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Serum CA125: a prognostic biomarker for mortality in chronic heart failure

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Abstract

Objective To examine the relationship between serum Carbohydrate Antigen 125 (CA125) levels and long-term mortality in Chronic Heart Failure (CHF) patients and to assess its predictive value as a biomarker.

Methods This was a retrospective cohort study. We reviewed the medical records of 4,442 consecutive patients admitted to the First Affiliated Hospital of Xinjiang Medical University with a diagnosis of CHF since July 2012. After applying inclusion and exclusion criteria, 1,413 patients with available CA125 level measurements were included. The patients were categorized into three groups based on ejection fraction: HFrEF, HFmrEF, and HFpEF. Demographic details, comorbidities, and laboratory parameters were collected. CA125 levels were measured using an automated chemiluminescent immunoassay. Survival analysis was performed using the Kaplan-Meier method and Cox proportional hazards regression.

Results The median follow-up was 22.75 months. Elevated CA125 levels were significantly associated with increased all-cause mortality (ACM) across all CHF subtypes (HR = 2.05, 95% CI: 1.60–2.64, $P < 0.001$), especially in the HFpEF group (HR = 2.32, 95% CI: 1.59–3.40, $P < 0.001$). The area under the ROC curve for CA125 was 0.655, indicating moderate predictive accuracy. Multivariate analysis revealed that patients with CA125 levels ≥ 20.8 U/mL had a significantly higher risk of ACM (HR = 2.05). Adjustments for confounding factors did not alter these findings.

Conclusion Our findings suggest that serum CA125 levels may serve as a potential prognostic biomarker for mortality in CHF patients, particularly in the HFpEF subgroup. However, further research is needed to confirm these findings and elucidate the underlying mechanisms.

Keywords Chronic heart failure, CA125, All-cause mortality, Prognostic biomarker

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Introduction

Chronic heart failure (CHF) is a complex and multifaceted clinical syndrome [1], characterized by significant impairments in cardiac structure and function ([2], leading to a notable reduction in myocardial contractility or relaxation ([3]. This condition, which has profound implications for the heart's proper functioning ([4], results in congestion of both the pulmonary and systemic circulations ([5], causing a cascade of symptoms and complications that can be debilitating for patients ([6]. As a major global health concern ([7], CHF affects millions of individuals worldwide and contributes to a substantial burden on healthcare systems ([8].

Despite advancements in the management of CHF ([9], the associated high mortality rates and the condition's impact on patients' quality of life persist as critical issues ([10]. Early diagnosis and accurate assessment of CHF severity are crucial for developing effective treatment strategies aimed at enhancing patient outcomes. In this context, the identification of robust biomarkers for CHF has become increasingly important.

In the pursuit of improved diagnostic accuracy and prognostic stratification in heart failure, numerous biomarkers have been identified. Among these, N-terminal pro-brain natriuretic peptide (NT-proBNP) is a well-established biomarker. However, its utility is limited in patients with impaired renal function, where its diagnostic specificity decreases, particularly when NT-proBNP levels fall within a borderline range ([11].

In the process of identifying meaningful biomarkers for CHF, Carbohydrate Antigen 125 (CA125) has emerged as a candidate of particular interest ([12–14]. Traditionally utilized in the diagnostic workup for ovarian cancer ([15], CA125 has more recently been associated with the prognosis of cardiovascular diseases, including CHF ([16]. This association suggests a role for CA125 in the pathophysiology of CHF, although the precise mechanisms remain to be elucidated.

The potential involvement of CA125 in CHF could be multifactorial. One hypothesis is that CA125, through its interaction with inflammatory pathways, may exacerbate the inflammatory burden known to accompany CHF ((17–18). Additionally, CA125 has been implicated in the regulation of fluid balance, which could influence the edema often observed in CHF patients ([19]. Furthermore, CA125's role in the modulation of the immune response could also be a factor, as immune activation is a recognized component of CHF progression ([20].

Previous studies have demonstrated the association between CA125 levels and heart failure prognosis. However, these studies have limitations in terms of population diversity and detailed subgroup analysis. Our study aims to fill these gaps by examining a large cohort of CHF patients across different ejection fraction subtypes, with a particular focus on HFpEF, which is less well-understood in terms of biomarker associations. Additionally, we provide a comprehensive analysis of CA125 levels in relation to long-term mortality, aiming to enhance our understanding of its role in risk stratification and clinical management.

Methods

Research design and participant recruitment

This was a retrospective cohort study. We reviewed the medical records of 4,442 consecutive patients admitted to the First Affiliated Hospital of Xinjiang Medical University with a diagnosis of CHF from July 2012 to October 2023. The study included all patients who met the predefined inclusion criteria without selective exclusion. The patient enrollment process was systematic and based on well-defined criteria. Initially, we identified 4,442 consecutive patients admitted with a diagnosis of CHF. We then applied our inclusion criteria, which were based on the 2021 European Society of Cardiology (ESC) guidelines for diagnosing and treating chronic heart failure ([21]. This process required patients to be at least 18 years old and have had CHF for a minimum of three months. The age range of the participants in this study was from 18 to 97 years old.

Notably, this dataset has been previously utilized to explore the role of high-density lipoprotein cholesterol (HDL-C) levels as a novel predictor of long-term adverse outcomes in HF patients, as detailed in a recent publication ([22]. The current analysis focuses on the prognostic significance of serum CA125 levels in CHF, providing insights into disease management and prognosis.

We excluded patients with conditions that could confound the study results, including advanced cancers, severe organ dysfunction, immunological disorders, hematological conditions, a family history of psychiatric disorders, or those who had undergone recent surgical procedures (within the last three months) or experienced severe trauma. After applying these criteria, the study cohort comprised 1,413 individuals with accessible CA125 level measurements. Our study protocol, adhering to the ethical standards of the Declaration of Helsinki, was registered on ClinicalTrials.gov (identifier: NCT06092658) on October 19, 2023, and received approval from the hospital's Ethics Committee, with a waiver for informed consent due to the retrospective nature of the research. The patient enrollment process is detailed in Fig. 1, which illustrates the flow from the initial identification of 4,442 cases to the final enrollment of 1,413 participants suitable for the study analysis.

Data collection and laboratory procedures

For this retrospective cohort study, we utilized medical records from consecutive patients admitted to the First

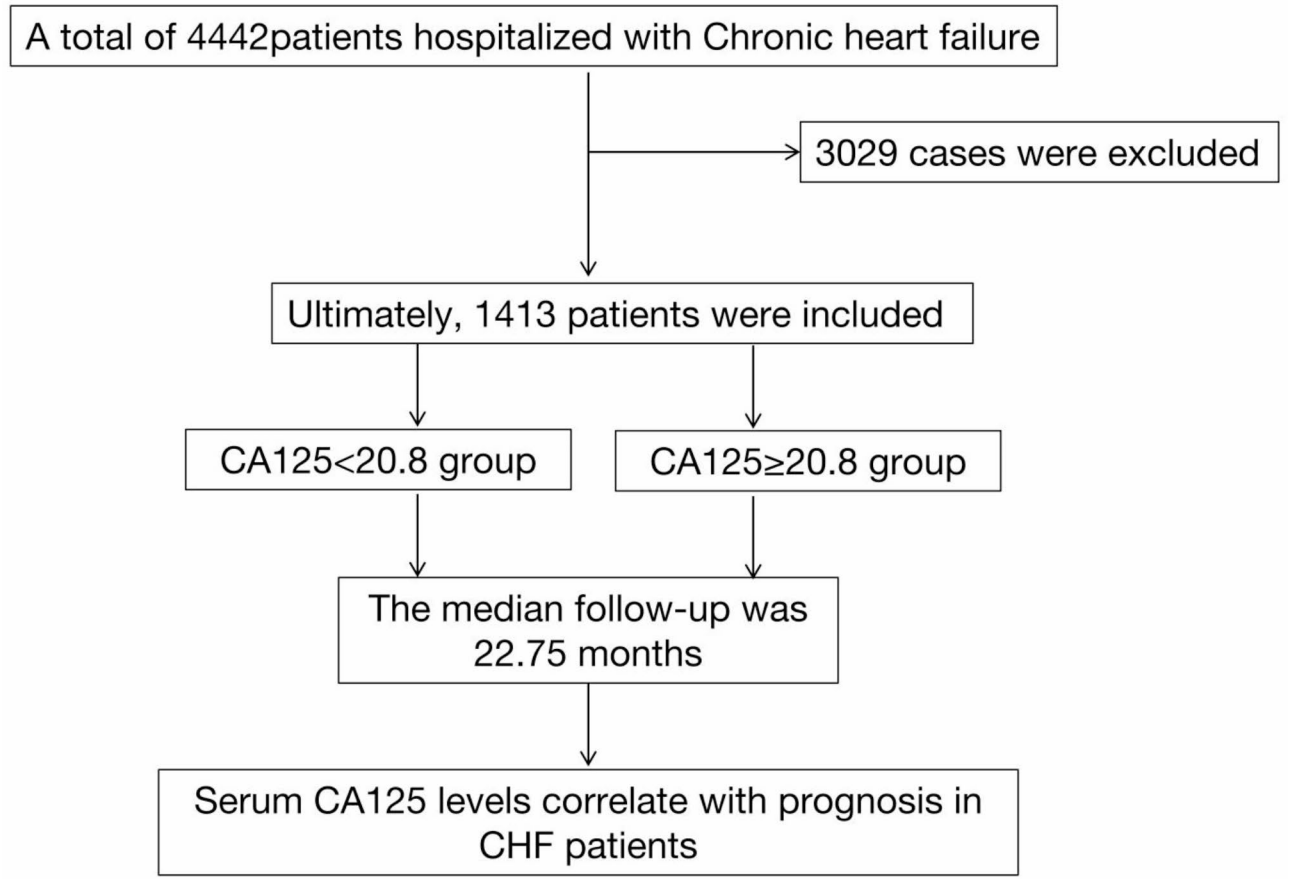

Fig. 1 Enrollment flowchart of CHF patients in the retrospective study. The flowchart outlines the recruitment process for the study, showing the number of patients initially identified with CHF, those excluded based on specific criteria, and the final number of participants included. The study focused on the association between serum CA125 levels and patient outcomes, with a median follow-up of 22.75 months

Affiliated Hospital of Xinjiang Medical University. A thorough chart review was conducted to retrospectively analyze the clinical data of all patients who fulfilled the predefined inclusion criteria, thereby ensuring a representative sample of the patient population. The data collection encompassed a range of parameters, including demographic details, medical history, findings from physical examinations, and outcomes of laboratory tests. Specifically, we assessed laboratory indices such as CA125, white blood cell count, hemoglobin, platelet count, potassium, sodium, creatinine, triglycerides, total cholesterol, total protein, as well as levels of serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT). These indices were determined from fasting peripheral venous blood samples collected either on the day of admission or the subsequent morning.

CA125 levels were measured as part of the routine clinical evaluation for patients admitted with a diagnosis of chronic heart failure. The measurement of CA125 was guided by clinical considerations, including its potential role as a marker of inflammation and fluid retention, both of which are common in heart failure patients. Additionally, CA125 was included in our biomarker panel for research purposes, aiming to explore its prognostic value in heart failure management.

Echocardiographic assessments were also incorporated, with results derived from ultrasonography conducted during the patients' hospital stay. The CA125 levels were measured at the hospital's Testing Center, with blood sera extracted within 24 h post-admission, adhering to standardized procedures for venipuncture via the brachial route. Serum samples were centrifuged at 3,000 revolutions per minute for 10 min to separate serum from blood cells. The CA125 levels were quantified using an automated chemiluminescent immunoassay with a double-antibody sandwich method, which is recognized for its sensitivity and specificity in clinical diagnostics ([23]. The testing was performed on a Cobas 8000 analyzer from Roche Diagnostics, utilizing reagents and quality control materials provided by the manufacturer, thus ensuring the consistency and reliability of CA125 level measurements. This rigorous approach to data collection and laboratory analysis is critical for the validity of our findings, providing a robust basis for

our investigation into the relationship between serum CA125 levels and the long-term prognosis of heart failure patients.

Diagnostic criteria

For this study, the diagnosis of CHF was made in accordance with the 2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure ([21]. The diagnostic criteria encompassed the following: (1) the presence of characteristic symptoms of heart failure, including dyspnea and fatigue; (2) clinical signs indicative of heart failure, such as elevated jugular venous pressure, pulmonary rales, and peripheral edema; (3) categorization based on left ventricular ejection fraction (LVEF): heart failure with reduced ejection fraction (HFrEF, LVEF < 40%), heart failure with mid-range ejection fraction (HFmrEF, LVEF 40–49%), and heart failure with preserved ejection fraction (HFpEF, LVEF ≥ 50%) ((24–25); (4) assessment of diastolic dysfunction, which was defined based on echocardiographic parameters, including an E/A ratio < 0.8 (impaired relaxation) or > 2.0 (restrictive filling), an E/e' ratio > 14 (indicative of elevated left ventricular filling pressures), and a left atrial volume index (LAVI) > 34 mL/m² (reflecting left atrial remodeling). HFpEF was further characterized by the presence of significant structural heart disease (e.g., left ventricular hypertrophy) and/or diastolic dysfunction, in the absence of left ventricular dilation.

The diagnosis of hypertension and diabetes mellitus was established according to standard clinical criteria ([26–28].

Follow-up procedures

In this study, we implemented a thorough follow-up strategy to monitor the long-term outcomes of patients diagnosed with CHF at the First Affiliated Hospital of Xinjiang Medical University. Post-hospitalization for CHF, patients underwent a structured follow-up protocol that included regular contact via telephone or mail, ensuring compliance with ethical standards and privacy regulations. The follow-up was designed to evaluate key health outcomes, document adverse events, and assess medication adherence among participants. This process was essential for tracking the progression of CHF and evaluating the efficacy of prescribed treatment regimens. Additionally, the follow-up aimed to offer ongoing support and ensure continuity of care after hospital discharge. The follow-up duration was meticulously recorded, with a median of 22.75 months, providing a robust framework for assessing patients' health status and the influence of CHF on their quality of life and survival. The interquartile range (IQR) of the follow-up period, spanning from 12.37 to 47.11 months, reflects the diversity in patient follow-up while ensuring a comprehensive observational period. The primary clinical endpoint of the study was all-cause mortality (ACM), defined as death from any cause during the follow-up period, regardless of the underlying cause. This endpoint was chosen to provide a comprehensive assessment of the overall mortality risk in the study population. Although ACM is a broad measure, it reflects the cumulative impact of various factors, including heart failure progression, comorbidities, and other potential complications.

Baseline characteristics and admission details

We collected detailed information on the reasons for admission and the clinical status of patients at the time of admission. The primary reasons for admission included heart failure decompensation, diagnostic evaluation, and medication adjustment. The majority of patients ($n = 1,200$, 85.0%) were admitted due to heart failure decompensation, characterized by worsening symptoms such as dyspnea, peripheral edema, and fatigue. A smaller proportion of patients ($n = 150$, 10.6%) were admitted for diagnostic evaluation to confirm the diagnosis of CHF or to rule out other conditions. The remaining patients ($n = 63$, 4.5%) were admitted for medication adjustment to optimize their treatment regimens.

Additionally, we assessed the New York Heart Association (NYHA) functional class at admission for all patients. The distribution of NYHA classes was as follows: Class I ($n = 100$, 7.1%), Class II ($n = 500$, 35.4%), Class III ($n = 600$, 42.5%), and Class IV ($n = 213$, 15.1%). This classification provides a standardized measure of the severity of heart failure symptoms and helps in understanding the clinical context of the patients included in the study.

Statistical analysis

For this study, we applied a rigorous statistical approach to ensure the precision and reliability of our findings. All statistical analyses were performed using IBM SPSS Statistics Software (SPSS) version 25.0, a robust tool for managing and analyzing complex datasets. Quantitative data, assuming a normal distribution, were expressed as mean values ± standard deviation, offering a concise summary of the central tendency and variability within the dataset. For data that did not conform to a normal distribution, we employed non-parametric methods, with results presented as quartiles to accurately reflect the distribution without the influence of outliers. Categorical data, encompassing variables such as gender and the presence of specific conditions, were tabulated as frequencies and percentages. These were analyzed using the chi-square test, a standard method for evaluating associations between categorical variables. When comparing mean values between two independent groups, we utilized the independent samples t-test, which is widely

recognized for assessing mean differences across groups, under the assumption of normal distribution and homogeneity of variance. For non-normally distributed data, the Mann-Whitney U test was applied, a non-parametric test suitable for comparing distributions of continuous or ordinal data that do not meet the assumptions for a t-test. Survival analysis was conducted using the Kaplan-Meier method, designed to estimate survival probabilities over time, allowing us to assess the duration until the event of interest, specifically mortality, occurred within the study population. To evaluate the impact of multiple variables on survival outcomes, we performed Cox proportional hazards regression analysis, a multivariate approach that helps to ascertain the independent effects of each variable while controlling for others, thus providing a nuanced understanding of the data relationships. To address the concern raised by the reviewer regarding the consideration of multiple testing, we implemented the Bonferroni correction when performing multiple statistical comparisons. This method adjusts the alpha level to control the family-wise error rate, thus preventing an inflated type I error rate and ensuring the integrity of our statistical inferences.

Results

Baseline data

Our study enrolled a total of 1,413 patients diagnosed with CHF, comprising 900 males (63.7%) and 513 females (36.3%), with an average age of 66.04 ± 13.08 years and a median follow-up period of 22.75 months. The patient cohort was categorized into three groups based on ejection fraction: HFrEF ($n = 360$), HFmrEF ($n = 379$), and HFpEF ($n = 674$). Table 1 details the demographic and clinical characteristics, including gender, age, comorbidities, and all-cause mortality rates for each group. Interestingly, the HFrEF group did not exhibit higher all-cause mortality compared to the HFmrEF and HFpEF groups. This finding may be attributed to the more aggressive treatment strategies typically employed for HFrEF patients, including guideline-directed medical therapy and device interventions. Additionally, differences in baseline characteristics, such as age and comorbidities, may have influenced the mortality outcomes. Further subgroup analyses adjusting for these factors are warranted to explore this observation in greater detail.

Baseline characteristics across CA125 categories

We stratified the study population into two groups based on the median CA125 level (20.8 U/mL). As shown in Table 2, patients with higher CA125 levels were significantly older in the HFmrEF subgroup ($P < 0.05$). Higher CA125 levels were associated with lower prevalence of coronary artery disease (CAD) and hypertension in the Total, HFmrEF, and HFpEF groups, while lower CA125 levels were linked to reduced valvular heart disease (VHD) in the Total and HFpEF groups. Patients with lower CA125 levels had higher LVEF in the Total, HFrEF, and HFmrEF groups ($P < 0.05$). Additionally, lower CA125 levels were associated with reduced creatinine and NT-proBNP levels across all subgroups ($P < 0.05$), indicating better renal function and less severe heart failure.

In terms of diastolic function, the E/A ratio was significantly lower in patients with higher CA125 levels across all subgroups ($P < 0.001$), suggesting impaired diastolic function. The E/e' ratio was significantly higher in patients with elevated CA125 levels ($P < 0.001$), indicating increased left ventricular filling pressure. Furthermore,

Table 1 Demographic and clinical characteristics of chronic heart failure patients by ejection fraction subtype

Variable	Total($n = 1413$)	HFrEF($n = 360$)	HFmrEF($n = 379$)	HFpEF($n = 674$)	*P*
Age, years	66.04 ± 13.08	62.62 ± 13.60	65.31 ± 9.28	68.65 ± 24.29	**< 0.001**
Sex, male, n(%)	900(63.7%)	257(71.4%)	254(61%)	389(57.7%)	**0.002**
CAD, n(%)	552(39.1%)	151(41.9%)	126(33.2%)	275(40.8%)	0.214
HTN, n(%)	623(44.1%)	175(48.6%)	177(46.7%)	271(40.2%)	**0.045**
VHD, n(%)	1081(76.5%)	262(72.8%)	300(79.2%)	519(77%)	0.123
CHD, n (%)	1390(98.4%)	351(97.5%)	378(99.7%)	661(98.1%)	0.089
DM, n(%)	1025(77.5%)	266(73.9%)	267(70.4%)	492(73%)	0.156
Cardiomyopathy, n(%)	1234(87.3%)	250(69.4%)	340(89.7%)	644(95.5%)	**< 0.001**
Arrhythmia, n (%)	734(51.9%)	156(43.3%)	193(50.9%)	385(57.1%)	**0.012**
ACM, n(%)	840(59.5%)	212(58.9%)	239(63.1%)	389(57.7%)	0.456

Notes: Age is expressed as the mean ± standard deviation (SD). Percentages indicate the proportion of patients within each Chronic Heart Failure (CHF) subtype who exhibit the specified characteristic or outcome. "Sex, male" refers to the number and percentage of male patients within each HF subtype group. Comorbid conditions include coronary artery disease (CAD), hypertension (HTN), valvular heart disease (VHD), congenital heart disease (CHD), diabetes mellitus (DM), cardiomyopathy, and arrhythmia. All-cause death indicates the number and percentage of patients who experienced death from any cause during the study's follow-up period. CHF subtypes are defined by ejection fraction (EF) as follows: Heart Failure with Reduced Ejection Fraction (HFrEF) with an EF ≤ 40%, Heart Failure with Mid-range Ejection Fraction (HFmrEF) with an EF between 41–49%, and Heart Failure with Preserved Ejection Fraction (HFpEF) with an EF ≥ 50%. *P*-value indicates the statistical significance of differences between the groups. A *P*-value < 0.05 suggests a significant difference. "Cardiomyopathy" refers to the presence of structural heart disease characterized by abnormal myocardial function, including both ischemic and non-ischemic forms. "Arrhythmia" includes all types of abnormal heart rhythms, ranging from premature ventricular contractions (PVCs) to more severe forms such as atrial fibrillation and ventricular tachycardia. ACM: All-cause mortality, was defined as death from any cause, confirmed through hospital records, telephone follow-up, and death certificates

Table 2 Baseline characteristics of participants stratified by CA125 levels

	Total($n=1413$)				HFrEF($n=360$)				HFmrEF($n=379$)				HFpEF($n=674$)			
Variable	**CA125<20.8 ($n=554$)**	**CA125 ≥ 20.8 ($n=859$)**	**F/χ^2/H value**	***P*-value after correction**	**CA125<20.8($n=90$)**	**CA125 ≥ 20.8($n=270$)**	**F/ χ^2/H value**	***P*-value after correction**	**CA125<20.8 ($n=152$)**	**CA125 ≥ 20.8 ($n=227$)**	**F/ χ^2/H value**	***P*-value after correction**	**CA125<20.8 ($n=312$)**	**CA125 ≥ 20.8 ($n=362$)**	**F/ χ^2/H value**	***P*-value after correction**
Age, years	66.51 ± 13.08	67.37 ± 13.67	0.77	0.32	62.05 ± 14.02	63.02 ± 13.87	0.39	0.76	66.1 + 10.5	67.4 + 9.50	9.75	**0.02**	68 ± 7.22	67 ± 9.34	0.13	0.965
Sex, male, n(%)	367 (66.2%)	533 (62.0%)	2.93	0.087	72(80.0%)	185(68.5%)	4.36	**0.037**	104(68.4%)	150(66.1%)	0.23	0.635	191(61.2%)	198(54.7%)	2.92	0.087
Coronary artery disease, n(%)	400 (72.2%)	461 (53.7%)	66.91	**<0.001**	57(63.3%)	152(56.3%)	1.37	0.241	115(75.7%)	138(60.8%)	9.07	**0.003**	228(73.1%)	171(47.2%)	46.32	**<0.001**
Hypertension, n(%)	340 (61.4%)	450 (52.4)%	14.59	**<0.001**	51(56.7%)	134(49.6%)	1.34	0.247	90(59.2%)	112(49.3%)	13.56	**0.005**	199(63.8%)	204(56.4%)	13.85	**0.003**
Valvular heart disease, n(%)	104 (18.8%)	228 (26.5%)	14.36	**<0.001**	24(26.7%)	74(27.4%)	0.02	0.891	29(19.1%)	50(22.0%)	0.48	0.489	51(16.3%)	104(28.7%)	14.51	**<0.001**
Diabetes mellitus, n(%)	160 (28.9%)	228 (26.5%)	3.51	0.061	25(27.8%)	69(25.6%)	0.17	0.678	43(28.3%)	69(30.4%)	0.19	0.659	92(29.5%)	90(24.9%)	1.82	0.104
Cardiomyopathy, n(%)	63 (11.4%)	116 (13.5%)	0.61	0.433	26(28.9%)	84(31.1%)	0.16	0.692	22(14.5%)	17(7.5%)	4.81	**0.028**	15(4.8%)	15(4.1%)	0.17	0.677
Arrhythmia, n (%)	253 (45.7%)	426 (49.6%)	1.58	0.209	54(60.0%)	150(55.6%)	0.54	0.461	72(47.4%)	114(50.2%)	0.3	0.586	127(40.7%)	162(44.8%)	0.17	0.163
Potassium, mmol / L	4.21 ± 0.51	4.40 ± 0.65	335.21	**<0.001**	4.29 ± 0.64	4.36 ± 0.66	0	0.999	4.19 ± 0.50	4.43 ± 0.63	7.35	**<0.001**	4.24 ± 0.50	4.44 ± 0.62	17.01	**<0.001**
Sodium, mmol / L	141.02 ± 3.81	141.80 ± 4.50	26.21	**<0.001**	142.71 ± 3.22	141.96 ± 3.92	3.96	0.303	142.08 ± 2.95	141.98 ± 4.72	14.44	**<0.001**	141.55 ± 4.22	141.88 ± 4.65	14.96	**0.003**
Creatinine, μmol / L	85.96(73.02–98.10)	91.82(75.00-136.23)	10.68	**<0.001**	88.76(75.00–98.00)	91.00(76.00–99.00)	10.04	<0.001	83.75(69.48–99.40)	94.06(73.90-107.02)	3.78	**0.021**	84.00(74.00-97.72)	91.82(76.38-109.62)	10.04	**0.002**
Albumin, g/L	39.50 ± 4.32	36.86 ± 5.07	17.72	**<0.001**	41.13 ± 4.03	38.83 ± 4.55	11.56	**<0.001**	40.01 ± 4.29	37.49 ± 4.93	12.31	**<0.001**	38.93 ± 4.26	36.25 ± 4.84	12.91	**<0.001**
LVEF%	50.50 ± 12.24	46.77 ± 12.98	15.49	**<0.001**	35.24 ± 3.96	30.42 ± 4.26	6.04	**<0.001**	44.70 ± 2.49	43.92 ± 2.56	8.56	**0.007**	59.35 ± 4.38	59.59 ± 4.51	0.07	0.795
E/A ratio	1.3 ± 0.4	1.1 ± 0.3	12.34	**< 0.001**	1.2 ± 0.3	1.0 ± 0.2	8.56	**0.003**	1.4 ± 0.5	1.2 ± 0.4	10.23	**0.001**	1.5 ± 0.6	1.3 ± 0.5	14.78	**< 0.001**
E/e' ratio	11.5 ± 3.2	14.2 ± 4.1	15.67	**< 0.001**	12.0 ± 3.5	14.5 ± 4.3	9.87	**0.002**	10.8 ± 3.0	13.8 ± 3.9	11.45	**0.001**	13.2 ± 3.8	15.0 ± 4.5	16.89	**< 0.001**
LAVI, mL/m^2	36.5 ± 10.5	42.3 ± 12.7	18.23	**< 0.001**	38.2 ± 11.0	43.0 ± 13.2	10.34	**0.001**	35.8 ± 10.2	41.5 ± 12.5	12.56	**0.001**	40.5 ± 11.8	44.0 ± 13.5	19.45	**< 0.001**
NT-proBNP, ng/L	2,647 (1,439,5,319)	3,058 (1,351,5,737)	24.78	**<0.001**	4380 (2491,6235)	5670 (3735,10,950)	21.83	**< 0.001**	3366(3274,4257)	4374(1837,7940)	32.43	**<0.001**	1029.47(939.37,1119.59)	1038.23 (951.41,1125.05)	19.21	**<0.001**

Notes: A *P*-value < 0.05 was considered statistically significant. The Bonferroni correction was applied to all statistical tests involving multiple comparisons to control the family-wise error rate. Data are presented as mean ± standard deviation for normally distributed data or median (interquartile range) for non-normally distributed data. "n" indicates the number of participants, and "%" indicates the percentage within each subgroup. The Chi-squared test (χ^2) was used for categorical variables, the t-test for continuous variables, and the Mann-Whitney U test for non-parametric comparisons between two groups. Abbreviations: CA125: Cancer Antigen 125;HFmrEF: Heart Failure with Mid-range Ejection Fraction; HFrEF: Heart Failure with Reduced Ejection Fraction; HFpEF: Heart Failure with Preserved Ejection Fraction; LVEF: Left Ventricular Ejection Fraction; NT-proBNP: N-terminal pro-B-type Natriuretic Peptide; E/A ratio: Ratio of early diastolic mitral inflow velocity (E) to late diastolic mitral inflow velocity (A), used to assess diastolic function; E/e' ratio: Ratio of early diastolic mitral inflow velocity (E) to early diastolic mitral annular velocity (e'), used to estimate left ventricular filling pressure; LAVI, mL/m^2: Left Atrial Volume Index, measured in milliliters per square meter, used to assess left atrial size

the LAVI, mL/m² was significantly larger in patients with higher CA125 levels ($P < 0.001$), reflecting greater left atrial enlargement. These findings suggest that higher CA125 levels are associated with more pronounced diastolic dysfunction and structural changes in the heart. For further details, see Supplementary Table S2: Table 2 Complete Version.

CA125 and clinical outcomes

The predictive accuracy of CA125 and NT-proBNP for ACM was evaluated using ROC curve analysis, as shown in Fig. 2. For the total population, the area under the curve (AUC) for CA125 was 0.666 (95% CI: 0.631–0.680, $P < 0.001$), while the AUC for NT-proBNP was 0.710 (95% CI: 0.685–0.735, $P < 0.001$), indicating that both biomarkers have significant discriminatory power for ACM. The ROC curves for CA125 and NT-proBNP are presented for each subgroup: HFrEF (CA125 AUC = 0.619, NT-proBNP AUC = 0.719), HFmrEF (CA125 AUC = 0.678, NT-proBNP AUC = 0.706), and HFpEF (CA125 AUC = 0.684, NT-proBNP AUC = 0.699).

The optimal cut-off value for CA125, determined to maximize sensitivity and specificity, was 20.8 U/mL, with 60% sensitivity and 70% specificity. This value defines the high CA125 group (levels ≥ 20.8 U/mL) and signifies a robust correlation with an increased risk of mortality, as evidenced by the AUC value and a *P*-value less than 0.001. The ROC curves for both CA125 and NT-proBNP are consistently above the line of no discrimination, confirming their diagnostic utility in identifying patients at varying risks of ACM across different CHF subtypes.

As shown in Table 3, in the overall population, the incidence of All-cause mortality (ACM) in the low CA125 group was 135 (24.4%), and in the high CA125 group, it was 438 (51%), with a significant difference between the two groups ($P < 0.001$). Concurrently, we observed that in each subgroup, including HFrEF (26.7% vs. 45.9%, $P < 0.001$), HFmrEF (20.4% vs. 48.0%, $P < 0.001$), and HFpEF (25.6% vs. 56.6%, $P < 0.001$), the aforementioned differences were present.

The Kaplan-Meier curves for CA125 and adverse outcomes are depicted in Fig. 3. Overall, patients in the low CA125 group (< 20.8 U/mL) exhibited a significantly reduced risk of All-cause mortality (ACM) compared to those in the high CA125 group. This distinction was consistent across each subgroup, including HFrEF, HFmrEF, and HFpEF.

A multivariate analysis, accounting for potential confounders, was performed to evaluate the prognostic significance of CA125 levels regarding ACM. Long-term follow-up data revealed that patients with CA125 levels ≥ 20.8 U/mL had a significantly higher risk of ACM compared to those with lower levels (HR = 2.05, 95% CI: 1.60–2.64, $P < 0.001$). This association was consistent in all subgroups, with the HFpEF subgroup showing the most pronounced increase in risk (HR = 2.32, 95% CI: 1.59–3.40, $P < 0.001$). Adjustments for variables including age and NT-proBNP did not alter these findings, as indicated by the maintained statistical significance (all $P < 0.05$) (Table 4).

Discussion

Our study evaluated the prognostic significance of serum CA125 in 1,413 patients with CHF, demonstrating a significant association between elevated CA125 levels and increased all-cause mortality across different subtypes (HFrEF, HFmrEF, and HFpEF). Notably, the association was particularly strong in the HFpEF subgroup, underscoring CA125's potential as a biomarker for risk stratification in this understudied population. These findings extend previous research by providing a comprehensive analysis across ejection fraction subtypes and emphasizing CA125's role in CHF prognosis.

In the baseline analysis, we observed a prevalence of comorbidities such as CAD and hypertension, which is in concordance with previous reports ([29]. The distribution of these comorbidities exhibited notable differences among the CHF subtypes, further accentuating the complexity and heterogeneity inherent in CHF. Importantly, the significant association between CA125 and ACM persisted even after accounting for these comorbidities. This persistence suggests that CA125 may capture unique pathophysiological facets of CHF, potentially related to its role in inflammatory pathways, fluid balance regulation, and myocardial remodeling—processes not fully explicable by traditional risk factors alone ([30–32]. The sustained association implies that CA125 could be reflective of underlying biological changes that contribute to the severity and progression of CHF, beyond the scope of common comorbidities.

The multivariate Cox regression analysis underscored the independent prognostic value of CA125 in our study. The HR for the high CA125 group (≥ 20.8 U/mL), compared to the low CA125 group, was 2.05. This finding is consistent with prior studies that have established CA125 as a significant prognostic biomarker across various clinical contexts, including CHF ([33]. Notably, our study further advanced these findings by conducting a comprehensive analysis of different CHF subtypes, providing a more nuanced understanding of the role of CA125 in heart failure prognosis.

The subgroup analysis revealed a particularly strong association between high CA125 levels and ACM in the HFpEF group, with a HR of 2.32. This finding is novel and significant because HFpEF has historically been less well - understood in terms of biomarker associations. The heightened risk observed in the HFpEF group may be attributed to its complex pathophysiology, which often

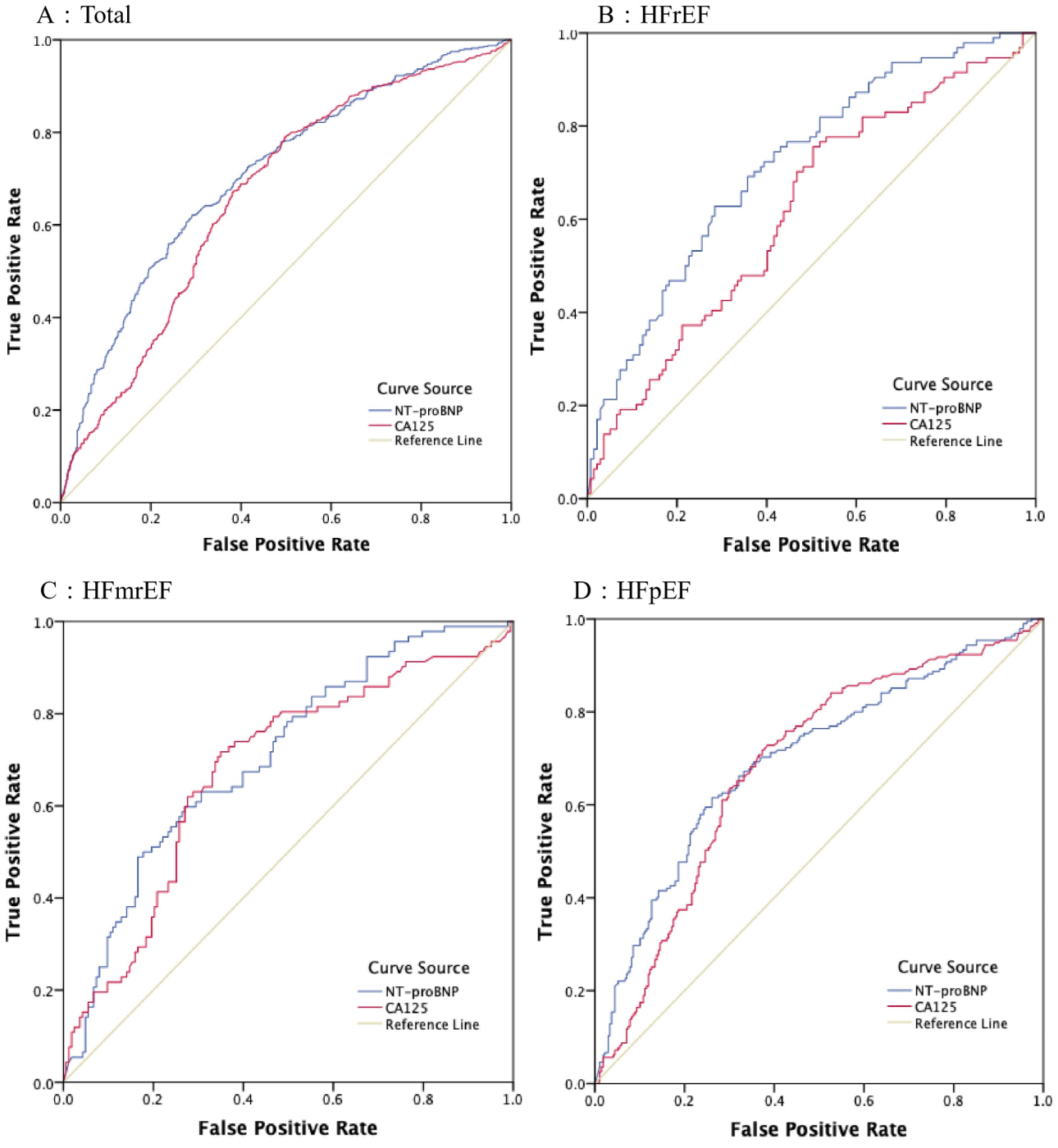

Fig. 2 ROC curves for predicting all-cause mortality based on CA125 and NT-proBNP levels. Panels **A-D** represent the total population, HFrEF, HFmrEF, and HFpEF subgroups, respectively. CA125: Cancer Antigen 125, a biomarker used to assess risk in certain conditions; NT-proBNP: N-terminal pro-B-type Natriuretic Peptide, a biomarker used to diagnose heart failure; AUC (Area Under the Curve): A measure of the test's ability to discriminate between patients with and without all-cause mortality (ACM). An AUC of 1 indicates perfect discrimination, while an AUC of 0.5 indicates no discrimination; 95% CI: 95% Confidence Interval, indicating the range within which the true AUC is likely to fall, with 95% probability; ACM: All-cause mortality, defined as death from any cause; *P*-value: The probability value indicating the statistical significance of the difference between the AUCs of the two groups, with "$P < 0.001$" indicating a highly significant difference; High CA125 Group: Patients with CA125 levels ≥ 20.8 U/mL; Low CA125 Group: Patients with CA125 levels < 20.8 U/mL

Table 3 Comparison of All-cause mortality in relation to CA125 levels in heart failure subgroups

Variable	Total($n=1413$)				HFrEF($n=360$)				HFmrEF($n=379$)				HFpEF($n=674$)			
	CA125<20.8 ($n=554$)	CA125≥20.8 ($n=859$)	χ^2 value	*P*-value	CA125<20.8($n=90$)	CA125≥20.8($n=270$)	χ^2 value	*P*-value	CA125<20.8 ($n=152$)	CA125≥ 20.8 ($n=227$)	χ^2 value	*P*-value	CA125<20.8 ($n=312$)	CA125≥20.8 ($n=362$)	χ^2 value	*P*-value
ACM(%)	135 (24.4%)	438 (51.0%)	145.71	**<0.001**	24(26.7%)	124(45.9%)	10.34	**<0.001**	31(20.4%)	109(48.0%)	29.82	**<0.001**	80(25.6%)	205(56.6%)	14.06	**<0.001**

Notes: CA125: Cancer Antigen 125, a biomarker used in the management of ovarian cancer and other conditions. ACM: All-cause mortality, was defined as death from any cause, confirmed through hospital records, telephone follow-up, and death certificates. HFrEF: Heart Failure with Reduced Ejection Fraction. HFmrEF: Heart Failure with Mid-range Ejection Fraction. HFpEF: Heart Failure with Preserved Ejection Fraction;χ^2 value: Chi-squared test statistic value indicating the magnitude of the difference between observed and expected frequencies.*P*-value: The probability value indicating the significance of the observed difference between groups. Statistical Methods: Chi-squared test used for categorical variables to assess the association between

involves diastolic dysfunction and pulmonary hypertension ([34].

In terms of diastolic function, the E/A ratio was significantly lower in patients with higher CA125 levels across all subgroups ($P<0.001$), suggesting impaired diastolic function. The E/e' ratio was significantly higher in patients with elevated CA125 levels ($P<0.001$), indicating increased left ventricular filling pressure. Furthermore, the LAVI, mL/m² was significantly larger in patients with higher CA125 levels ($P<0.001$), reflecting greater left atrial enlargement. These findings suggest that higher CA125 levels are associated with more pronounced diastolic dysfunction and structural changes in the heart.

Recent studies have highlighted the utility of biomarkers in the diagnosis and risk stratification of diastolic dysfunction. For example, a study by Călburean PA et al. ([35] demonstrated that biomarkers such as CA125 can complement echocardiographic parameters in identifying patients with diastolic dysfunction, particularly in HFpEF. Our findings align with this evidence, as elevated CA125 levels were associated with worse diastolic function, as indicated by higher E/e' ratios and larger LAVI values. This suggests that CA125 may serve as a valuable adjunct to echocardiography in the assessment of diastolic dysfunction, especially in patients with HFpEF.

The ROC curve analysis substantiated CA125's role as a predictive biomarker, with an AUC of 0.655 for the overall population. This indicates that CA125 levels can effectively distinguish between patients at higher and lower risk of ACM. The AUC values were consistently higher across all CHF subtypes, suggesting that CA125 may serve as a universal biomarker for risk stratification in CHF.

The Kaplan - Meier survival curves visually depicted the association between CA125 levels and ACM, revealing that patients with higher CA125 levels experienced significantly poorer survival across all CHF subtypes. This finding is clinically pertinent, as it suggests that monitoring CA125 levels could be instrumental in informing treatment strategies and guiding patient management.

Our study also revealed a statistically significant association between elevated baseline CA125 levels and increased ACM in heart failure patients with hypertension. Prior research has highlighted differences in CA125 levels between hypertension and non - hypertension groups ([36]. Additionally, Huang Qi et al. found a positive correlation between CA125 and B - type Natriuretic Peptide (BNP) in hypertension patients with heart failure ([37], which aligns with our findings.

Previous studies have shown that plasma CA125 levels in patients with CHF and atrial fibrillation are inversely related to LVEF and positively related to left atrial diameter (LAD) ([38]. Kouris et al. found that CA125 levels

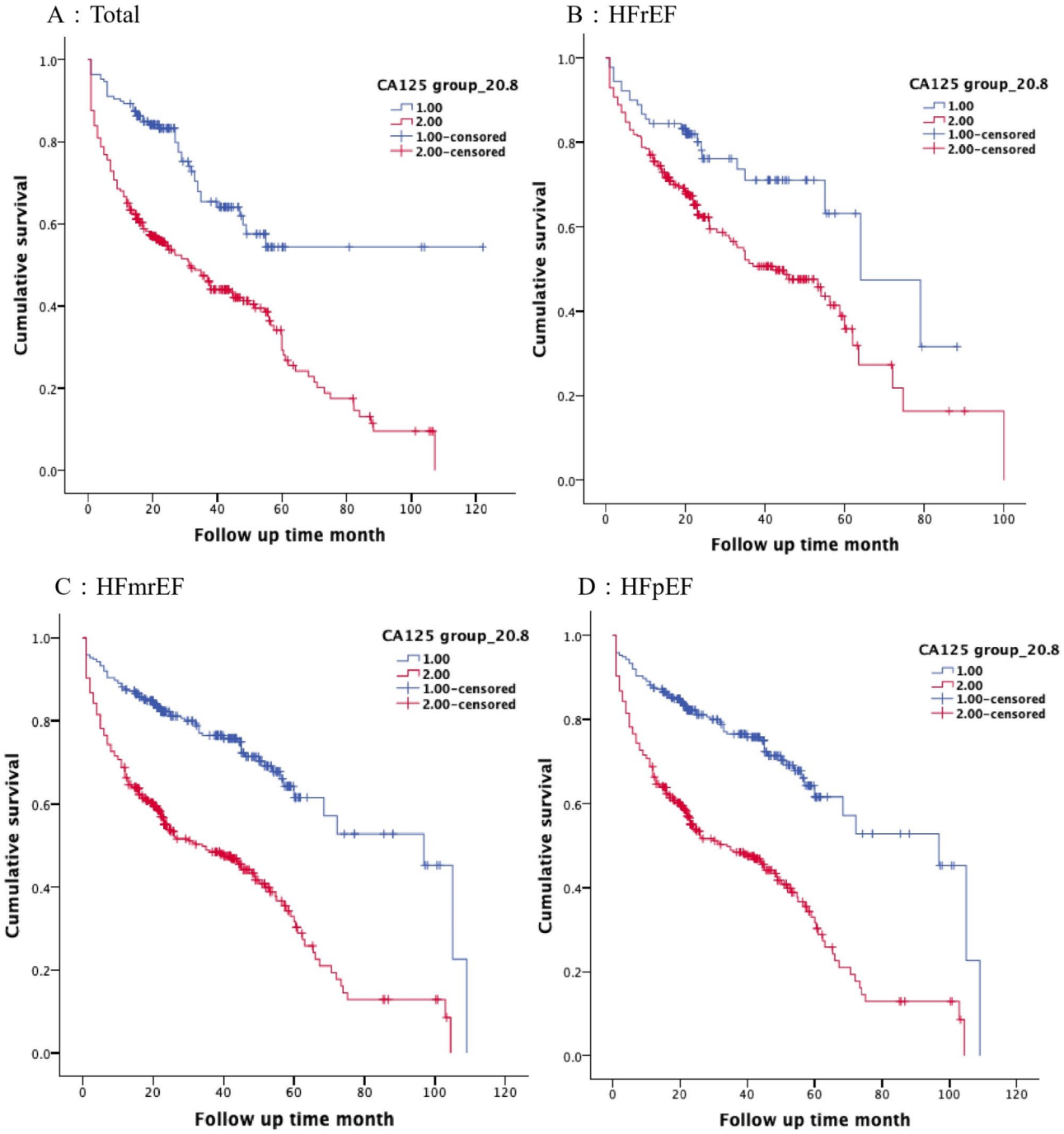

Fig. 3 Kaplan-meier survival curves for all-cause mortality based on CA125 levels: **A:** Total Population; **B:** Heart Failure with Reduced Ejection Fraction (HFrEF) Subgroup; **C:** Heart Failure with Mid-range Ejection Fraction (HFmrEF) Subgroup; **D:** Heart Failure with Preserved Ejection Fraction (HFpEF) Subgroup; CA125:Cancer Antigen 125, a biomarker associated with certain diseases including ovarian cancer. HFrEF: Heart Failure with Reduced Ejection Fraction. HFmrEF: Heart Failure with Mid-range Ejection Fraction. HFpEF: Heart Failure with Preserved Ejection Fraction. Statistical Method: Kaplan-Meier estimation used for survival analysis. Low CA125 Group (< 20.8 U/mL); High CA125 Group (≥ 20.8 U/mL)

in chronic heart failure patients increased with higher NYHA heart failure classifications and were also correlated with pulmonary hypertension. Duman et al. and Vizzardi et al. measured CA125 in the serum of heart failure patients and discovered that elevated levels were associated with right atrial pressure, pulmonary arterial systolic pressure, pulmonary capillary wedge pressure, and left atrial volume ((39–40).

Previous studies have extensively examined the relationship between serum Carbohydrate Antigen CA125

Table 4 Multivariable Cox regression analysis for All-cause mortality

Variables	Total($n=1413$)				HFrEF($n=360$)				HFmrEF($n=379$)				HFpEF($n=674$)			
	Z value	*P* value	HR	95% CI	Z value	*P* value	HR	95% CI	Z value	*P* value	HR	95% CI	Z value	*P* value	HR	95% CI
CA125	31.56	**<0.001**	2.05	1.60–2.64	5.49	**0.019**	2.2	1.14–4.24	0.56	**<0.001**	1.28	0.67–2.45	18.9	**<0.001**	2.32	1.59–3.40
Age, years	27.43	**<0.001**	1.02	1.01–1.03	5.96	**0.015**	1.03	1.01–1.05	13.43	**<0.001**	2.32	1.48–3.63	22.9	**<0.001**	1.04	1.02–1.05
WBC, $*10^9$/L	3.17	0.075	1.01	0.99–1.02	1.72	0.19	1	1.00-1.01	0.53	0.467	1.02	0.97–1.07	0.68	0.409	1.01	0.99–1.02
Hb, g / L	5.92	0.015	0.999	0.981–1.017	0.1	0.746	1.01	0.99–1.01	0.47	0.494	0.99	0.98–1.01	5.31	0.021	0.99	0.98–0.99
Potassium, mmol / L	0.06	**<0.001**	1.742	1.078–2.814	2.78	**<0.001**	1.37	0.95–1.98	0.65	**<0.001**	1.989	1.393–2.840	1.16	**<0.001**	1.632	1.282–2.079
Total cholesterol, mmol / L	2.1	0.147	0.93	0.85–1.02	0.36	0.55	1.07	0.86–1.33	1.14	0.285	0.86	0.66–1.13	0.01	0.923	1.01	0.86–1.18
Albumin, g/L	4.07	0.044	1.01	1.00-1.03	0.01	0.934	0.99	0.96–1.04	0.88	0.347	1.01	0.98–1.04	1.11	0.292	1.01	0.99–1.03
Serum alanine transferase, U / L	0.09	0.764	1.01	1.00-1.01	0.64	0.423	0.99	0.99–1.01	1.81	0.179	1.01	1.00-1.01	3.28	0.07	1	1.00-1.01
NT-proBNP, ng/L	7.93	**0.001**	2.007	1.302–2.977	11.22	**0.001**	1.31	1.12–1.54	5.04	**0.025**	2.158	1.271–3.665	11.02	**0.001**	1.63	1.22–2.18

Notes: CA125: Cancer Antigen 125, a biomarker used to assess risk in certain conditions. ACM: All-cause mortality, the total number of deaths from any cause. HR: Hazard Ratio, a measure of the risk of an event occurring in the observed group compared to a reference group. CI: Confidence Interval, indicating the range within which the true HR is likely to fall with a certain level of confidence (95%). *P*-value: The probability value indicating the statistical significance of the results. WBC: White Blood Cell count, a measure of the number of white blood cells per liter. Hb: Hemoglobin, the protein in red blood cells that carries oxygen. NT-proBNP: N-terminal pro-B-type Natriuretic Peptide, a biomarker used to diagnose heart failure

and HF with atrial fibrillation ([41]. However, there is a relative dearth of domestic research on HF coexisting with coronary artery disease, diabetes, and valvular disease. Our study demonstrated significant differences in the proportion of heart failure caused by these conditions between the two groups in the overall HF patient population. Additionally, there is a scarcity of classification analysis for heart failure patients based on LVEF types worldwide. Our research confirmed that elevated CA125 levels remain an independent risk factor for all - cause mortality in chronic heart failure patients, irrespective of different LVEF types ([33].

Existing research has shown that the combination of CA125 and BNP is beneficial in assessing the efficacy of heart failure treatment, providing clinicians with more comprehensive feedback on treatment outcomes ([42]. Since serum NT - proBNP levels can be affected by factors like age, infection, and hypoxemia, this study compared hemoglobin, blood potassium, total cholesterol, serum albumin, and alanine transaminase levels in the two groups. All of these parameters showed statistically significant differences, offering greater reliability than previous studies ([43].

Studies have demonstrated that CA125 is highly expressed in HF patients and tends to increase with higher NYHA functional classes, indicating a significant association with the severity of heart failure ([44]. Additionally, investigations have suggested that serum CA125 is implicated in disease progression in HF patients and positively correlates with the NYHA functional class ([45]. However, our study did not directly compare the NYHA functional classes of the HF patients. Future research could explore whether serum CA125 levels differ between groups and subgroups of patients based on their heart function status, which could provide further insights into its role as a potential biomarker.

CA125 is a glycoprotein antigen that has been extensively studied for its role in tumor diseases. Recently, its significant value in cardiovascular diseases such as pericardial effusion and heart failure has come to light ([46]. In 1999, Nagele et al. proposed a link between plasma CA125 and HF ([47]. Since then, researchers worldwide have explored CA125's role in the diagnosis, severity, and prognosis of heart failure. Elevated plasma CA125 levels have been observed not only in ovarian cancer but also in conditions such as peritonitis, liver cirrhosis, lung cancer, gastric cancer, colon cancer, and fallopian tube tumors, both benign and malignant ([48]. Additionally, CA125 levels are elevated in heart failure patients with pleural or pericardial effusions ([44]. Huang et al. suggested that mechanical stress, inflammation, trauma, or fluid accumulation trigger a cellular response through the c - Jun N - terminal kinase (JNK) signaling pathway, leading to CA125 synthesis within mesothelial cells in

the pleura, pericardium, and peritoneum ([37]. Changes in the cell membrane's morphology and stability further facilitate the release of CA125 from mesothelial cells into the peripheral serum, resulting in elevated CA125 levels. Previous research indicated that this association might be related to myocardial remodeling and neuroendocrine activation ([43].

Contrary to expectations, the HFrEF group did not demonstrate higher all-cause mortality compared to the HFmrEF and HFpEF groups. This observation may be explained by the more intensive management strategies typically applied to HFrEF patients, including the use of beta-blockers, ACE inhibitors, and implantable devices such as ICDs and CRT. Additionally, the baseline characteristics of the HFrEF group, such as younger age or fewer comorbidities, may have contributed to this finding. Future studies with larger cohorts and longer follow-up periods are needed to validate these results and explore potential underlying mechanisms.

This study validates previous perspectives, showing that CA125 has significant clinical utility in the diagnosis and prognosis prediction of HF. Limitations include the lack of statistical analysis on the NYHA functional classification and the absence of investigation into differences and implications of CA125 levels among patients with different stages of heart failure. Future work should further explore these aspects.

Currently, there is no research that fully explains the mechanism behind the elevation of CA125 in heart failure patients, which requires further investigation for better diagnostic and prognostic assessment of these patients.

Confounders and adjustments

We recognize that although we adjusted for several potential confounders, including age and NT - proBNP, there may be other variables that could influence the relationship between CA125 and ACM. For example, the impact of renal function, which is known to affect CA125 levels ([49], should be considered in future studies.

Limitations and future directions

Our study has limitations. Firstly, the retrospective design of our study may introduce selection bias, as only patients with available CA125 measurements were included. This could limit the generalizability of our findings. Furthermore, CA125 levels were measured at a single time point, which may not capture dynamic changes over time. Future prospective studies with serial CA125 measurements are needed to validate our results and explore the temporal relationship between CA125 levels and outcomes. Additionally, the measurement of CA125 was done at a single time point, which may not reflect longitudinal changes in CA125 levels. Future studies with serial measurements of CA125 and a larger cohort are needed to validate our findings.

In conclusion, our study provides strong evidence supporting the prognostic value of serum CA125 in patients with CHF. The consistent association across different CHF subtypes highlights the potential of CA125 as a biomarker in clinical practice. Further research is required to clarify the mechanisms underlying the relationship between CA125 and ACM in CHF.

Conclusion

In conclusion, our study suggests that serum CA125 levels may serve as a potential prognostic biomarker for mortality in CHF patients, with significant associations observed across various subtypes, particularly HFpEF. While our findings highlight CA125's potential clinical utility, the study's observational nature and limitations (e.g., single-time point measurement) necessitate further research, including longitudinal studies and larger cohorts, to clarify the mechanisms underlying CA125's prognostic value in CHF.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12872-025-04685-w.

Supplementary Material 1

Supplementary Material 2

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Author contributions

Ruzeguli Tuersun and Aihaidan Abudouwayiti contributed equally to this work and are co-first authors. They were involved in the conception and design of the study, data collection, and initial drafting of the manuscript. Yan Xiao Li, Ying Pan, Salamaiti Aimaier, Zhi-Ying Wen, Wei-Tong Gao, and Li-Juan Ma contributed to the data collection, analysis, and interpretation. They also participated in revising the manuscript for important intellectual content. Ailiman Mahemuti and Ying-Ying Zheng contributed equally to this work and are co-corresponding authors. They provided substantial contributions to the conception and design of the study, supervised the research, and critically revised the manuscript for important intellectual content. They also provided final approval of the version to be published. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work.

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Data availability

The datasets generated and analyzed during the current study are not publicly available. This is because the database contains sensitive and valuable information that is integral to ongoing projects. However, for researchers who may request access to the data for legitimate purposes, please contact Dr. Prof.

Ying-Ying Zheng at zhengying527@163.com to discuss potential data sharing arrangements.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University. The protocol was registered on ClinicalTrials.gov (identifier: NCT06092658) on October 19, 2023, and adhered to the ethical standards of the Declaration of Helsinki and national guidelines.

Consent for publication

Not Applicable.

Competing interests

The authors declare no competing interests.

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