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Elevated CA125 values predict adverse outcomes in acute heart failure.

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Keywords: carbohydrate antigen 125; risk prediction; N-terminal pro-B-type natriuretic peptide; acute heart failure.

Abstract. In acute heart failure (AHF), elevated carbohydrate antigen 125 (CA125) and N-terminal pro-B-type natriuretic peptide (NTproBNP) have been shown to correlate with adverse events. We sought to quantify their prognostic usefulness in predicting the six-month combined death/heart failure readmission endpoint. The study included 352 patients admitted for AHF. The primary endpoint was the six-month combined endpoint of death/AHF rehospitalization. CA125 and NTproBNP were dichotomized according to the best cut-offs to predict the six-month primary endpoint. The independent association of CA125 and NTproBNP with the primary endpoint was assessed by multivariate Cox regression analysis, and their incremental prognostic utility was evaluated by net reclassification improvement (NRI) and integrated discrimination improvement (IDI) index. Forty-seven (13.4%) deaths and 113 (32.1%) AHF rehospitalizations were identified at the six-month follow-up. The subjects with CA125≥39.7 U/mL and NTproBNP≥3900 pg/mL had significantly higher cumulative event rates (56.1% vs. 33.3% and 53.3% vs. 33.8%, both p<0.001). Elevated CA125 (HR 1.93; 95% CI [1.32-2.83]; p=0.001) was associated with a higher HR (hazard ratio) than NTproBNP≥3900 pg/mL (HR 1.71; 95% CI [1.19-2.48]; p=0.004) after adjusting for established risk factors. Elevated CA125 still independently predicted adverse events when CA125 and NTproBNP entered the same multivariate model. Furthermore, risk reclassification analyses demonstrated significant improvements in NRI of 22.3% (p=0.014) and IDI of 2.7% (p=0.012) when adding CA125 to the base model + NTproBNP. Elevated CA125 and NTproBNP predicted adverse outcomes in AHF patients. CA125 added prognostic value to NTproBNP; thus, their combination conferred greater predictive capacity.

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Valores elevados de CA125 predicen resultados adversos en la insuficiencia cardíaca aguda.

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Palabras clave: antígeno carbohidrato 125; predicción del riesgo; péptido natriurético tipo pro-B N-terminal; insuficiencia cardíaca aguda.

Resumen. En la insuficiencia cardíaca aguda, se ha demostrado que el antígeno de carbohidratos 125 (CA125) elevado y el péptido natriurético tipo B N-terminal (NTproBNP) se correlacionan con eventos adversos. Intentamos cuantificar su utilidad pronóstica al predecir el punto final combinado de 6 meses de readmisión por muerte/insuficiencia cardíaca. El estudio incluyó a 352 pacientes ingresados por insuficiencia cardíaca aguda. El punto final principal fue el punto final combinado de 6 meses de muerte/rehospitalización aguda. CA125 y NTPROBNP se dicotomizaron de acuerdo con los mejores límites para predecir el punto final primario de 6 meses. La asociación independiente de CA125 y NTPROBNP con el punto final primario se evaluó mediante análisis multivariado de regresión de Cox, y su utilidad pronóstica incremental se evaluó mediante la mejora de la reclasificación neta (NRI) y el índice de mejora de la discriminación integrada (IDI). En el seguimiento a los 6 meses se identificaron un total de 47 (13,4%) muertes y 113 (32,1%) rehospitalizaciones por insuficiencia cardíaca aguda. Los sujetos con CA125≥39,7 U/mL y NTproBNP≥3900 pg/mL presentaron tasas de acontecimientos acumulativos significativamente más altas (56,1% frente a 33,3% y 53,3% frente a 33,8%, p<0,001 en ambos casos). CA125 elevado (HR: 1,93; IC del 95% [1,32-2,83]; p = 0,001) se asoció con un HR superior al NTproBNP ≥3900 pg/mL (HR 1,71; IC del 95% [1,19-2,48]; p = 0,004) después del ajuste por los factores de riesgo establecidos. CA125 elevado aún predijo de forma independiente los acontecimientos adversos cuando tanto CA125 como NTproBNP se introdujeron juntos en el mismo modelo multivariante. Además, los análisis de reclasificación del riesgo demostraron mejoras significativas en el NRI del 22,3% (p = 0,014) y en el IDI del 2,7% (p = 0,012) al añadir CA125 al modelo base + NTproBNP. Los niveles elevados de CA125 y NTproBNP predijeron los resultados adversos en los pacientes con insuficiencia cardíaca aguda. CA125 añadió valor pronóstico al NTproBNP y, por lo tanto, su combinación confirió una mayor capacidad predictiva.

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INTRODUCTION

Given the variations in clinical presentation and the impact of comorbidities in acute heart failure (AHF) patients, risk prediction remains challenging. Identifying high-risk subjects will help in further management by optimizing diuretic therapy, increasing the frequency of monitoring visits, and other therapeutic measures.

Published studies indicate that high levels of several biomarkers [1], including natriuretic peptides [2,3], sST-2 [4-6], cardiac troponins [7,8], and carbohydrate antigen 125 (CA125) [9,10], correlate with AHF severity and adverse outcomes. Based on different patho-

physiological pathways involving heart failure progression and response patterns for modification over time, we speculate that integrating multiple biomarkers will improve prognostic power in subjects admitted for AHF. As a widely used biomarker for monitoring ovarian cancer [11], CA125 has been studied in heart disease patients [10,12-14] and especially in heart failure [10,12,15], emerging as a surrogate for fluid overload and/or cytokine production in AHF [16].

Our study was performed to evaluate the prognostic utility of CA125 in predicting the six-month combined endpoint of death/AHF rehospitalization among AHF patients.

METHODS

Study population and design

This prospective, observational cohort study from a single centre included 352 patients consecutively admitted to the cardiology ward from December 2019 to September 2020 due to AHF following current guidelines [17,18]. AHF was the primary diagnosis of hospitalization for our study. Patients with a diagnosis of severe hepatic disease, sepsis, ongoing dialysis treatment for end-stage renal disease, pulmonary embolism, or acute rheumatic and autoimmune diseases were excluded by design. Demographic information, vital signs, medications, and medical history were collected, along with standard echocardiographic evaluation, laboratory results and 12-lead electrocardiogram during index admission. Intravenous furosemide or torasemide was used in all patients at least 24 h after admission. 11.4% and 4.5% of the patients received intravenous treatment with vasodilators and vasopressors, respectively. The established treatment guidelines were followed [17-19]. Time to death/AHF readmission, whichever occurred first, was the primary endpoint at the six-month follow-up.

Subjects were followed up through outpatient service or by telephone. Three patients were lost to follow-up during the study period. Patients were censored free of events or lost to follow-up at last contact within this period or at six months. The local ethics committee approved this study, and all patients provided informed consent for their participation following the Declaration of Helsinki.

Biomarker measurement

CA125 serum levels were obtained between 5:30 and 8:00 h on the second day of admission. In contrast, N-terminal pro-B-type natriuretic peptide (NTproBNP) serum levels were immediately determined after admission using commercially available immunoassay kits (Elecsys CA125 II assay, Roche Diagnostics and Vitros Immunodiagnostic Products NT-proBNP Reagent Pack, Ortho-Clinical Diagnostics, respectively). A technician blinded to the clinical information performed the biomarker assay.

Statistical analysis

Categorical variables are presented as frequencies and percentages, and continuous variables are summarized as the mean ± standard deviation or median (interquartile range). We dichotomized both biomarkers according to the best predictive cut-offs and compared between-group baseline characteristics using the t-test, Mann–Whitney test, chi-square or Fisher exact test, as appropriate. The resulting cut-off values were 39.7 U/mL for CA125 and 3900 pg/mL for NTproBNP. The cumulative rate of events (death or AHF readmission) among CA125 or NTproBNP categories was estimated and compared using the Kaplan–Meier method and log-rank test. Univariate and multivariate Cox analyses determined the relationship of CA125 and NTproBNP with the primary endpoint. Candidate variables in the initial multivariate model included clinical characteristics such as age, sex, weight, history of atrial fibrillation, diabetes, hypertension and acute myocardial infarction on admission. The biochemical variables included were serum creatinine, blood hemoglobin, and serum sodium. We also included left ventricular ejection fraction (LVEF>50% [reference], 36%-50%, and ≤35%), admission heart rate, admission

systolic blood pressure, evidence of pleural effusion, peripheral oedema, and AHF category (worsening heart failure [WHF] or new-onset heart failure) in our analyses. For multivariate Cox regression analyses, we retained factors with $p<0.15$ in univariate Cox analysis and those clinically relevant. Given the number of events available, the included variables were carefully chosen, and a parsimonious multivariate Cox model was derived. CA125, NTproBNP, or both biomarkers were first entered individually in the multivariate model. The Schoenfeld residuals were used to test the assumption of proportional hazards over time.

Harrell's C-statistics measured the discriminative ability of the models. The incremental prognostic utility of CA125 for NTproBNP and baseline variables was evaluated using integrated discrimination improvement (IDI) and net reclassification improvement (NRI) with the corresponding P values. We performed two multiple linear analyses to examine the relations of log-transformed CA125 and NTproBNP to clinical variables.

A 2-sided p value of <0.05 was considered statistically significant in all analyses. The principal analysis was performed using SPSS 26.0. Risk reclassification was calculated in R 4.0.3.

RESULTS

Baseline characteristics

Of 352 subjects, 49.4% had LVEF>50%. Heart failure with preserved ejection fraction predominated in our population, with only 17.0% and 21.2% exhibiting LVEF≤35% for patients with CA125<39.7 U/mL and patients with CA125≥39.7 U/ mL, respectively. The sample consisted of 46.9% females, and the mean age was 76±11 years. The median baseline levels of CA125 and NTproBNP in the entire population were 43.2 U/mL (21.6-102.7) and 5170 pg/mL (2748-10000), respectively. The baseline characteristics of the study participants by CA125 categories are shown in Tables 1, 2 and 3. Patients with elevated CA125 (CA125≥39.7 U/mL) exhibited a worse clinical profile. Lower LVEF and pleural effusion were more prevalent when CA125 was elevated. Subjects with CA125 ≥39.7 U/mL had a higher proportion of treatment with digitalis at discharge and a lower proportion with sodium-glucose cotransporter 2 inhibitor. Lower LVEF, pleural effusion, peripheral edema and paroxysmal nocturnal dyspnea were more prevalent when CA125 was elevated. No differences were detected in the presence of orthopnea and moist rales in lung fields.

Clinical predictors of CA125 and NTproBNP

Table 4 lists those variables independently correlated with log-transformed CA125 and NTproBNP. We identified different clinical predictors of these two biomarkers in the AHF setting. For lnCA125, the most important predictors were pleural effusion and WHF (standardized β coefficients 0.392 and 0.231, respectively). The most important predictors of lnNTproBNP were serum creatinine, weight and LVEF (standardized β coefficients 0.382, -0.306 and -0.286, respectively).

Moreover, we found differential associations of CA125 and NTproBNP with clinical presentations of AHF. A presentation as WHF was associated with higher CA125 levels; conversely, admission for new-onset heart failure was independently and positively related to NTproBNP values.

CA125 levels, NTproBNP levels, and the primary endpoint

In total, 47 patients (13.4%) died (12 deaths occurred during the index admission and 35 post-discharge), and 113 (32.1%) AHF rehospitalizations were identified at the six-month follow-up. CA125 and NTproBNP values in subjects experiencing death/AHF rehospitalization were significantly higher when compared with those free of events (56.3 U/mL [27.2-135.6] vs. 33.9 U/mL [18.4-79.8] and 6255 pg/mL [3425-6255] vs. 4085 pg/mL [2390-8015], respectively, $p<0.001$ for both).

Table 1
Demographic and medical characteristics stratified by CA125 categories.

	CA125<39.7U/mL (n=159)	CA125≥39.7U/mL (n=193)	*p*
Age, years	77±9	75±12	0.085
Female, n (%)	83 (52.2)	82 (42.5)	0.069
Weight, kg	60.4±12.3	59.4±12.1	0.425
Hypertension, n (%)	108 (67.9)	112 (58.0)	0.056
Diabetes mellitus, n (%)	44 (27.7)	55 (28.5)	0.864
Atrial fibrillation, n (%)	76 (47.8)	107 (55.4)	0.153
Previous coronary artery disease, n (%)	38 (23.9)	33 (17.1)	0.114
Previous myocardial infarction, n (%)	19 (11.9)	15 (7.8)	0.187
Acute myocardial infarction, n (%)	25 (15.7)	11 (5.7)	0.002
Previous PCI, n (%)	15 (9.4)	9 (4.7)	0.077
Valvular heart disease, n (%)	17 (10.7)	24 (12.4)	0.612
WHF, n (%)	131 (82.4)	182 (94.3)	<0.001
Previous pacemaker, n (%)	4 (2.5)	5 (2.6)	1.000
Anemia, n (%)	43 (27.0)	51 (26.4)	0.896
Previous stroke, n (%)	17 (10.7)	22 (11.4)	0.833
COPD, n (%)	35 (22.0)	45 (23.3)	0.771
Previous malignancy, n (%)	2 (1.3)	12 (6.2)	0.018
Pleural effusion, n (%)	59 (37.1)	140 (72.5)	<0.001
Peripheral oedema, n (%)	38 (23.9)	96 (49.7)	<0.001

CA125, carbohydrate antigen 125; PCI, percutaneous coronary intervention; WHF, worsening heart failure; COPD, chronic obstructive pulmonary disease. Anemia, defined as a hemoglobin level <120g/L in men and <110g/L in women.

By the Kaplan–Meier method, subjects with CA125≥39.7 U/mL and NTproBNP≥3900 pg/mL exhibited significantly higher cumulative event rates (56.1% vs. 33.3% and 53.3% vs. 33.8%, both p<0.001, Fig. 1A, B). When combined (Fig. 1C), patients with both biomarkers elevated had the highest cumulative event rate (61.5%); intermediate when only one of them was elevated: 44.2% for those with only CA125 elevated and 40.5% for subjects with only NTproBNP elevated, respectively, and lower (25.3%) for patients with values below the chosen biomarker cutpoints, p trend <0.001.

Table 5 displays the results of univariate and multivariate modelling. In the multivariate Cox analysis, elevated CA125 (HR 1.93; 95% CI [1.32-2.83]; p=0.001) was associated with a higher adjusted HR than NTproBNP≥3900 pm/mL (HR 1.71; 95% CI [1.19-2.48]; p=0.004). Elevated CA125 still independently predicted adverse events when CA125 and NTproBNP entered in the same multivariate model. In the final Cox model, serum creatinine and NTproBNP≥3900 pm/mL were other independent predictors. No interactions were found when these two biomarkers were included in the final Cox model (p=0.508).

We compared the performance of each regression model by using Harrell's C-statistic as a discrimination measure. Compared with the model including NTproBNP alone (0.623), CA125 alone (0.635) or none (0.606), the Cox model including CA125 and NTproBNP had a higher C-statistic (0.648).

Table 2
Vital signs, laboratory and echocardiography data stratified by CA125 categories.

	CA125<39.7U/mL (n=159)	CA125≥39.7U/mL (n=193)	*p*
Heart rate, b.p.m.	87±22	93±24	0.033
Systolic blood pressure, mmHg	136±24	135±23	0.564
Diastolic blood pressure, mmHg	80±16	83±15	0.150
Haemoglobin, g/L	123.6±24.0	126.3±25.6	0.314
Serum creatinine, umol/L	86 (69–117)	83 (66–114)	0.340
Sodium, mmol/L	140.1±5.3	139.0±5.3	0.057
NTproBNP, pg/mL	4200 (2510–7940)	5990 (3245–11400)	0.002
CA125, U/mL	21 (13-27)	91 (56-173)	<0.001
LVEF, %	50±13	47±13	0.020
LVEF ≤ 35%, n (%)	27 (17.0)	41 (21.2)	0.313
LVEF ≤ 50%, n (%)	43 (27.0)	67 (34.7)	0.122
LVDD, mm	53±9	53±10	0.802
LVSD, mm	39±10	40±11	0.317
LAD, mm	46±8	48±9	0.035

CA125, carbohydrate antigen 125; NTproBNP, N-terminal pro-B-type natriuretic peptide; LVEF, left ventricular ejection fraction; LVDD, left ventricular diastolic diameter; LVSD, left ventricular systolic diameter; LAD, left atrial diameter.

Table 3
Medical treatment stratified by CA125 categories

	CA125<39.7U/mL	CA125≥39.7U/mL	*p*
Intravenous administration of vasopresors , n (%)	8(5.0)	8(4.1)	0.691
Intravenous administration of vasodilators, n (%)	21(13.2)	19(9.8)	0.322
Medication before admission			
Loop diuretic, n (%)	61(38.4)	64(33.2)	0.310
Spironolactone, n (%)	55(34.6)	60(31.1)	0.486
ACEI/ARB/ARNI, n (%)	48(30.2)	50(25.9)	0.372
Beta-blocker, n (%)	46(28.9)	48(24.9)	0.391
Digitalis, n (%)	17(10.7)	25(13.0)	0.515
SGLT2 inhibitor, n (%)	20(12.6)	17(8.8)	0.251
Medication at discharge (340 cases discharged after improvement)			
Loop diuretic, n (%)	138(89.0)	172(93.0)	0.202
Spironolactone, n (%)	122(78.7)	159(85.9)	0.079
ACEI/ARB/ARNI, n (%)	105(67.7)	112(60.5)	0.169
Beta-blocker, n (%)	106(68.4)	130(70.3)	0.649
Digitalis, n (%)	30(19.4)	56(30.3)	0.021
SGLT2 inhibitor, n (%)	61(39.4)	47(25.4)	0.006

CA125, carbohydrate antigen 125; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor neprilysin inhibitor; SGLT2, sodium-glucose co-transporter 2.

Table 4
Clinical predictors of lnCA125 and lnNTproBNP.

	Standardized β regression coefficient	*p*
Ln (CA125)		
Pleural effusion, n (%)	0.392	<0.001
WHF, n (%)	0.231	<0.001
Peripheral oedema, n (%)	0.173	<0.001
Weight, kg	-0.154	0.002
Age, years	-0.151	0.003
LVEF, %	-0.132	0.006
Sodium, mmol/L	-0.106	0.018
Ln (NTproBNP)		
Serum creatinine, umol/L	0.382	<0.001
Weight, kg	-0.306	<0.001
LVEF, %	-0.286	<0.001
Pleural effusion, n (%)	0.154	<0.001
WHF, n (%)	-0.141	0.001
LVDD, n (%)	0.139	0.019

Ln(CA125), antigen carbohydrate 125 natural logarithm; Ln(NTproBNP), N-terminal pro–B-type natriuretic peptide natural logarithm; WHF, worsening heart failure; LVEF, left ventricular ejection fraction; LVDD, left ventricular diastolic diameter.

IDI and NRI values were significantly higher when adding each biomarker or both to the baseline variables model. Furthermore, a significant improvement in NRI of 22.3% (p=0.014) and IDI of 2.7% (p=0.012) was observed when adding CA125 to the base model + NTproBNP, supporting the incremental prognostic effect on top of NT-proBNP (Table 6).

DISCUSSION

Our study compared the risk prediction capacity of NTproBNP and CA125 in the setting of AHF. After multivariate adjustment, the elevation of CA125 and NTproBNP had a positive prognostic effect on adverse events. Not only elevated NTproBNP but also CA125 remained independent predictors of poor outcomes by combining both biomarkers. Additionally, adding CA125 to the model, including NTproBNP, significantly improved the predictive power.

Congestion, as a strong predictor of heart failure-related readmission and death [20], is responsible for most heart failure decompensation and is an essential therapeutic target in AHF [17,18]; however, evaluation of congestion remains a challenge in the routine management of AHF [21]. Perhaps due to the limited accuracy of signs and symptoms for quantifying fluid overload severity [22,23], signs of congestion (peripheral edema, pleural effusion, and other signs) are not routinely used for risk stratification. Suitable biomarkers would optimize risk prediction. CA125 levels correlate well with signs of fluid congestion[9,10,16] and pulmonary artery wedge pressure [10,16]. In this study, the most important clinical predictor of serum CA125 levels was the presence of pleural effusion. As a marker of congestion, CA125 is related to adverse events in heart failure patients [9,10] and indicates heart failure severity. However, in the BIOSTAT-CHF study, CA125 levels were highly predictive of adverse outcomes, beyond and independently of surrogates of congestion [9]. We also confirmed the predictive value of CA125 in stage D heart failure independently of pleural effusion or ascites. Therefore, we think CA125 could provide added prognostic value over surrogates of congestion [24]. Elevated CA125 is an independent predictor with incremental prognostic value over traditional prognosticators and natriuretic peptides [9], and thus, combining both biomarkers improved risk stratification in AHF [10].

Interestingly, although CA125 has been shown to be a potential tool for treatment guidance in AHF [12,25], little support is available regarding the benefits of NP-guided therapy over usual care [26]. In the CHANCE-HF trial, compared to the standard of care, a CA125-guided therapy characterized by a higher frequency of furosemide equivalent dose adjustments and ambulatory intravenous furosemide administrations according to CA125 response and clinical

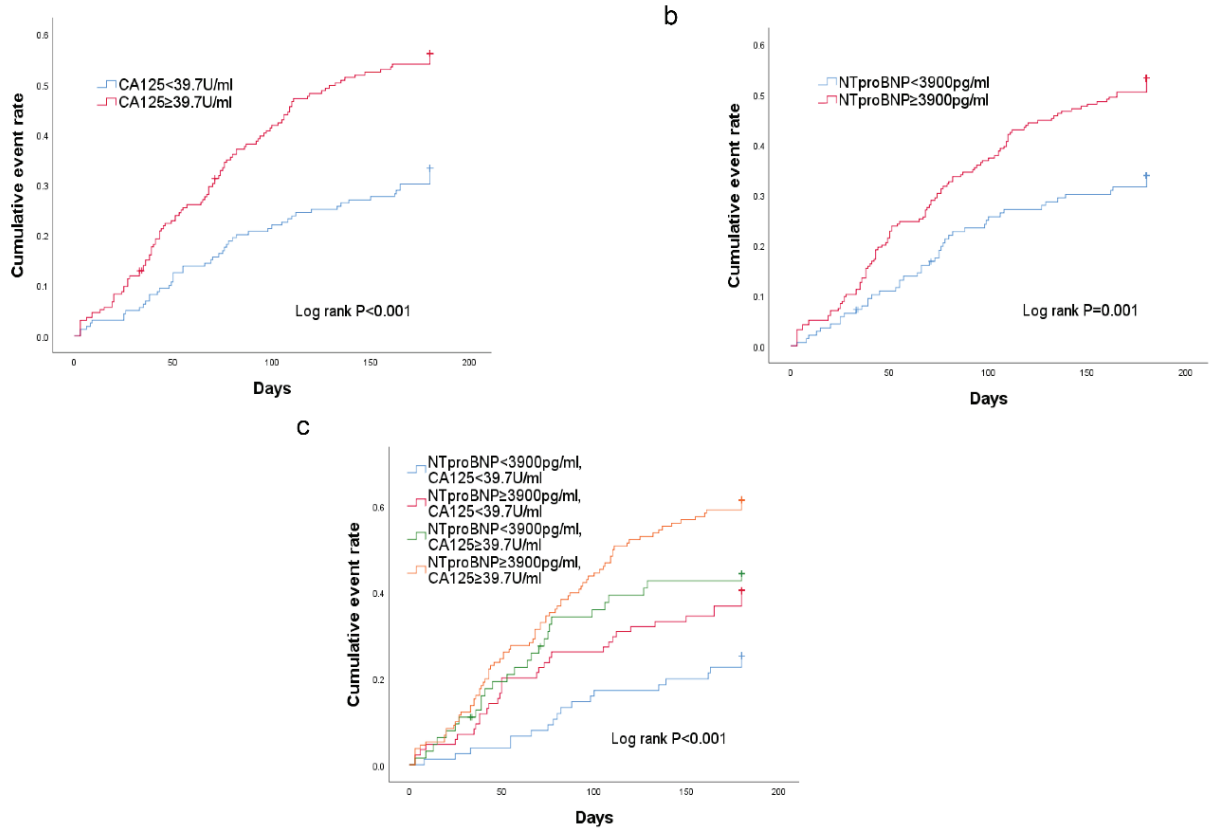

Fig. 1. Kaplan–Meier estimates for the six-month combined endpoint of death/AHF rehospitalization stratified by CA125 (A), NTproBNP (B) and the combination of CA125 and NTproBNP (C). AHF: acute heart failure.

Table 5

CA125 and NTproBNP hazard ratios for 6-month combined endpoint of death/AHF readmission.

Variables	Univariate		Multivariate	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age, /10 years increase	1.10 (0.96-1.29)	0.167	1.06 (0.90-1.24)	0.457
Atrial fibrillation, n (%)	1.38 (1.01-1.89)	0.046	1.21 (0.85-1.71)	0.291
Serum creatinine, /SD increase	1.20 (1.00-1.01)	0.004	1.20 (1.04-1.38)	0.014
LVEF≤35%, n (%)	0.76 (0.48-1.21)	0.251	0.75 (0.45-1.27)	0.285
LVEF≤50%, n (%)	1.37 (0.98-1.92)	0.069	1.30 (0.92-1.86)	0.142
Systolic blood pressure, /10 mmHg increase	0.93(0.87-1.00)	0.042	0.96(0.90-1.03)	0.222
Sodium, /SD increase	0.90 (0.79-1.03)	0.112	0.92 (0.79-1.06)	0.243
WHF, n (%)	1.39 (0.80-2.40)	0.244	1.15 (0.63-2.08)	0.647
Pleural effusion, n (%)	1.32 (0.96-1.82)	0.086	0.99 (0.69-1.42)	0.955
Peripheral oedema, n (%)	1.40 (1.04-1.91)	0.034	1.14 (0.82-1.60)	0.430
CA125≥39.7U/mL, n (%)	2.00 (1.44-2.79)	<0.001	1.78 (1.22-2.61)	0.003
NTproBNP≥3900pg/mL, n (%)	1.78 (1.26-2.50)	0.001	1.57 (1.08-2.27)	0.018

HR from Cox regression analysis. Multivariate HR from the model containing CA125 + NTproBNP + baseline variables. HR, hazard ratio; CI, confidence intervals; SD, standard deviation.

Table 6
Reclassification results for 6-month combined endpoint of death/AHF rehospitalization.

	NRI (%) (*p*-value)	IDI (%) (*p*-value)
Model 2 vs. 1	16.2(0.014)	2.6(0.010)
Model 3 vs. 1	23.8(0.008)	3.5(0.002)
Model 4 vs. 1	27.0(0.002)	5.3(<0.001)
Model 4 vs. 2	22.3(0.024)	2.7(0.020)

NRI, net reclassifification improvement; IDI, integrated discrimination improvement. Model 1 = base model. Model 2 = base model + NTproBNP categories. Model 3 = base model + CA125 categories. Model 4 = base model + NTproBNP categories + CA125 categories.

profile indicated a significantly reduced risk of 1-year mortality or AHF readmission [12]. In a recent multicentre randomized study of 160 AHF subjects with renal dysfunction, a CA125-guided diuretic strategy with an admission loop diuretics dose determined based on CA125 levels significantly improved 72-h eGFR [25]. Briefly, in subjects with high CA125 levels, high-intensity diuretic treatment and/or closer follow-up were advocated. When CA125 was low or decreased, a down-titration was recommended in both trials, which endorsed the role of CA125-guided decongestion treatment in AHF.

This study included a non-selected hospitalized population of patients with AHF. Based on this, we think many patients hospitalized for AHF have preserved ejection fraction in the real world. Although we pay more attention to heart failure with reduced ejection fraction, Dunlay *et al.* reported that two-thirds of advanced heart failure subjects had LVEF>40% [27]. The predominance of preserved ejection fraction in our population may explain a slightly lower proportion of treatment with renin–angiotensin system inhibitors and beta-blockers. Advanced heart failure occurs primarily in the elderly, and the cardiorenal syndrome is common. Sodium-glucose cotransporter 2 inhibitors may carry a higher risk of hypotension in older adults, in patients with renal dysfunction and taking loop diuretics. We know that patients with elevated CA125 had a worse clinical profile, which may be one possible explanation for a lower proportion of treatment with sodium-glucose cotransporter 2 inhibitor and a higher proportion of treatment with digitalis in patients with elevated CA125 values.

In this study, we used a cut-off value of 39.7 U/mL for CA125, but our previous paper confirmed that CA125≥65.7 U/mL was highly predictive of adverse outcomes in stage D heart failure patients [24]. We noticed that some researchers divided patients based on the normal CA125 levels (<35 U/mL) derived primarily from cancer studies[28]. The optimal cut-off for defining normal vs. elevated values in different heart failure scenarios has not been established. We think the value of CA125 we obtained could provide a particular reference value in the setting of AHF and stage D heart failure.

Given the long half-life of CA125 (approximately 5-12 days) [16] and the shorter mean half-life of NTproBNP (60-120 min) [29], CA125 potentially provides pathophysiological information several weeks prior, and NTproBNP could provide acute hemodynamic information, similar to glycated hemoglobin and serum glucose in diabetes. One study reported that levels of CA125 and NTproBNP represent distinct pathophysiological states related to heart failure severity [10]. The combined use of CA125 and NTproBNP improved risk stratification, and this multimarker approach holds promise in guiding depletion therapy, showing the need to incorporate CA125 into daily clinical practice. In addition, conversely to natriuretic peptides, age, sex, body weight, and renal function did not significantly influence CA125 levels [12,21]. In the current study, we found that NTproBNP strongly depended on serum creatinine, weight, and LVEF, while CA125 appeared not to be significantly influenced by these factors. Beyond these considerations, additional benefits for implementing CA125

testing in daily clinical practice arise from its standardized measurement, low cost, and wide availability.

Our study had some limitations. First, its observational design makes it susceptible to confounding factors and bias. Second, it is a single-centre study that precludes the extrapolation of results. Third, it is impossible to extrapolate findings to patients undergoing renal dialysis because this study included patients with baseline serum creatinine values ≤360 μmol/L. Finally, we measured CA125 levels at the one-time point after an overnight fast on the second day of admission; however, peak CA125 levels might better reflect fluid overload in patients with AHF.

In conclusion, in AHF patients, elevated CA125 levels were highly predictive of six-month death/AHF readmission, adding prognostic value to NTproBNP and clinical risk factors. Measuring simultaneously these two biomarkers conferred greater predictive capacity when compared with either of them alone. Hence, this glycoprotein should be considered a complement for optimal risk prediction. The underlying mechanisms of CA125 in AHF syndromes remain unclear, and more research is needed.

Conflict of interest

The authors have no conflicts of interest to declare.

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Participation of the authors

JZ and WHL wrote and designed the study. JZ and JH wrote and revised the manuscript. JQX collected data. All authors read and approved the final manuscript.

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