), were included according to the 2021 European Society of Cardiology guidelines. The diagnosis of AHF was based on patient history, clinical signs of volume overload (e.g., orthopnea, peripheral edema, jugular venous distension, pleural effusion, or ascites), appropriate evaluations such as electrocardiogram, echocardiography, chest X-ray, lung ultrasound, and an NT-proBNP level greater than 2,000 pg/mL [14, 20]. The main exclusion criteria were conditions that could influence mortality in AHF, such as acute coronary syndrome, end-stage renal or liver disease, or an expected life expectancy of less than one year due to other causes. We also excluded patients whose high CA125 levels were not associated with heart

failure, such as those due to pregnancy, cancer, or pelvic inflammatory disease.

The study protocol adhered to the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of Biomedical Research at the University of Medicine and Pharmacy at Ho Chi Minh City (21598-DHYD). All patients provided written informed consent.

Study procedure and measurements

Data on anthropometry, comorbidities, vital signs, biomarkers, echocardiography, and medications were collected from patients prior to hospital discharge. Patients were then scheduled for follow-up visits at the Heart Failure Unit of Nhan Dan Gia Dinh Hospital once a month. Most patients were interviewed directly during clinical visits. If patients were unable to attend in person, researchers conducted phone interviews to gather information about symptoms, medications, and outcomes. Patients were followed up for a period of 12 months after admission.

Atrial fibrillation was diagnosed based on a 12-lead ECG. Chronic coronary disease was identified by a positive angiogram, non-invasive imaging, or a stress test. Chronic obstructive pulmonary disease (COPD) and asthma were diagnosed based on pulmonary function testing or a documented prior diagnosis. Chronic kidney disease (CKD) was diagnosed according to the 2012 KDIGO (Kidney Disease: Improving Global Outcomes) guidelines, which define CKD as structural or functional abnormalities of the kidney persisting for at least 3 months. Diabetes was diagnosed with HbA1c ≥ 6.5% or fasting plasma glucose ≥ 126 mg/dL, or by a previous diagnosis. Hypertension was defined based on the 2018 European Society of Cardiology guidelines as a systolic blood pressure ≥ 140 mmHg or a diastolic blood pressure ≥ 90 mmHg, or by a previous diagnosis of hypertension. Stroke, including cerebral hemorrhage or cerebral ischemia, was diagnosed based on neurological dysfunction or imaging evidence. Primary valvular heart disease was diagnosed based on echocardiographic findings and a documented prior diagnosis.

Clinical examination was conducted by an experienced cardiologist, with clinical variables analyzed including heart rate and blood pressure. Tests such as hemoglobin, potassium, creatinine, and sodium were performed within 48 h after hospital admission. Echocardiography was performed once during hospitalization by a cardiologist, according to the recommendations of the American Society of Echocardiography [21]. The parameters analyzed included left ventricular ejection fraction, left ventricular end-diastolic diameter, left atrial diameter, systolic pulmonary pressure, and tricuspid annular plane systolic excursion.

Plasma CA125 and NT-proBNP levels were measured within the first 48 h after hospital admission. CA125 and NT-proBNP were measured using commercially available immunoassays (the Elecsys CA125 II assay and the Elecsys NT-proBNP assay, both from Roche Diagnostics). Assays were conducted using an electrochemiluminescence immunoassay on the cobase 801 system. For CA125, the intra-assay precision is 1.4–2.0%, and the inter-assay precision is 0.0–0.9%, with an analytical range of 0.6–5000 U/mL [22]. The normal range for healthy individuals for CA125 is under 35 U/mL. For NT-proBNP, the intra-assay precision is 1.2–1.5%, and the inter-assay precision is 4.4–5.0%, with an analytical range of 5–35,000 pg/mL [23].

Data on treatment medications were collected, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor-neprilysin inhibitors, antiplatelets, beta-blockers, furosemide, mineralocorticoid receptor antagonists, oral anticoagulants, sodium-glucose co-transporter 2 inhibitors, and statins. All participants received guideline-directed medical therapy during hospitalization, managed by cardiologists and internal medicine specialists. The primary endpoints were cardiovascular mortality and all-cause mortality, while the secondary endpoint was a composite of all-cause mortality or first rehospitalization due to heart failure. Deaths and rehospitalizations were determined through review of death certificates, telephone interviews, and data from the eHospital system at Nhan Dan Gia Dinh Hospital. All clinical events were adjudicated by the principal investigator. The cause of death was determined based on the guidelines from the 2014 American College of Cardiology Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials [20]. Cardiovascular death was defined to include deaths resulting from acute myocardial infarction, sudden cardiac death, heart failure, stroke, cardiovascular procedures, aortic aneurysm, cardiac tamponade, pulmonary embolism, or peripheral arterial disease. Rehospitalization due to heart failure was defined as hospitalization for dyspnea or congestion, with a minimum hospital stay of more than 24 h.

Statistical analysis

Baseline categorical variables were summarized as frequency and percentage, and differences were compared using the Chi-squared test or Fisher's exact test when appropriate. Continuous variables were summarized as mean (standard deviation) or median (interquartile range), and comparisons between groups were conducted using the independent t-test or Wilcoxon rank-sum test, as appropriate.

We assessed the associations of CA125 and NT-proBNP with mortality and with the composite outcome

of mortality or rehospitalization, both as continuous variables and as categorical variables. Spline plots were constructed to evaluate whether the associations of CA125 and NT-proBNP with outcome variables were linear. Interaction effects between CA125 and NT-proBNP (both modeled as continuous variables) were assessed by including an interaction term in the regression models. Receiver operating characteristic (ROC) analysis were conducted to evaluate the discriminative ability of CA125 and NT-proBNP in identifying cardiovascular mortality, all-cause mortality and composite events (all-cause mortality or rehospitalization due to heart failure). The Youden index was used to determine the optimal cut-off points for CA125 and NT-proBNP for all outcomes. Patients were first classified into low and high groups for CA125 and NT-proBNP based on the determined thresholds. Following methods used in previous studies [24], patients were then categorized into four groups: low CA125 and low NT-proBNP (Group 1), low CA125 and high NT-proBNP (Group 2), high CA125 and low NT-proBNP (Group 3), and high CA125 and high NT-proBNP (Group 4).

Kaplan-Meier survival analysis was conducted across the four groups, and the log-rank test was used to assess the differences in event rates. The associations between these groups and clinical outcomes were evaluated using univariate and multivariate Cox regression models. In the multivariate Cox model, we included prognostic variables that were statistically significant in univariate analysis ($p < 0.05$). The improvement in the discriminative ability for predicting outcomes from the combination of CA125 and NT-proBNP was assessed using areas under the curve (AUC). The statistical difference in the AUC was tested using DeLong's test. The area under the precision-recall curve (AUC-PR) was also used to evaluate the predictive accuracy of the combined use of CA125 and NT-proBNP. All hypothesis testing was two-sided, and a p-value of less than 0.05 was considered statistically significance.

Results

Between 14 February 2022, and 30 November 2023, a total of 324 patients admitted to Nhan Dan Gia Dinh Hospital for AHF were included in this study. Eight patients were excluded from the analysis due to data deficiency in echocardiography or laboratory results ($n = 6$), and extreme outliers of CA125 ($n = 2$). Therefore, a total of 316 patients were included in the final analysis (Fig. 1).

Table 1 presents the characteristics of 316 patients stratified by outcomes (survivor vs. mortality, no events vs. mortality/rehospitalization). The mean (SD) age was 66.7 (14.8) years and 164 (51.9%) were female. Common comorbidities included hypertension, coronary artery disease, diabetes mellitus, atrial fibrillation, and chronic kidney disease. In-hospital mortality occurred in 10 patients (3.2%). During the 12-month follow-up period after hospital admission, there were 38 cardiovascular deaths (12.0%), 81 all-cause deaths (25.6%), and

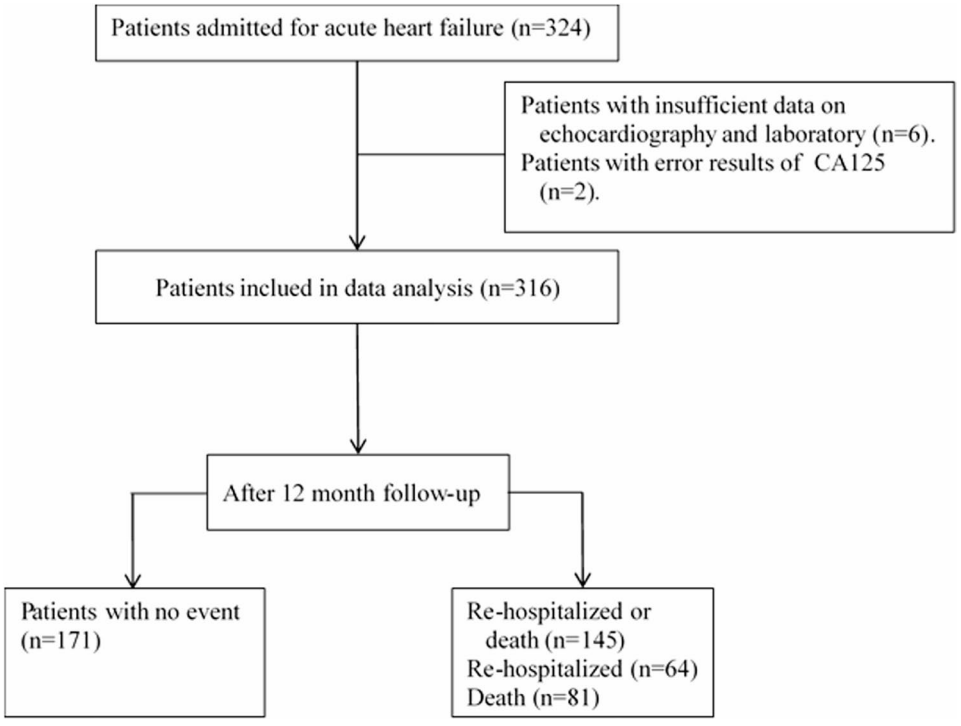

Fig. 1 Flowchart of patient enrollment, exclusion, and follow-up in the study cohort

Table 1 Baseline characteristics of patients with acute heart failure ($n = 316$)

Characteristic	All patients $n = 316$	Survivor $n = 235$	Death $n = 81$	p value	No events $n = 171$	Death/rehospitalization $n = 145$	p value
Demographic profile							
Age, mean (SD), years	66.7 ± 14.8	64.8 ± 14.3	72.3 ± 14.8	**< 0.001**[a]	64.7 ± 14.7	68.8 ± 14.7	**0.013**[a]
Gender (Female), *n* (%)	164 (51.9)	115 (48.9)	49 (60.5)	0.073[c]	87 (50.9)	77 (53.1)	0.693[c]
History of comorbidity							
Atrial fibrillation (yes), *n* (%)	107 (33.9)	71 (30.2)	36 (44.4)	**0.019**[c]	51 (29.8)	56 (38.6)	0.099[c]
Chronic coronary disease (yes), *n* (%)	127 (40.2)	91 (38.7)	36 (44.4)	0.365[c]	63 (36.8)	64 (44.1)	0.188[c]
COPD/asthma (yes), *n* (%)	38 (12.0)	24 (10.2)	14 (17.3)	0.092[c]	17 (9.9)	21 (14.5)	0.216[c]
Chronic kidney disease (yes), *n* (%)	99 (31.3)	65 (27.7)	34 (41.9)	**0.017**[c]	45 (26.3)	54 (37.2)	**0.037**[c]
Diabetes mellitus (yes), *n* (%)	125 (39.6)	91 (38.7)	34 (41.9)	0.606[c]	61 (35.7)	64 (44.1)	0.125[c]
Hypertension (yes), *n* (%)	230 (72.8)	175 (74.5)	55 (67.9)	0.252[c]	126 (73.7)	104 (71.7)	0.697[c]
Hemorrhagic stroke/ischemic stroke, (yes), *n* (%)	31 (9.8)	24 (10.2)	7 (8.6)	0.682[c]	15 (8.8)	16 (11.0)	0.500[c]
Valvular heart disease (yes), *n* (%)	50 (15.8)	37 (15.7)	13 (16.0)	0.948[c]	29 (16.9)	21 (14.5)	0.548[c]
Vital signs							
Heart rate, mean (SD), beats per minute	96.6 ± 23.3	96.1 ± 22.8	98.1 ± 24.8	0.519[a]	96.2 ± 23.6	97.1 ± 22.9	0.746[a]
Diastolic blood pressure at admission, mean (SD), mmHg	78.0 ± 14.6	79.3 ± 14.6	74.4 ± 14.3	**0.010**[a]	78.5 ± 12.2	77.5 ± 17.1	0.567[a]
Systolic blood pressure at admission, mean (SD), mmHg	132.1 ± 27.3	133.1 ± 27.4	129.2 ± 27.0	0.261[a]	133.6 ± 25.2	130.4 ± 29.6	0.311[a]
Laboratory data							
CA125 at admission, median (IQR), U/mL	56.0 (27.0–140.0)	53.0 (25.0–127.5)	70.0 (38.0–186.0)	**0.010**[b]	43.0 (21.0–115.5)	86.0 (40.0–167.0)	**< 0.001**[b]
Hemoglobin at admission, mean (SD), g/dl	119.4 ± 23.8	111.2 ± 25.1	122.2 ± 22.6	**< 0.001**[a]	122.8 ± 23.5	115.3 ± 23.5	**0.005**[a]
Potassium at admission, mean (SD), mmol/l	3.9 ± 0.6	3.9 ± 0.6	4.1 ± 0.7	**0.036**[a]	3.9 ± 0.6	3.9 ± 0.7	0.089[a]
NT-proBNP at admission, median (IQR), pg/ml	6644 (3973–12360)	6248 (3690–11280)	8546 (4892–18308)	**0.001**[b]	6005 (3639–11466)	7451 (4276–14256)	**0.031**[b]
Serum creatinine at admission, median (IQR), µg/l	112.0 (90.0–152.0)	109.0 (91.0–151.0)	117.0 (90.0 − 156.0)	0.641[b]	107.0 (91.0–145.5)	117.0 (90.0 − 160.0)	0.224[b]
Sodium at admission, mean (SD), mmol/l	135.4 ± 6.3	136.1 ± 5.9	133.5 ± 7.0	**0.003**[a]	136.6 ± 5.7	134.1 ± 6.7	**< 0.001**[a]
Echocardiography data							
Left ventricular ejection fraction, mean (SD), %	42.5 ± 16.4	41.2 ± 16.6	46.2 ± 15.2	**0.015**[a]	41.6 ± 16.8	43.6 ± 15.8	0.294[a]
Left ventricular end-diastolic diameter, mean (SD), mm	52.6 ± 10.6	53.6 ± 10.5	49.8 ± 10.7	**0.007**[a]	53.2 ± 9.8	51.9 ± 11.5	0.267[a]
Left atrial diameter, mean (SD), mm	40.3 ± 8.7	40.2 ± 8.9	40.7 ± 8.0	0.645[a]	39.3 ± 8.8	41.5 ± 8.4	**0.022**[a]
Systolic pulmonary pressure, median (IQR), mm Hg	35.0 (26.0–44.3)	35.0 (26.0–45.0)	33.0 (28.0–44.0)	0.701[b]	35.0 (26.0–44.0)	35.0 (27.0–45.0)	0.442[b]
TAPSE, mean (SD), mm	19.2 ± 4.2	19.1 ± 4.4	19.6 ± 3.6	0.352[a]	19.2 ± 4.4	19.2 ± 3.9	0.991[a]
Medication at discharge							
ACEI at discharge (yes), *n* (%)	89 (28.2)	66 (28.1)	23 (28.4)	0.957[c]	51 (29.8)	38 (26.2)	0.476[c]
ARB at discharge (yes), *n* (%)	84 (26.6)	66 (28.1)	18 (22.2)	0.303[c]	47 (27.5)	37 (25.5)	0.693[c]
ARNI at discharge (yes), *n* (%)	48 (15.2)	43 (18.3)	5 (6.2)	**0.009**[c]	32 (18.7)	16 (11.0)	0.058[c]
Beta-blockers at discharge (yes), *n* (%)	250 (79.1)	194 (82.6)	56 (69.1)	**0.010**[c]	142 (83.0)	108 (74.5)	0.062[c]
SGLT2i at discharge (yes), *n* (%)	133 (42.1)	110 (46.8)	23 (28.4)	**0.004**[c]	81 (47.4)	52 (35.9)	**0.039**[c]

Table 1 (continued)

Characteristic	All patients $n=316$	Survivor $n=235$	Death $n=81$	*p* value	No events $n=171$	Death/rehospitalization $n=145$	*p* value
MRA at discharge (yes), *n* (%)	195 (61.7)	158 (67.2)	37 (45.7)	**< 0.001**[c]	113 (66.1)	82 (56.6)	0.082[c]
Furosemide at discharge (yes), *n* (%)	220 (69.6)	169 (71.9)	51 (62.9)	0.131[c]	118 (69.0)	102 (70.3)	0.797[c]
Antiplatelet at discharge (yes), *n* (%)	111 (35.1)	85 (36.2)	26 (32.1)	0.508[c]	58 (33.9)	53 (36.6)	0.625[c]
Oral anticoagulants at discharge (yes), *n* (%)	111 (35.1)	79 (33.6)	32 (39.5)	0.338[c]	56 (32.7)	55 (37.9)	0.336[c]
Statins at discharge (yes), *n* (%)	244 (77.2)	192 (81.7)	52 (64.2)	**0.001**[c]	136 (79.5)	108 (74.5)	0.286[c]

ACEI Angiotensin-converting Enzyme Inhibitor, ARB Angiotensin Receptor Blocker, ARNI Angiotensin Receptor-neprilysin Inhibitor, *COPD* Chronic obstructive pulmonary disease, *CA125* Antigen Carbohydrate 125, *IQR* Interquartile Range, *MRA* Mineralocorticoid Receptor Antagonist, *NT-proBNP* N-terminal proBNP, *SD* Standard Deviation, *SGLT2I* Sodium-Glucose Co-transporter 2 inhibitors, *TAPSE* Tricuspid Annular Plane Systolic Excursion

[a] Independent Samples t-test

[b] Wilcoxon Rank Sum test/Mann-Whitney test

[c] Chi-squared Test

Bold-faced values indicate statistical significance at $p < 0.05$

145 patients (45.9%) experienced all-cause mortality or rehospitalization due to heart failure.

Patients experiencing all-cause mortality were older and had higher rates of comorbidities such as atrial fibrillation and chronic kidney disease. They exhibited lower levels of hemoglobin and sodium compared to patients without events and had higher levels of CA125 and NT-proBNP. Additionally, the use of angiotensin receptor-neprilysin inhibitors, mineralocorticoid receptor antagonists, beta-blockers, sodium-glucose co-transporter 2 inhibitors, and statins before discharge was lower among patients who died from all causes.

Cutoff of CA125 and NT-proBNP

Based on ROC analysis and the Youden index, the optimal cutoff point for predicting cardiovascular mortality was 113 U/mL for CA125 (sensitivity of 60.5% and specificity of 73.0%) and 7,856 pg/mL for NT-proBNP (sensitivity of 65.8% and specificity of 62.2%). For the all-cause mortality outcome, the optimal cutoff was 40 U/mL for CA125 (sensitivity of 74.1% and specificity of 42.1%) and 6,634 pg/mL for NT-proBNP (sensitivity of 65.4% and specificity of 54.9%). For the prediction of the composite outcome, the optimal cutoff was 28 U/mL for CA125 (sensitivity of 88.3% and specificity of 37.4%) and 6,634 pg/mL for NT-proBNP (sensitivity of 58.6% and specificity of 56.7%).

Kaplan-Meier endpoint analysis according to the levels of CA125 and NT-proBNP

We categorized the study cohort into four groups based on cutoff values of CA125 and NT-proBNP. For cardiovascular mortality, groups were categorized using CA125 (113 U/mL) and NT-proBNP (7,856 pg/mL). Kaplan-Meier survival analysis revealed significant differences in survival across these groups ($p < 0.0001$, log-rank test). Group 1, characterized by low levels of both CA125 and NT-proBNP, had the lowest cumulative rate of cardiovascular mortality at 3.2% (Confidence Interval, 95% CI: 0.1–6.2%). Group 2, with low CA125 and high NT-proBNP, had a cumulative cardiovascular mortality rate of 14.5% (95% CI: 6.2–22.2%). Group 3, defined by high CA125 and low NT-proBNP, had a cumulative cardiovascular mortality rate of 20.0% (95% CI: 7.4–30.9%). Group 4, comprising individuals with elevated levels of both markers, had the highest cumulative cardiovascular mortality rate at 29.8% (95% CI: 15.4–41.7%) (Fig. 2).

For all-cause mortality, groups were categorized using CA125 (40 U/mL) and NT-proBNP (6,634 pg/mL). Kaplan-Meier survival analysis also indicated significant differences in survival across these groups ($p = 0.001$, log-rank test). Group 1, with low levels of both CA125 and NT-proBNP, had the lowest cumulative all-cause mortality rate at 9.5% (95% CI: 2.5–15.9%). Group 2, with low

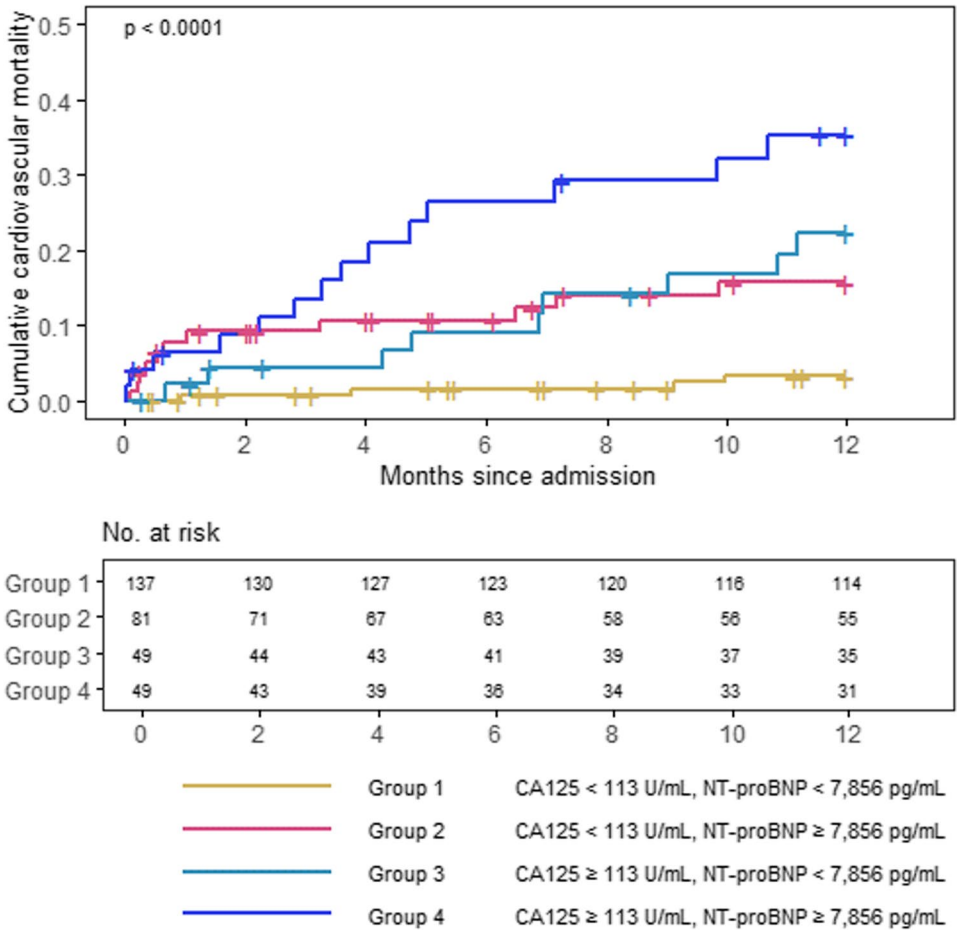

Fig. 2 Kaplan-Meier analysis of 12-month cardiovascular mortality by CA125 and NT-proBNP Levels

CA125 and high NT-proBNP, had a cumulative all-cause mortality rate of 30.4% (95% CI: 15.8–42.5%). Group 3, characterized by high CA125 and low NT-proBNP, had a cumulative all-cause mortality rate of 25.3% (95% CI: 15.3–34.1%). Group 4, with elevated levels of both markers, had the highest cumulative all-cause mortality rate at 34.5% (95% CI: 25.1–42.7%) (Fig. 3).

A similar analysis was conducted for the combined outcome of all-cause mortality or rehospitalization due to heart failure, with cutoff values of 28 U/mL for CA125 and 6,634 pg/mL for NT-proBNP. Kaplan-Meier survival analysis showed that Group 1, with low levels of both markers, had the lowest cumulative combined endpoint rate of 13.2% (95% CI: 3.6–21.9%). Group 2, with high NT-proBNP and low CA125, had a cumulative rate of 35.7% (95% CI: 15.3–51.2%), while Group 3, with low NT-proBNP and high CA125, had a cumulative rate of 51.0% (95% CI: 40.3–59.7%). Group 4, with high levels of both markers, had the highest cumulative combined endpoint rate at 57.3% (95% CI: 47.9–64.9%). The log-rank test was significant ($p < 0.001$) (Fig. 4).

Prognostic value of CA125 and NT-proBNP

CA125 was significantly associated with adverse outcomes in patients with AHF. CA125, analyzed as a continuous variable, demonstrated a positive, nonlinear association with cardiovascular mortality, all-cause mortality, and the composite outcome of all-cause mortality or rehospitalization for heart failure, as shown in multivariable regression and spline analysis. (Figure A1, A2 and A3 in the Appendix).

High CA125 levels were independently associated with an increased risk of cardiovascular mortality (adjusted Hazard Ratio [aHR] = 3.96, 95% CI: 2.03–7.72, $p < 0.001$), all-cause mortality (aHR = 2.16, 95% CI: 1.29–3.59, $p = 0.003$), and the composite outcome of all-cause mortality or rehospitalization due to heart failure (aHR = 3.34, 95% CI: 1.99–5.59, $p < 0.001$), after adjustment for other prognostic variables (Table 2). Similarly, high NT-proBNP levels were independently associated with an increased risk of cardiovascular mortality (aHR = 3.03, 95% CI: 1.47–6.22, $p = 0.003$), all-cause mortality (aHR = 1.96, 95% CI: 1.21–3.18, $p = 0.006$), and the composite outcome of all-cause mortality or rehospitalization due to heart failure (aHR = 1.55, 95% CI:

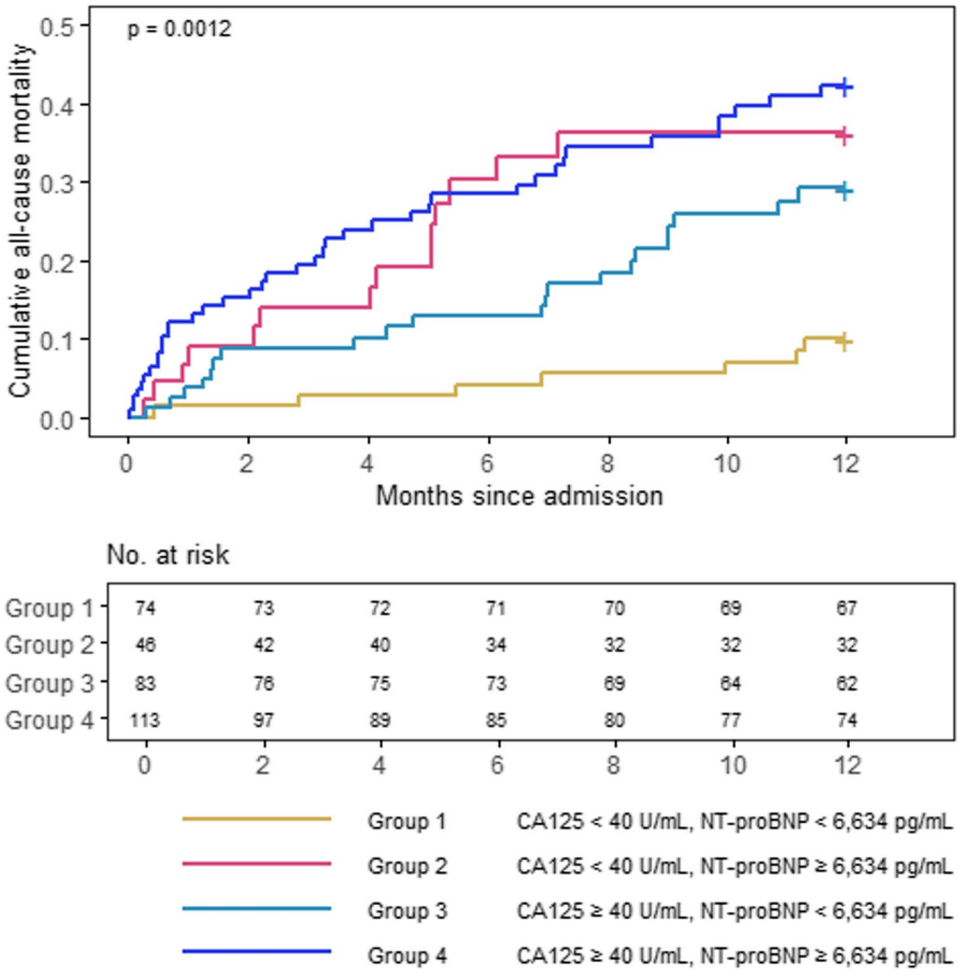

Fig. 3 Kaplan-Meier analysis of 12-month all-cause mortality by CA125 and NT-proBNP Levels

1.09–2.19, $p = 0.013$), after adjustment for other prognostic variables.

In contrast, when NT-proBNP was analyzed as a continuous variable, the increase in risk was less pronounced after multivariable adjustment (Figure A1, A2 and A3 in the Appendix). Analyses using categorized NT-proBNP levels revealed that high levels were significantly associated with increased risks of cardiovascular mortality, all-cause mortality, and the composite outcome (Table 2). Furthermore, a significant interaction was observed between NT-proBNP and CA125 (both treated as continuous variables) for cardiovascular mortality ($p = 0.034$) and for the composite outcome ($p = 0.048$), but not for all-cause mortality ($p = 0.207$). These interaction results were adjusted for age, chronic kidney disease, atrial fibrillation, hemoglobin, sodium levels, and the use of sodium-glucose co-transporter 2 inhibitors in the Cox regression model.

Prognostic value of CA125 in combination with NT-proBNP

Overall, the combination of CA125 and NT-proBNP levels demonstrated good predictive performance for 12-month mortality and rehospitalization in patients with AHF. For cardiovascular mortality, patients with high levels of either CA125 or NT-proBNP or both had an increased risk of 12-month cardiovascular death. Specifically, the risk of cardiovascular death was 11 times higher in patients with high CA125 and NT-proBNP levels (HR = 11.25, 95% CI: 3.70–34.18, $p < 0.001$) compared to those with low levels of both biomarkers.

Similarly, high levels of either CA125, NT-proBNP or both was associated with an increased risk of 12-month all-cause mortality. Patients with high levels of both biomarkers had a more than fourfold higher risk of death (HR = 4.43, 95% CI: 1.98–9.90, $p < 0.001$) compared to those with low levels of both biomarkers. This association remained significant even after adjusting for age, chronic kidney disease, atrial fibrillation, hemoglobin, sodium levels, and the use of sodium-glucose co-transporter 2 inhibitors (Table 3).

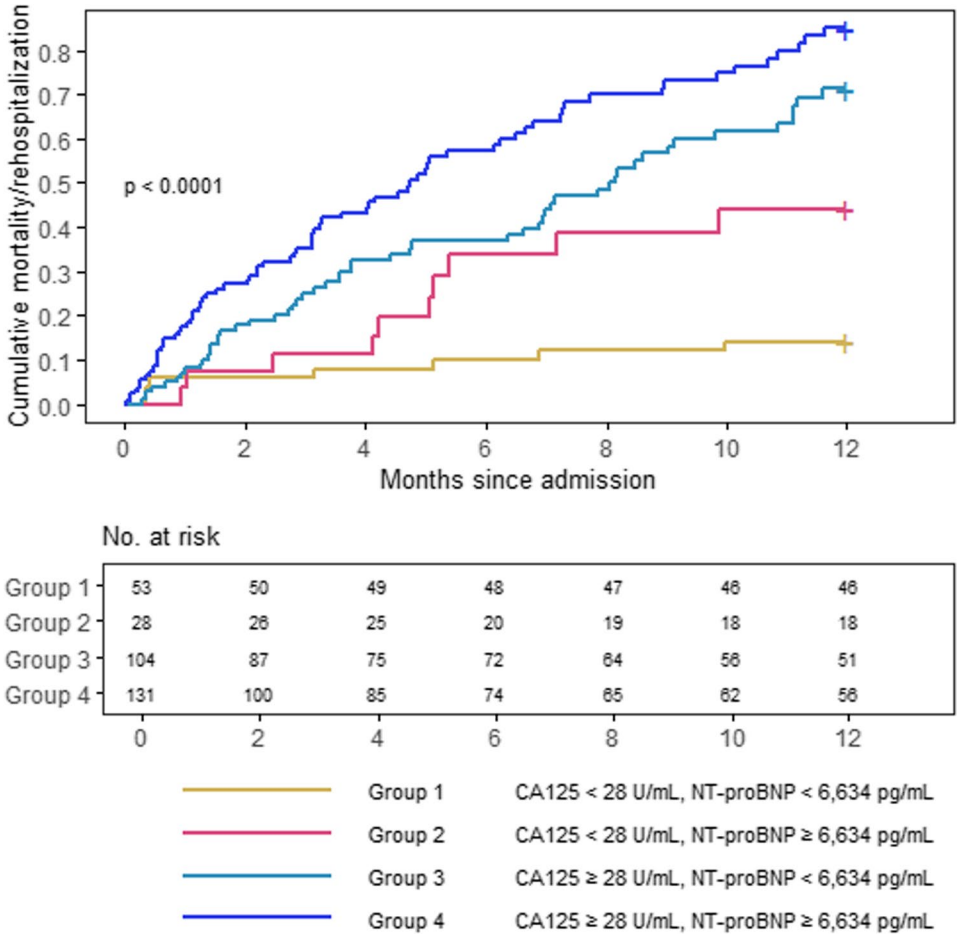

Fig. 4 Kaplan-Meier analysis of 12-month all-cause mortality or heart failure rehospitalization by CA125 and NT-proBNP Levels

Table 2 CA125 Và NT-proBNP independently predicting 12-month mortality and composite outcome

Outcome	Predictor variable	Univariate analysis		Multivariate analysis[d]	
		HR (95% CI)	*p* value	aHR (95% CI)	*p* value
Cardiovascular Mortality[a]	Low CA125 vs. High CA125	3.60 (1.88–6.91)	**< 0.001**	3.96 (2.03–7.72)	**< 0.001**
	Low NT-proBNP vs. High NT-proBNP	3.08 (1.58–6.02)	**0.001**	3.03 (1.47–6.22)	**0.003**
All-cause Mortality[b]	Low CA125 vs. High CA125	1.91 (1.16–3.13)	**0.011**	2.16 (1.29–3.59)	**0.003**
	Low NT-proBNP vs. High NT-proBNP	2.15 (1.36–3.40)	**0.001**	1.96 (1.21–3.18)	**0.006**
Composite Outcome[c]	Low CA125 vs. High CA125	3.31 (1.99–5.49)	**< 0.001**	3.34 (1.99–5.59)	**< 0.001**
	Low NT-proBNP vs. High NT-proBNP	1.64 (1.18–2.28)	**0.003**	1.55 (1.09–2.19)	**0.013**

95% CI, 95% Confidence Interval, *HR* Hazard Ratio, *aHR* Adjusted Hazard Ratio

([a]) Cutoff points were 113 U/mL (CA125) and 7856 pg/mL (NT-proBNP)

([b]) Cutoff points were 40 U/mL (CA125) and 6634 pg/mL (NT-proBNP)

([c]) Cutoff points were 28 U/mL (CA125) and 6634 pg/mL (NT-proBNP)

([d]) Multivariate analysis adjusting for age, chronic kidney disease, atrial fibrillation, hemoglobin, sodium, use of sodium-glucose co-transporter 2 inhibitors

Bold-faced values indicate statistical significance at $p < 0.05$

Table 3 The combination of CA125 and NT-proBNP categories in predicting 12-month mortality and composite outcome

Outcome	Predictor variable	Univariate analysis		Multivariate analysis[d]	
		HR (95% CI)	*p* value	aHR (95% CI)	*p* value
Cardiovascular Mortality[a]	Low CA125 + Low NT-proBNP	Reference		Reference	
	Low CA125 + High NT-proBNP	5.26 [1.68–16.52]	**0.004**	5.13 [1.59–16.60]	**0.006**
	High CA125 + Low NT-proBNP	6.69 [2.06–21.72]	**0.002**	7.68 [2.32–25.36]	**< 0.001**
	High CA125 + High NT-proBNP	11.25 [3.70–34.18]	**< 0.001**	11.77 [3.73–37.09]	**< 0.001**
All-cause Mortality[b]	Low CA125 + Low NT-proBNP	Reference		Reference	
	Low CA125 + High NT-proBNP	3.78 [1.53–9.37]	**0.004**	3.88 [1.54–9.77]	**0.004**
	High CA125 + Low NT-proBNP	2.91 [1.24–6.84]	**0.015**	3.83 [1.61–9.08]	**0.002**
	High CA125 + High NT-proBNP	4.43 [1.98–9.90]	**< 0.001**	4.53 [1.99–10.28]	**< 0.001**
Composite outcome[c]	Low CA125 + Low NT-proBNP	Reference		Reference	
	Low CA125 + High NT-proBNP	3.02 [1.15–7.93]	**0.025**	3.21 [1.21–8.52]	**0.0195**
	High CA125 + Low NT-proBNP	4.77 [2.17–10.49]	**< 0.001**	5.17 [2.34–11.47]	**< 0.001**
	High CA125 + High NT-proBNP	6.09 [2.80–13.22]	**< 0.001**	6.03 [2.75–13.24]	**< 0.001**

95% CI 95% Confidence Interval, *HR* Hazard Ratio, *aHR* Adjusted Hazard Ratio

([a]) Cutoff points were 113 U/mL (CA125) and 7856 pg/mL (NT-proBNP)

([b]) Cutoff points were 40 U/mL (CA125) and 6634 pg/mL (NT-proBNP)

([c]) Cutoff points were 28 U/mL (CA125) and 6634 pg/mL (NT-proBNP)

([d])Multivariate analysis adjusting for age, chronic kidney disease, atrial fibrillation, hemoglobin, sodium, use of sodium-glucose co-transporter 2 inhibitors

Bold-faced values indicate statistical significance at $p < 0.05$

High levels of either CA125, NT-proBNP, or both were associated with an increased risk of the composite outcome of all-cause mortality or rehospitalization due to heart failure. Patients with high levels of both biomarkers had a six-fold higher risk compared to those with low levels of both biomarkers (HR = 6.09, 95% CI: 2.80 – 13.22, $p < 0.001$). This association persisted even after adjusting for other predictors such as age, chronic kidney disease, atrial fibrillation, hemoglobin, sodium levels, and the use of sodium-glucose co-transporter 2 inhibitors (Table 3).

Improvement in prognostic performance with the combination of CA125 and NT-proBNP

In univariate analysis, the combination of CA125 and NT-proBNP demonstrated the highest discriminative performance (Fig. 5). Combining CA125 and NT-proBNP significantly improved risk discrimination compared with NT-proBNP alone, for cardiovascular mortality (AUC = 0.746, 95% CI: 0.671–0.882 vs. 0.637, 95% CI: 0.540–0.734, $p = 0.021$) and for the composite outcome of all-cause mortality or rehospitalization due to heart failure (AUC = 0.648, 95% CI: 0.588–0.708 vs. 0.571, 95% CI: 0.507–0.634, $p = 0.009$). However, the combination of CA125 and NT-proBNP did not significantly improve the prediction of all-cause mortality compared with NT-proBNP alone ($p = 0.322$) and did not improve outcomes compared with CA125 alone (Table 4). Consistent findings were observed in time-to-event analyses using Cox regression and C-statistics.

Discussion

To the best of our knowledge, this study is among the first prospective cohort studies to evaluate the prognostic value of CA125 for mortality and the composite outcome of mortality or rehospitalization due to heart failure in patients with AHF in an Asian population. Previous research on CA125 has been predominantly conducted in Europe, with the largest body of work centered in Spain [14, 24]. In contrast, very few studies have been conducted in Asia on CA125 in patients with AHF, and none have evaluated cardiovascular mortality or rehospitalization outcomes [25, 26]. While previous studies have largely focused on mortality outcomes, our study extends the evidence by demonstrating that the combination of CA125 and NT-proBNP can also predict the composite outcome of all-cause mortality or rehospitalization due

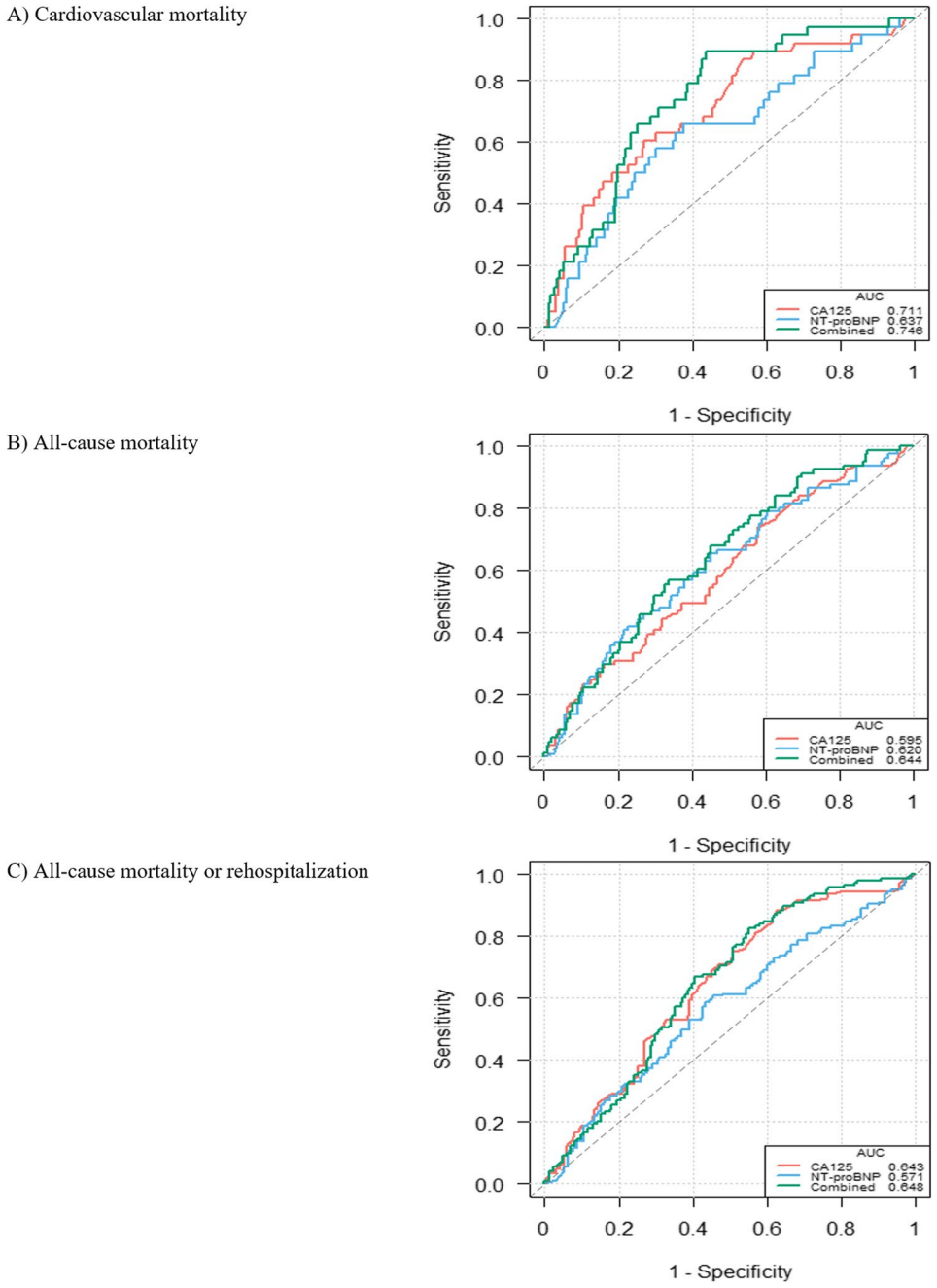

Fig. 5 Receiver operating characteristic (ROC) curves comparing the predictive performance of CA125, NT-proBNP, and their combination for clinical outcomes

to heart failure, an outcome not previously evaluated. In addition, to our knowledge, this is the first study to evaluate the prognostic value of CA125 in combination with NT-proBNP in patients with AHF who were treated with two recently recommended drug classes-angiotensin receptor-neprilysin inhibitors (ARNI) and sodium-glucose co-transporter 2 inhibitors (SGLT2i) - according to the 2021 European Society of Cardiology guidelines. In our cohort, 15.2% of patients received ARNI and 42.1% received SGLT2 inhibitors.

In our study, two key results were observed: (1) the combination of CA125 and NT-proBNP was associated with 12- month cardiovascular mortality, all-cause mortality and the composite outcome of all-cause mortality or rehospitalization, and (2) these two biomarkers improved the prognostic discrimination for these outcomes. Furthermore, the combined use of CA125 and

Table 4 Discriminative performance of CA125 and NT-proBNP combination for predicting 12-month mortality and composite outcome

Outcome	Predictor variable	AUC (95% CI)	*p* value	AUC-PR	C-statistics (95% CI)
Cardiovascular Mortality[a]	CA125	0.711 (0.621–0.801)		0.243	0.694 (0.609–0.778)
	NT-proBNP	0.637 (0.540–0.734)		0.176	0.648 (0.558–0.737)
	CA125 + NT-proBNP	0.746 (0.671–0.822)		0.248	0.738 (0.669–0.807)
	CA125 vs. CA125 + NT-proBNP		0.324[b]		
	NT-proBNP vs. CA125 + NT-proBNP		**0.021**[b]		
All-cause Mortality[a]	CA125	0.595 (0.524–0.666)		0.337	0.584 (0.523–0.645)
	NT-proBNP	0.620 (0.549–0.691)		0.334	0.616 (0.554–0.677)
	CA125 + NT-proBNP	0.644 (0.577–0.711)		0.363	0.634 (0.577–0.691)
	CA125 vs. CA125 + NT-proBNP		0.139[b]		
	NT-proBNP vs. CA125 + NT-proBNP		0.322[b]		
Composite outcome[a]	CA125	0.643 (0.582–0.704)		0.564	0.595 (0.548–0.641)
	NT-proBNP	0.571 (0.507–0.634)		0.507	0.565 (0.517–0.613)
	CA125 + NT-proBNP	0.648 (0.588–0.708)		0.559	0.601 (0.554–0.648)
	CA125 vs. CA125 + NT-proBNP		0.784[b]		
	NT-proBNP vs. CA125 + NT-proBNP		**0.009**[b]		

95% CI 95% Confidence Interval, *AUC* Area Under the Curve, *AUC-PR* Area Under the Precision Recall Curve

CA125 and NT-proBNP modeled as continuous variables

Bold-faced values indicate statistical significance at $p < 0.05$

NT-proBNP may facilitate individualized risk stratification, enabling more targeted monitoring and intensified therapeutic strategies for patients identified as high-risk.

Both CA125 and NT-proBNP, individually or in combination, have demonstrated prognostic value for predicting adverse outcomes in patients with AHF. Our study shows that elevated levels of either or both biomarkers significantly increases the risk of mortality and/or rehospitalization due to heart failure. These findings are consistent with previous research on mortality outcomes. An observational study involving 413 patients with AHF by Joon YJ [26], with a two-year follow-up, reported that each logarithmic increase in CA125 (U/mL) was associated with a 23% higher risk of mortality (HR = 1.23, 95% CI: 1.02–1.48, $p = 0.030$). Similarly, each logarithmic increase in NT-proBNP (pg/mL) increased the risk of mortality by 22% (HR = 1.22, 95% CI: 1.01–1.48, $p = 0.044$). Likewise, Núñez J evaluated 1,111 patients admitted with AHF and found that elevated levels of either CA125 or BNP, or both, were associated with increased risks of all-cause and cardiovascular mortality within six months [19]. Another study conducted by Núñez J [27], involving 946 patients with AHF, further demonstrated that the longitudinal trajectories of both CA125 and NT-proBNP were significantly associated with survival status, with persistently higher values observed among patients who died. In contrast, changes in NT-proBNP levels were less pronounced among survivors during the first two years of follow-up.

Additionally, our study demonstrated that the combination of CA125 and NT-proBNP improved discrimination for cardiovascular mortality, all-cause mortality, and rehospitalization due to heart failure compared with NT-proBNP alone. In the study by Joon YJ [26], adding CA125 to a baseline model significantly enhanced the predictive power for mortality, whereas incorporating NT-proBNP into the baseline model did not significantly enhance mortality prediction. Similarly, CA125 has been demonstrated to improve risk discrimination for heart failure-related outcomes in other settings. In the study by Núñez J [19], the addition of CA125 to the baseline model significantly improved the prediction of all-cause mortality, cardiovascular mortality, and heart failure-related mortality. In contrast, adding BNP to the baseline model did not significantly enhance discrimination for heart failure-related mortality.

CA125 and NT-proBNP are two biomarkers with distinct but complementary characteristics. CA125 increases in heart failure due to inflammation and mesothelial cell activation, with inflammatory processes and cytokine activation being the primary mechanisms for CA125 synthesis [28, 29]. CA125 is considered a marker of systemic congestion and right heart dysfunction [30]. In a prospective study involving 2,949 patients admitted with AHF, Miñana G [30] found that the strongest factors influencing CA125 levels were pleural effusion and severe tricuspid regurgitation, both markers of impaired right heart function. Similarly, Núñez J [14] evaluated 2,356 patients with AHF and severe outpatient heart failure and demonstrated that congestion-related factors such as elevated NT-proBNP, composite congestion scores, low serum sodium, pulmonary crackles, and hepatomegaly accounted for 79.4% of the variability in CA125 levels. In contrast, NT-proBNP is predominantly a biomarker of left heart function. It increases in response to elevated wall stress, particularly in the left ventricle. Research has

shown that changes in NT-proBNP levels are primarily driven by factors related to left-sided cardiac dysfunction, including impaired renal function and reduced left ventricular ejection fraction [30].

The combined use of CA125 and NT-proBNP offers several distinct advantages that enhance their utility in clinical practice. First, CA125 and NT-proBNP provide complementary temporal insights: NT-proBNP, with its short half-life of approximately 120 min [31], reflects acute hemodynamic changes, whereas CA125, with a longer half-life of 5–12 days [32], offers information on fluid redistribution and congestion over preceding weeks. This relationship is analogous to the complementary roles of blood glucose and HbA1C in diabetes management, offering both short- and long-term perspectives. Second, unlike natriuretic peptides, CA125 levels are relatively unaffected by factors such as age, renal function, or left ventricular ejection fraction, making it a more stable and reliable biomarker across diverse clinical scenarios [11]. Third, both biomarkers demonstrate independent prognostic thresholds that are not confounded by conventional clinical or laboratory variables, thereby enhancing their predictive accuracy for adverse outcomes in patients with acute heart failure. Finally, the widespread availability of these biomarkers in healthcare settings, combined with the particularly low cost of CA125, supports their integration into routine clinical practice alongside NT-proBNP, promoting broader application and accessibility. Risk stratification using these markers helps identify high-risk patients, enabling timely and targeted interventions to reduce mortality. Potential treatments include: (1) addressing the underlying cause of heart failure; (2) early initiation of guideline-directed therapies, such as ARNI/ACEi/ARBs, beta-blockers, MRAs, SGLT2 inhibitors, and device therapy when indicated; and (3) structured follow-up and patient education to promote long-term adherence.

Our study had several potential limitations. First, as a single-center investigation, the results require external validation in broader populations. Second, we did not examine certain variables that could influence patient outcomes, such as specific outpatient medication regimens, dosages, and adherence to therapy. Third, the study was conducted during the COVID-19 pandemic, which may have contributed to an overestimation of mortality and rehospitalization risks; Vietnam officially declared the end of the pandemic on July 7, 2023. Therefore, our findings should be confirmed in larger, multicenter prospective cohort studies involving Vietnamese and broader Southeast Asian populations.

Conclusion

This study suggests that both CA125 and NT-proBNP are significant prognostic biomarkers in patients with AHF. Moreover, the combination of CA125 with NT-proBNP significantly enhances the prediction of cardiovascular mortality, all-cause mortality, and the composite outcome of all-cause mortality or rehospitalization due to heart failure. These findings support the potential integration of CA125 alongside NT-proBNP in the routine risk stratification of patients with AHF.

Abbreviations

AHF	Acute Heart Failure
aHR	adjusted Hazard Ratio
AUC	Areas Under the receiver operating characteristic Curve
AUC-PR	Area Under the Precision-Recall Curve
CA125	Carbohydrate Antigen 125
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
KDIGO Kidney Disease	Improving Global Outcomes
NT-proBNP	N-terminal pro–B-type natriuretic peptide

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12872-025-04994-0.

Supplementary Material 1.

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Clinical trial number

Not applicable.

Authors' contributions

Conception and design: CMT; Data collection: CMT, HNC; Data analysis and result interpretation: TTT; Methodology guidance: HNC, NHND; Manuscript drafting: CMT, HNC, TTT; Manuscript editing: CMT, HNC, TTT, NHND. All authors read and approved the final manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study protocol adhered to the Declaration of Helsinki. This study was approved by the Ethics Committee of Biomedical Research at the University of Medicine and Pharmacy at Ho Chi Minh City (21598-DHYD). All patients provided written informed consent.

Consent for publication

Not applicable.

Competing interests
The authors declare no competing interests.

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