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The value of CA125 in predicting adverse outcomes in heart failure patients

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Abstract: In heart failure, elevated carbohydrate antigen 125 (CA125) has been shown to correlate with adverse events. We sought to quantify its prognostic usefulness in predicting the one-month combined death/heart failure readmission endpoint. Carbohydrate antigen 125 (CA 125), originally associated with ovarian cancer, has now garnered attention as a potential marker for fluid overload and pulmonary congestion in heart failure patients. However, determining the optimal CA 125 cutoff value for predicting one-month adverse outcomes in heart failure patients remains an area of variability across different research studies. While both biomarkers show promise, further research is needed to determine their comparative utility in predicting adverse outcomes in heart failure patients. Factors such as sensitivity, specificity, and optimal thresholds should be considered. Study objectives: determine the prevalence of in-hospital or one-month mortality and one-month readmission in heart failure patients; determine the cutoff point, AUC, sensitivity, and specificity of CA 125 in predicting in-hospital or one-month mortality and one-month readmission in heart failure patients. Our cross-sectional study enrolled 121 heart failure patients at the HCMC Hospital of Rehabilitation - Occupational Diseases during the period from September 1, 2023, to July 1, 2024. During the one-month follow-up period, there were 6 cases lost to follow-up, accounting for 6/121=4.95%. The mean age was 69.14 ± 12.96 years, with men comprising 51.2% of the cohort. The median CA 125 value was 29.28 U/mL (interquartile range: 22.57–37.24). There were 2 cases accounting for 1.7% of in-hospital mortality. There were 8 cases, accounting for 6.6%, who died one month after discharge from the hospital. There were 30 cases, accounting for 24.8%, of re-hospitalization within one month of discharge. The optimal CA 125 cutoff for predicting in-hospital mortality was > 91.6 U/mL, yielding an AUC ROC of 0.885 (95% CI: 0.812–0.937, p < 0.0001), sensitivity of 100%, and specificity of 85.8%. The optimal CA 125 cutoff for predicting one-month mortality was > 29.6 U/mL, yielding an AUC ROC of 0.667 (95% CI: 0.573–0.752, p = 0.120), sensitivity of 87.5%, and specificity of 53.3%. The optimal CA 125 cutoff for predicting one-month rehospitalization was ≤44.3 U/mL, yielding an AUC ROC of 0.508 (95% CI: 0.413–0.602, p = 0.889), sensitivity of 80%, and specificity of 35.3%. The optimal CA 125 cutoff for predicting the one-month combined endpoint of death/rehospitalization was > 26.05 U/mL, yielding an AUC ROC of 0.534 (95% CI: 0.438–0.627, p = 0.543), sensitivity of 66.67%, and specificity of 51.32%. CA 125 demonstrates good accuracy in predicting in-hospital mortality with a cutoff of > 91.6 U/mL, an AUC ROC of 0.885 (95% CI: 0.812–0.937, p < 0.0001), sensitivity of 100%, and specificity of 85.8%.

Keywords: *Carbohydrate antigen 125, Heart failure, In-hospital mortality, Predicting.*

1. Introduction

Heart failure is one of the chief cause leading to intensive care unit admission (18.6%)[1]. Organ congestion is a main feature of heart failure [2-4]. That is caused by excess fluid or fluid redistribution into the extravascular space[4]. In addition, during and after cardiac surgery or cardiac interventions, the infusion of considerable amounts of intravenous fluids may be necessary [5]. Due to cardiopulmonary bypass induced inflammation [5]. Blood loss, myocardial depression, rhythm disturbances, and impaired vascular tone[6]. Therefore, additional iatrogenic fluid overload is common

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at intensive care unit admission in patients with heart failure and may affect outcomes [7, 8]. Further, patients with heart failure often suffer from extravascular over-hydration due to fluid re-distribution while actually being intravascular fluid depleted [4]. This may lead to the administration of further fluids for resuscitation purposes[2, 9-11] and thus further aggravates organ dysfunction (heart, lung, and kidneys), leading to a vicious circle of organ failure [4].

NT-proBNP, a precursor of BNP synthesized in the left ventricle, responds to increased ventricular workload and remodeling. Notably, the immature NT-proBNP molecule has a longer half-life than its active counterpart, allowing for easier measurement. Importantly, its independence from acute fluctuations affecting other natriuretic peptides makes it a valuable marker. Elevated NT-proBNP levels serve a dual purpose, indicating both myocardial damage and fluid volume overload [12]. CA125, also referred to as MUC16, is a transmembrane protein characterized by high glycosylation and a substantial molecular weight. Its primary structure comprises three distinct domains: the N-terminal domain, the tandem repeat domain, and the C-terminal domain[13]. Studies indicate that CA125 is not produced by tumor cells; rather, it originates from the cell surfaces of various coelomic epithelial tissues [14]. Primarily, CA125 serves to hydrate, lubricate, and safeguard the epithelial cavity surface from physical pressure [15]. CA125 serves as a valuable biomarker for both diagnosing ovarian cancer and assessing the therapeutic prognosis of patients [16]. Research has emphasized that congestive heart failure (HF) is a notable factor contributing to elevated serum CA125 levels. Furthermore, CA125 levels exhibit a strong correlation with the severity of congestion and are frequently observed alongside substantial volume overload and fluid accumulation[17]. Indeed, in acute heart failure, CA125 levels often exceed the normal range, with up to two-thirds of patients showing values between 35 and 200 U/mL [18], and in patients with stable HF is mostly lower than 35 U/mL. The precise mechanism underlying the elevation of serum CA125 levels in patients with congestive heart failure (HF) remains unconfirmed. Existing studies suggest that mechanical stress and inflammatory stimulation play pivotal roles in this process, leading to the formulation of two hypotheses: (1) Mechanical stress resulting from tissue tension due to fluid overload stimulates mesothelial cells, leading to the release of CA125 [19]. (2) The upregulation of CA125 in mesothelial cells is triggered by the activation of the inflammatory cytokine network [18]. According to Colombo et al.[20], In congestive heart failure (HF), venous congestion triggers endothelial activation, leading to the upregulation of inflammatory cytokines, hepatic dysfunction, and intestinal villus ischemia. The latter condition disrupts normal intestinal epithelial cell function and compromises the epithelial barrier, allowing lipopolysaccharides and endotoxins produced by gram-negative bacteria in the intestinal lumen to enter the circulation. This further exacerbates the inflammatory environment already established by venous congestion and neurohormonal activity. The interplay between fluid overload and inflammatory processes creates a vicious cycle in congestive HF. Published studies indicate that high levels of several biomarkers [21], including natriuretic peptides[22], sST-2[23], cardiac troponins [24], and carbohydrate antigen 125 (CA125) [15], correlate with AHF severity and adverse outcomes. Based on different pathophysiological 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 [25], CA125 has been studied in heart disease patients [26] and especially in heart failure, emerging as a surrogate for fluid overload and/or cytokine production in AHF [27]. When interpreting elevated CA125 levels, it is essential to differentiate accurately between ovarian cancer and HF. Although both conditions can cause tissue damage and elevate CA125 levels due to fluid retention, ovarian cancer patients typically exhibit significantly higher CA125 levels compared to HF patients [28]. Furthermore, it is important to note that CA125 alone is not an ideal diagnostic tool for either condition due to its limited specificity and sensitivity [28]. In order to enhance clinical effectiveness in screening and early detection, CA125 should be considered in conjunction with symptoms, signs, other biomarkers, and multimodal methods such as ultrasound. 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

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management by optimizing diuretic therapy, increasing the frequency of monitoring visits, and other therapeutic measures. However, it's important to note that the cutoff value for CA125 in predicting adverse outcomes in heart failure patients varies across different research studies. Our study three objectives:

1. Determine the prevalence of the in-hospital or one-month mortality and one-month readmission in heart failure patients
2. Determine the cutoff point, AUC, sensitivity, specificity of CA 125 in predicting the in-hospital or one-month mortality and one-month readmission in heart failure patients

2. Methods

2.1. Study population

- We included adult patients admitted during the study period with heart insufficiency.
- Inclusion criteria: heart failure patients at the HCMC Hospital of Rehabilitation - Occupational Diseases from September 1, 2023 to July 1, 2024.

2.1.1. Fluid Overload

Definition: Fluid overload occurs when there is excessive accumulation of bodily fluids. Specifically, it's defined as the weight-adjusted cumulative fluid balance, where total fluid intake exceeds total fluid output. Clinically, fluid overload is significant if the weight-adjusted cumulative fluid body at ICU discharge is 5% or more. Indicators: Symptoms: Dyspnea, orthopnea, fatigue. Physical Signs: Elevated jugular venous pressure (JVP), rales, pedal edema. Radiological Findings: Chest X-rays may show increased pulmonary circulation or pulmonary edema.

2.1.2. Pulmonary Congestion

Definition: Pulmonary congestion is the accumulation of fluid within pulmonary vasculature and lung tissue. It results from fluid overload and impairs gas exchange. Manifestations: Symptoms: Dyspnea, cough, orthopnea. Physical Exam: Elevated JVP, rales, peripheral edema. Radiological Features: Chest X-rays reveal increased vascular markings and, in severe cases, diffuse opacities due to pulmonary edema [29].

- The exclusion criteria for this study were as follows:

Patients younger than 18 years.
Cases with insufficient available data.
Patients with a cancer diagnosis.

2.2. Methods

Study design: cross-sectional. This study complies with the Declaration of Helsinki and was approved by HCMC Hospital of Rehabilitation - Occupational Diseases Ethics committee with numbers CS/PHCN/24/07. All patients provided written informed consent.

Sample size:

$$n = Z^2_{1-\alpha/2} \frac{p(1-p)}{d^2}$$

Where: p = 8.6% according to Waskowski J et al[30].
We chose d = 0,1, n = $1{,}96^2$ x 0,086 x 0,914/$0{,}1^2$ = 30.2.
So minimum sample size was 31 cases.
Laboratory data: CA125 Measurement:

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Method: Plasma concentrations of CA125 were determined using the commercially available electrochemiluminescent sandwich immunoassay, specifically the Roche Elecsys® CA 125 assay. Precision: Intra-assay precision (coefficient of variation): 1.4–2.0%. Inter-assay precision (coefficient of variation): 0.0–0.9%. Analytical Range: The assay covers a range from 0.6 to 5000 U/mL. NT-proBNP Measurement: Method: NT-proBNP levels were measured using Elecsys® proBNP II from Roche Diagnostics, Bromma, Sweden, with the Cobas e411 analyzer.

Statistical analysis: we conducted all statistical analyses using SPSS for Windows (version 26.0; SPSS Inc., Chicago, IL, USA). To assess normal distribution, we employed either the Kolmogorov–Smirnov test or Pearson's chi-squared test. For quantitative variables, we used Student's t-test when data were normally distributed and the Mann–Whitney U test for non-normally distributed data. Qualitative variables were analyzed using either the chi-square test or Fisher's exact test, as appropriate. To evaluate the diagnostic performance of CA125 in predicting mortality or readmission, we constructed receiver operating characteristic (ROC) curves. The optimal cut-point, representing the best balance between sensitivity and specificity, was determined using the Youden method. A 2-sided p value of <0.05 was considered statistically significant in all analyses.

3. Results

Between September 1, 2023, and July 1, 2024, a total of 121 patients met the inclusion criteria and had no exclusion criteria.

3.1. Baseline characteristics

In our study involving 121 patients, here are the notable results:

Demographics and Clinical Characteristics: Mean age: 69.14 years (±12.96 years); Gender distribution: 62 (51.2%) male; Prevalence of heart failure history: 54 (44.6%); History of chronic kidney disease: 20 (16.5%); Acute pulmonary edema cases: 8 (6.6%); Acute decompensated heart failure diagnoses: 23 (19%). Biomarker Levels: Median NT-proBNP level: 1832 pg/ml (interquartile range: 1254.07–2300.33). Median CA 125 level: 29.28 U/ml (interquartile range: 22.57–37.24). Fluid Overload: Notably, 87 subjects (71.9%) exhibited fluid overload. During the 1-month follow-up period, there were 6 cases lost to follow-up, accounting for 6/121=4.95%. There were 2 cases accounting for 1.7% of in-hospital mortality. There were 8 cases, accounting for 6.6%, who died one month after discharge from the hospital. There were 30 cases, accounting for 24.8%, re-hospitalization within one month of discharge. Baseline characteristics were showed in Table 1.

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Table 1.
Baseline characteristics.

Variables	**Total (n=121)**
Age (Years)	69.14 ± 12.96
Male sex	62 (51.2)
BMI (kg/m2)	21.77 [20.89 – 22.6]
HTA	105 (86.8)
Dyslipidemia	84 (69.4)
HF	54 (44.6)
DM	45 (37.2)
CAD	68 (56.2)
CKD	20 (16.5)
SBP, mmHg	120 [120-120]
DBP, mmHg	70 [70-70]
HR, b.p.m	85 [82-88]
NYHA II	11 (9.1)
NYHA III	76 (62.8)
NYHA IV	34 (28.1)
LVEF (%)	53 [48.24-57]
Sodium (mmol/L)	138.51 ± 6.27
Creatinine (µmol/L)	90.5 [85.42- 99.01]
eGFR (mL/min/1.73m2)	69.0 [60.05-78.48]
Ure (mmol/L)	6.7 [5.88-7.41]
Hb (g/dL)	12.53 ± 2.64
NT-proBNP (pg/mL)	1832 [1254.07- 2300.33]
CA 125 (U/mL)	29.28 [22.57-37.24]

Data are expressed as n (%); medium± SD; median [interquartile range] as appropriate. B.p.m: beat per minute. CA.125, carbohydrate antigen 125; CAD, coronary artery disease; DBP, diastolic blood pressure, DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; Hb: hemoglobin; HF, heart failure; HR, heart rate; HTA, hypertension; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; CKD: Chronic kidney disease was defined as eGFR eGFR <60 mL/min/1.73 m^2 using creatinine obtained at the admission

3.2. The value of CA 125 in predicting adverse outcomes in heart failure patients

We assessed the diagnostic accuracy of CA.125 using receiver operating characteristic (ROC) curve analysis. The optimal CA 125 cutoff for predicting in-hospital mortality was > 91.6 U/mL, yielding an AUC ROC of 0.885 (95% CI: 0.812–0.937, p < 0.0001), sensitivity of 100%, and specificity of 85.8%. The optimal CA 125 cutoff for predicting one month mortality was > 29.6 U/mL, yielding an AUC ROC of 0.667 (95% CI: 0.573–0.752, p = 0.120), sensitivity of 87.5%, and specificity of 53.3%. The optimal CA 125 cutoff for predicting one month rehospitalization was ≤44.3 U/mL, yielding an AUC ROC of 0.508 (95% CI: 0.413–0.602, p = 0.889), sensitivity of 80%, and specificity of 35.3%. The optimal CA 125 cutoff for predicting one-month combined endpoint of death/rehospitalization was > 26.05 U/mL, yielding an AUC ROC of 0.534 (95% CI: 0.438–0.627, p = 0.543), sensitivity of 66.67%, and specificity of 51.32%.. The results were presented in Figure 1, Figure 2, Figure 3 and Figure 4.

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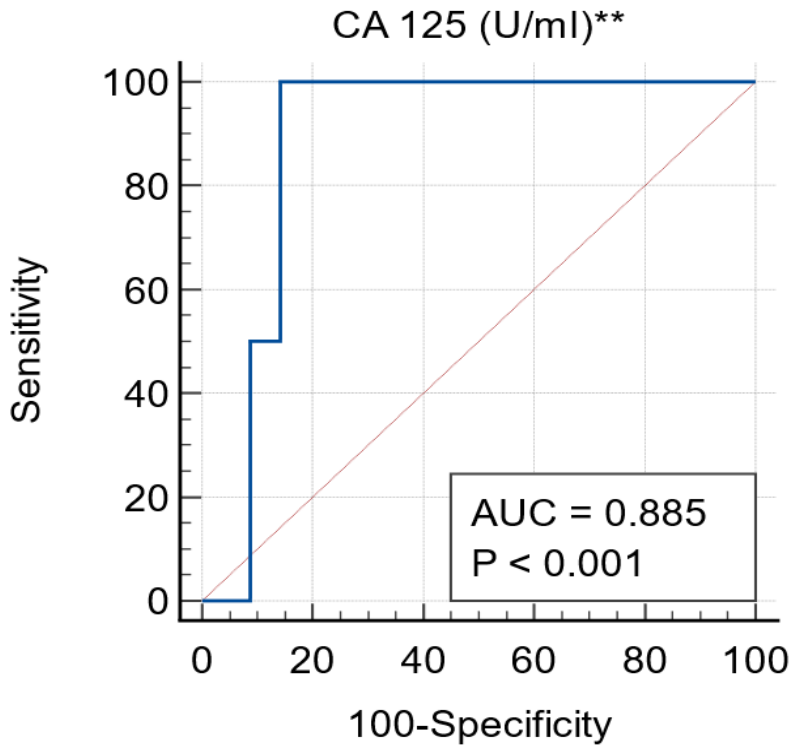

Figure 1.
Cut-off point, AUC, sensivity, specificity of CA 125 in predicting in-hospital mortality.

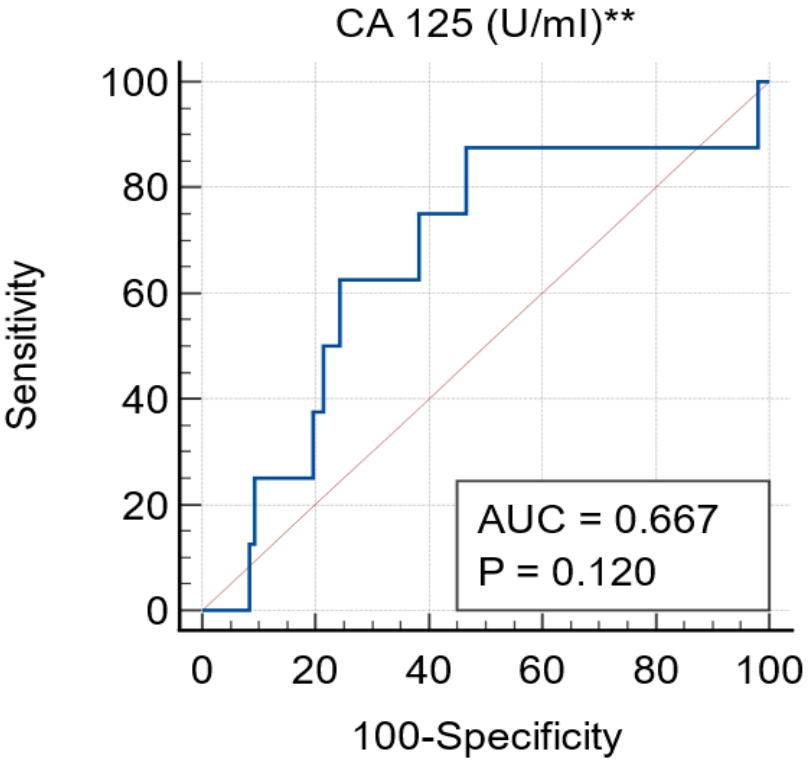

Figure 2.
Cut-off point, AUC, sensivity, specificity of CA 125 in predicting one month mortality.

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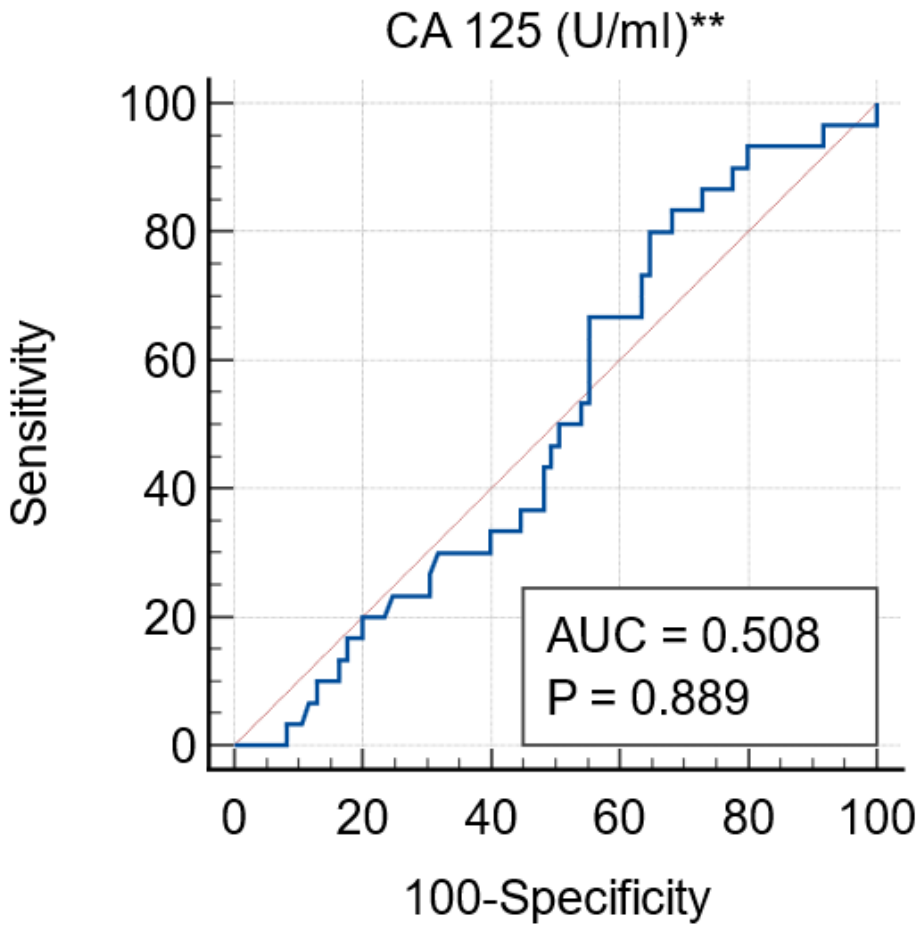

Figure 3.
Cut-off point, AUC, sensivity, specificity of CA 125 in predicting one month readmission.

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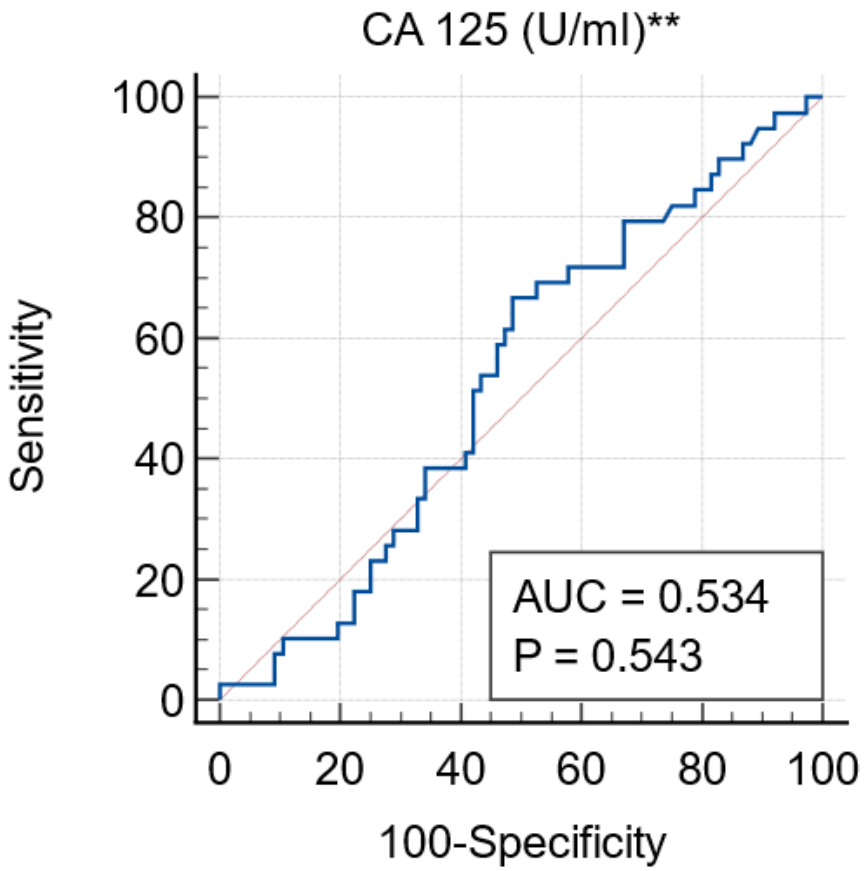

Figure 4.
Cut-off point, AUC, sensivity, specificity of CA 125 in predicting one-month combined endpoint of death/rehospitalization

4. Discussion

CA125, originally known for its connection to ovarian cancer, has now become a helpful marker for fluid congestion in acute heart failure [31]. The exact reasons behind increased CA125 synthesis in acute heart failure (AHF) aren't fully clear. However, one proposed mechanism involves the activation of mesothelial cells. These cells respond to factors like elevated hydrostatic pressure, mechanical stress, and cytokines.[31]. In our recent study, we found that the presence of pleural effusion and the severity of tricuspid regurgitation were the most significant factors related to CA125 levels in patients with acute heart failure (AHF).[32]. It's fascinating how CA125 levels can serve as a valuable indicator for fluid overload and right-sided heart failure [32]. Elevated CA125 levels may indicate more advanced heart failure patients with significant congestion and a higher risk of decompensations. In contrast, natriuretic peptides (like NT-proBNP) serve as reliable biomarkers reflecting increased ventricular pressures and myocardial strain[33]. Research on natriuretic peptides (like NT-proBNP) has primarily focused on heart failure with reduced ejection fraction (HFrEF). In heart failure with preserved ejection fraction (HFpEF), evidence is scarcer. NT-proBNP's predictive ability for total AHF readmission remains unclear in HFpEF. Possible reasons include the prevalence of right-sided dysfunction and systemic congestion in HFpEF. CA125, as a surrogate for systemic congestion, may be more relevant than NT-proBNP (a proxy for left-sided filling pressure) in predicting morbidity burden in this population. Notably, in HFpEF patients with predominant right-sided heart failure, CA125—but not NT-proBNP—has been associated with worse outcomes. Elderly HFpEF patients with renal dysfunction often have elevated natriuretic peptide levels regardless of HF severity.[32]. In contrast,

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clinical indicators related to congestion and the severity of tricuspid regurgitation emerged as the primary predictors for CA125 levels[32]. Furthermore, there exists compelling evidence suggesting that natriuretic peptides are not precise or dependable indicators of tissue congestion [33]. CA125 in Decompensated HF: NT-proBNP is typically measured early during hospitalization. However, studies suggest that assessing natriuretic peptides before discharge may offer better prognostic insights. CA125, beyond its association with HF admission burden, could complement risk prediction for subsequent decompensations. Monitoring CA125 levels during decompensation might guide depletion therapy intensity, length of hospital stay, and postdischarge follow-up. Recent studies highlight how high CA125 identifies patients benefiting from intensive diuretic regimens and closer monitoring. Our research confirms CA125's value as a circulating biomarker for predicting predicting in-hospital mortality in heart failure patients. The optimal CA 125 cutoff for predicting in-hospital mortality was > 91.6 U/mL, yielding an AUC ROC of 0.885 (95% CI: 0.812–0.937, $p < 0.0001$), sensitivity of 100%, and specificity of 85.8%. The optimal CA 125 cutoff for predicting one month mortality was > 29.6 U/mL, yielding an AUC ROC of 0.667 (95% CI: 0.573–0.752, $p = 0.120$), sensitivity of 87.5%, and specificity of 53.3%. The optimal CA 125 cutoff for predicting one month rehospitalization was ≤44.3 U/mL, yielding an AUC ROC of 0.508 (95% CI: 0.413–0.602, $p = 0.889$), sensitivity of 80%, and specificity of 35.3%. The optimal CA 125 cutoff for predicting one-month combined endpoint of death/rehospitalization was > 26.05 U/mL, yielding an AUC ROC of 0.534 (95% CI: 0.438–0.627, $p = 0.543$), sensitivity of 66.67%, and specificity of 51.32%.. CA125's longer half-life makes it a reliable surrogate for reflecting fluid status over several weeks.

5. Limitations

Several limitations warrant consideration in interpreting the findings of this study:

Single-center Design: The study's single-center observational design introduces inherent limitations related to generalizability. Extrapolating results to broader populations should be done cautiously.

Sample Size Constraints: Given the limited sample size, some negative findings may be attributable to type II error (insufficient statistical power). Larger multicenter studies are needed for robust conclusions.

Lack of Invasive Hemodynamic Assessment: The absence of invasive hemodynamic measurements precludes direct correlations between fluid overload patterns and right-sided filling pressures. Future research should explore these associations.

Timing of CA125 Measurement: CA125 biomarker levels were assessed during early hospitalizations. Longitudinal evaluation of CA125 variations over time was not performed, potentially limiting our understanding of dynamic changes.

6. Conclusion

CA 125 demonstrates good accuracy in predicting in-hospital mortality was > 91.6 U/mL, AUC ROC of 0.885 (95% CI: 0.812–0.937, $p < 0.0001$), sensitivity of 100%, and specificity of 85.8%.

List of abbreviations:

CA.125: carbohydrate antigen 125

Transparency:

The author confirms that the manuscript is an honest, accurate, and transparent account of the study; that no vital features of the study have been omitted; and that any discrepancies from the study as planned have been explained. This study followed all ethical practices during writing.

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