

Prognostic Value of CA125 Serum Levels in Female Patients with Acute Coronary Syndrome

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Abstract

Background: carbohydrate antigen 125 (CA125) is an increasingly promising biomarker of heart failure (HF), but its prognostic value in female patients with acute coronary syndrome (ACS) is unclear. We aimed to determine the short-term and mid-term prognostic value of CA125 serum levels in female ACS patients.

Methods: A total of 131 consecutive female patients with ACS were retrospectively enrolled. Their CA125 levels, B-type natriuretic peptide (BNP) levels and biochemical parameters were measured, and echocardiography was performed at admission. All-cause mortality during hospitalization and two-year follow-up was investigated for the prognosis.

Results: The median value of CA125 serum level in the entire ACS patients was 13.85 U/mL. Patients in Killip I had the highest values of CA125 level, followed by Killip II and then Killip III ($p < 0.05$). However, no statistical difference was observed between Killip I and II–III groups respectively ($P > 0.05$). The CA125 serum levels showed weak positive correlation with left ventricular end-diastolic diameter (LVEDD) ($r = 0.3, P < 0.01$) and a weak negative correlation with left ventricular ejection fraction (LVEF) ($r = -0.23, p < 0.01$). A receiver operating characteristic (ROC) curve analysis showed that the AUC of CA125 in predicting acute heart failure (AHF) in ACS patients during hospitalization was 0.912, exhibiting higher sensitivity and specificity than BNP (0.846). The optimal cut-off value for CA125 in predicting AHF was 16.4 U/mL with a sensitivity of 0.916 and specificity of 0.893. The Kaplan-Meier survival analysis demonstrated that patients with high values of CA125 level had a poor overall survival than those with low values of CA125 level (log-rank, $p < 0.001$), whether during hospitalization or mid-term follow-up.

Conclusion: Elevated CA125 level can be used to predict AHF in female ACS patients. Patients with elevated CA125 levels had higher mortality in short-term and mid-term than those with low CA125 levels.

Background

Currently, acute coronary syndrome (ACS) is a major cause of morbidity and mortality worldwide despite advances in therapeutic techniques. Heart failure (HF) is the most common complication and leading cause across all types of ACS [1]. Women with ACS have higher adjusted risk than men of dying and developing HF during hospitalization and subsequent five years [2, 3].

Carbohydrate antigen 125 (CA125) is a well-known tumor biomarker associated with ovarian malignancy [4, 5]; moreover, CA125 level is also elevated in congestive HF (CHF) [6–8]. Several studies demonstrated that the CA125 levels correlate with clinical severity, parallel with NYHA class in CHF patients [9–11]. In the past two decades, the prognostic value of CA125 in HF has been extensively investigated, and increased CA125 levels have been identified as an independent predictor of poor short- and mid-term outcomes, including mortality and rehospitalization rates, in acute and chronic HF of any etiology [12–14]. De Gennaro L et al. evaluated the relationship between CA125 concentration and AHF in ACS patients, indicating that the CA125 levels were significantly proportional to Killip class [15].

However, the precise relationship between elevated CA125 concentrations and short-term and mid-term prognosis in ACS patients has not yet been sufficiently studied. The aim of this study was to determine the short-term and mid-term prognostic value of CA125 serum levels in female ACS patients.

Methods

Collection of case data

This was a retrospective study including 131 consecutive female ACS patients in our hospital between January and December 2018. Thirty-one patients were diagnosed with unstable angina (UA); 52 patients were diagnosed with non-ST-elevation myocardial infarction (NSTEMI); and 48 patients were diagnosed with ST-elevation myocardial infarction (STEMI). A total of 100 patients with acute myocardial infarction underwent Killip classification according to physical signs. Diagnosis criteria were referred to 2013ACCF/AHA guideline for the management of STEMI [16] and 2014 AHA/ACC guideline for the management of patients with non-ST-elevation ACS [17]. Patients with chronic HF, liver cirrhosis, ovarian malignancy, and peritoneal infections were excluded. This study was approved by the ethics committee of the Affiliated Hospital of Hangzhou Normal University.

Biochemical measurements

Blood samples for CA125 and other routine testing including B-type natriuretic peptide (BNP), creatinine, and cholesterol were taken from antecubital vein within 24 hours of admission in all patients. The CA125 serum levels were determined using a commercial chemiluminescence microparticle immunoassay kit (Fujirebio Diagnostics Inc., CA125 II Reagent Kit).

Echocardiography

Transthoracic echocardiography was performed by experienced echocardiographers using a Philip EPIQ 7C instrument equipped with an X5-1 probe according to the current guidelines of American Society of Echocardiography [18]. All patients underwent a comprehensive examination including M-mode, two-dimensional echocardiography, pulsed wave, continuous wave, and color-Doppler image within 72 h of admission. The left ventricular end-diastolic diameter (LVEDD) was measured in an optimized parasternal short axis at the level of mitral valve leaflets. The left ventricular ejection fraction (LVEF) was calculated from a maximized apical four-chamber and two-chamber view by measuring the end-systolic and end-diastolic volumes using the modified Simpson's method.

Statistical analysis

Continuous variables were expressed as mean value \pm standard deviation (SD), where categorical variables were expressed as absolute numbers (percentages). Pearson's test was conducted to examine the correlations between two parameters. Receive operating characteristic (ROC) curves were used to illustrate the diagnostic ability of CA125 and BNP. The area under the ROC curve (AUC), true positive rate (also known as sensitivity or recall), and false positive rate (specificity) are shown in a graphical plot [19]. Kaplan-Meier survival analysis of differences between and within groups was performed by conducting a log-rank test. A *p* value of less than 0.05 was considered statically significant. All the analyses conducted in this study were carried out using R statistical software (version 3.6.1).

Results

The mean age of enrolled patients was 69.3 ± 11.6 years; 94 patients (71.8%) had hypertension; 47 patients (35.9%) had diabetes mellitus, and 17 patients (13.0%) had atrial fibrillation. The clinical characteristics of the patient cohort are shown in Table 1.

Table 1

Clinical characteristics of the patient cohort (N=131)

Characteristic	
Age, yrs (mean ± sd)	69.3±11.6
Body mass index, kg/m ² (mean ± sd)	22.7±3.2
Hypertension % (N)	71.8 (94)
Diabetes mellitus % (N)	35.9 (47)
Atrial fibrillation % (N)	13.0(17)
Total cholesterol, mmol/L (mean ± sd)	4.55±1.46
High density lipoprotein, mmol/L (mean ± sd)	1.13±0.25
Low density lipoprotein, mmol/L (mean ± sd)	2.73±1.07
Triglyceride, mmol/L (mean ± sd)	1.75±1.23
Serum creatinine, mmol/L (mean ± sd)	80.0±58.1
STEMI % (N)	36.6 (48)
NSTEMI % (N)	39.7 (52)
UA % (N)	23.7 (31)
Left atrial diameter, mm (mean ± sd)	38.5±5.9
Right atrial diameter, mm (mean ± sd)	36.0±5.3
Left ventricular end-diastolic diameter, mm (mean ± sd)	47.8±6.0
Left ventricular ejection fraction, % (mean ± sd)	54.2±9.3
B-type natriuretic peptide, pg/ml (mean ± sd)	375.7±538.9

The median value of CA125 serum level in the entire ACS patients was 13.85 U/mL. CA125 levels in the STEMI and NSTEMI groups were significantly higher than those in the UA group ($p < 0.05$ and $p < 0.05$, respectively), but no significant difference was observed between the two groups ($p > 0.05$, Figure 1-A). Additionally, the serum levels of CA125 were higher in patients with pleural and pericardial effusion than those without pleural and pericardial effusion ($p < 0.05$, Figure 2-B). Patients who had developed AHF during hospitalization had higher levels of CA125 than those without AHF ($p < 0.05$, Figure 1-C). Patients in Killip I demonstrated having the highest levels of CA125, followed by Killip II, and then Killip III ($p < 0.05$, Figure 1-D). However, no statistical difference was observed between Killip I and II-III groups ($P > 0.05$, Figure 1-D).

The CA125 serum levels were evaluated to determine their correlation to echocardiographic parameters and plasma BNP. The CA125 levels showed a weak positive correlation with LVEDD ($r = 0.3$, $P < 0.01$,

Figure 2-A), and weak negative correlation with LVEF ($r = -0.23$, $p < 0.01$, Figure 2-B). No significant correlation was observed between the CA125 concentrations and plasma BNP levels ($r = 0.15$, $p > 0.05$).

A total of 26 patients developed AHF during hospitalization: nine patients died during hospitalization and five patients died during follow-up. The diagnosis of AHF requires the presence of crackles (Killip \geq II) or the use of intravenous diuretic agents or intravenous inotropes. The ROC curve analysis showed that the AUC of CA125 in predicting AHF in female ACS patients during hospitalization was 0.912, and that of BNP was 0.846 (Figure 3). Compared with BNP, CA125 showed higher sensitivity and specificity in predicting HF during hospitalization in ACS patients. The optimal cut-off value for CA125 in predicting AHF was 16.4 U/mL with a sensitivity of 0.916 and specificity of 0.893.

After a mean of 21.5 ± 7.0 months of follow-up duration, a total of 21 deaths were identified, 11 deaths during hospitalization and 10 deaths at follow-up. The patients were divided into high and low groups according to the optimal cut-off value of CA125 that predicted AHF during hospitalization. The Kaplan-Meier survival analysis demonstrated that patients with high levels of CA125 had a poor overall survival than those with low levels (log-rank, $p < 0.001$), whether during hospitalization or mid-term follow-up (Figure 4).

Discussion

In ACS patients, a number of novel biomarkers have been proposed in prognosis evaluation and risk stratification. CA125 is a well-known tumor marker for diagnosis, monitoring, and risk stratification in ovarian malignancy; it has become an increasingly promising biomarker in HF in the recent two decades [10, 20, 21].

In this study, the CA125 levels increased with the severity of HF in patients with Killip III-IV, but the CA125 levels did not increase significantly in patients with Killip II. This is probably because the Killip II patients developed AHF several days after admission; however, the CA125 levels were measured only at admission. Hemodynamic changes after ACS resulted in an increase in congestion and hydrostatic pressure in the mesothelium, thereby provoking mesothelial cells to initiate CA125 synthesis [22]. The kinetics of CA125 release from mesothelial cells in ACS patients is not known; it may be similar to NT-proBNP. The values obtained after a few days after onset of symptoms may have superior prognostic value when compared with the measurements on admission [23].

In this study, 19.8% of total patients suffered from AHF, which was consistent with the incidence of post-myocardial infarction HF [24]. Patients with acute myocardial infarction are more likely to have higher CA125 levels compared with those with UA, whether STEMI or NSTEMI. This is probably because patients with myocardial infarction lose more functional cardiomyocytes due to myocardial stunning and necrosis compared to UA patients, increasing the risk of AHF. A retrospective cohort study of ACS patients also revealed that the incidence of HF among STEMI and NSTEMI was higher than UA patients during hospitalization and one-year follow-up [25].

So far, the relationship between echocardiographic parameters and CA125 is not conclusive due to the controversial results obtained from different studies. This study focused on the relationship between CA125 and LVEDD, and LVEF in female ACS patients. CA125 showed a weak positive correlation with LVEDD and negative correlation with LVEF. CA125 also demonstrated weak negative correlation with LVEF in CHF patients in another retrospective study [9]. However, in another study of ACS patients, CA125 was found to be related to LVEDD ($r = 0.66, P < 0.001$) and LVEF ($r = -0.37, P < 0.01$) [15]. CA125 levels were correlated with the deceleration time of early filling on transmitral Doppler ($r = -0.63, p < 0.05$), pulmonary artery pressure ($r = 0.66, p < 0.05$) and right atrial pressure ($r = 0.69, p < 0.05$). However, no significant correlation was observed between CA125 concentration and LVEF or LVEDD. In another study including 77 CHF patients, a weak correlation was observed between the CA125 levels and right ventricular systolic pressure, but no significant correlation was observed between CA125 and LVEDD, LVEF, or DT [9]. Hakki Yilmaz et al. analyzed the relationship between CA125 levels and left ventricular function in patients with end-stage renal disease on maintenance hemodialysis [26]. CA125 levels showed a significant positive correlation with LVEDD ($r = 0.599, p < 0.001$), left ventricular end-systolic diameter (LVESD, $r = 0.750, p < 0.001$), and left ventricular mass index (LVMI, $r = 0.378, p < 0.05$) and negative correlation with LVEF ($r = -0.878, p < 0.001$).

In contrast to previous studies, CA125, as shown in this study, is not related to BNP, but it is an excellent predictor of AHF in ACS patients during hospitalization, even better than BNP. Robust data showed that elevated BNP is highly predictive of AHF and all-cause mortality in ACS patients when compared with lower levels. Our results are also different from those of Azra Durak-Nalbantic¹ et al., who found a significant although weak positive correlation of CA125 and BNP in CHF patients ($r = 0.293, p < 0.05$) [27]. Dursum Duman et al. studied the relationship between the CA125 and BNP concentrations in patients with advanced HF: LnCA125 was significantly correlated with LnBNP ($r = 0.78, p < 0.001$), and CA125 levels were independently associated with BNP ($\beta = 0.58, p < 0.001$) [11]. Luisa De Gennaro also revealed that elevated CA125 levels identified ACS patients with AHF with a higher specificity (97.1 vs. 31.4%), positive predictive value (83.3 vs. 33.3%), and accuracy (83.0 vs. 48.9%) when compared with BNP [15].

Many studies have already demonstrated that CA125 is a robust prognostic marker in both acute or chronic HF, and elevated CA125 level is associated with poor short-term and long-term outcomes, including mortality and rehospitalization rates. Julio Núñez et al. showed a positive trend between the quartile 1 to 4 of CA125 and 6 months' mortality in patients with AHF [28]; similar results also obtained in the latest research in patients with decompensated HF [21]. In a retrospective study of 55 CHF patients who underwent cardiac transplantation, the survival was significantly inferior in the group with elevated CA125 level compared with normal group at two-, five-, and eight-years follow-up [29]. A recent systematic meta-analysis including 16 studies showed that elevated CA125 levels were associated with a 68% increase in all-cause mortality (eight studies, HRs: 1.68, 95% CI: 1.36 to 2.07; $p < 0.001$; I^2 : 74%) and 77% increase in HF-related readmissions (five studies, HRs: 1.77, 95% CI: 1.22 to 2.59; $p < 0.01$; I^2 : 73%) in AHF patients [30]. In this study, we also confirm that elevated CA125 levels are associated with higher mortality in female ACS patients both during hospitalization and mid-term follow-up. Similar results were

obtained by Felipe Falcão et al.; patients with high CA125 values according to the optimal cutoff (11.48U/mL) had a higher rate of mortality at six months than those with low CA125 values in STEMI cohort [31].

Some limitations of this study should be highlighted. First, this is a relatively small-sized retrospective study of only female ACS patients conducted in a single center, which may limit the extrapolation of our results to all populations. The results of this study should be validated in larger trials and male crowd. Second, CA125 concentrations were determined only at hospital admission. The level might depend on the time elapsed from the onset of chest pain; serial measurement may provide more accurate prognostic value. Third, we cannot ignore the fact that factors that influence mortality were not been considered in our analysis (e.g., treatment during hospitalization and follow-up).

Conclusions

Elevated CA125 levels can be used to predict developing AHF in female ACS patients. Patients with elevated CA125 levels had higher mortality in short-term and mid-term than those with low CA125 levels.

Abbreviations

CA125: carbohydrate antigen 125; ACS: acute coronary syndrome; HF: heart failure; AHF: acute heart failure; CHF: chronic heart failure; BNP: B-type natriuretic peptide; UA: unstable angina; NSTEMI: non-ST-elevation myocardial infarction; STEMI: ST-elevation myocardial infarction; AHA: American Heart Association; ACCF: American College of Cardiology Foundation; ACC: American College of Cardiology; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; ROC: receive operating characteristic; AUC: area under the ROC curve

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of the Affiliated Hospital of Hangzhou Normal University (Ethics approval NO:2018(E2)-HS-012). All methods were carried out in accordance with relevant guidelines and regulations. This study had been performed in accordance with the Declaration of Helsinki. All enrolled subjects agreed to participate in this research, and the written informed consent was obtained.

Consent for publication

Not applicable

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

YHL participated in the study design, contributed to echocardiography data acquisition and drafted the manuscript. YRC contributed to data analysis and interpretation, performed the statistical analysis, and drafted the manuscript. XFZ contributed to data acquisition. MWW contributed to Funding acquisition. ZQY contributed to echocardiography data acquisition. ZJG contributed to data acquisition. XWZ participated in the study design. CQP participated in the whole study design, contributed to quality control of data and algorithms, and editing and review of the manuscript. All authors read and approved the final manuscript.

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Not applicable

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Figures

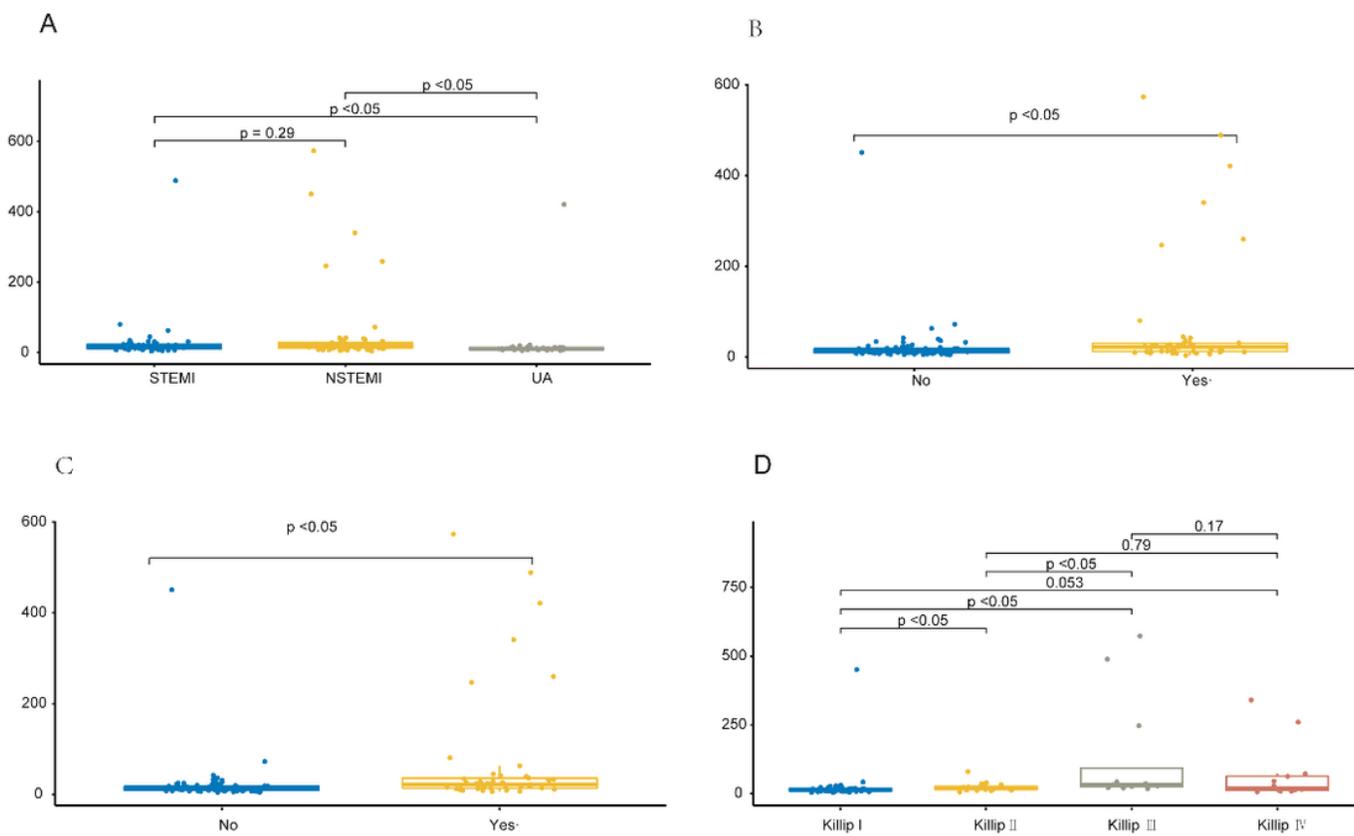


Figure 1

CA125 in patients with STEMI, NSTEMI and UA (A); CA125 in patients with and without pleural and pericardial effusion (B); CA125 in patients with and without AHF (C); CA125 in patients with Killip I-IV (D)

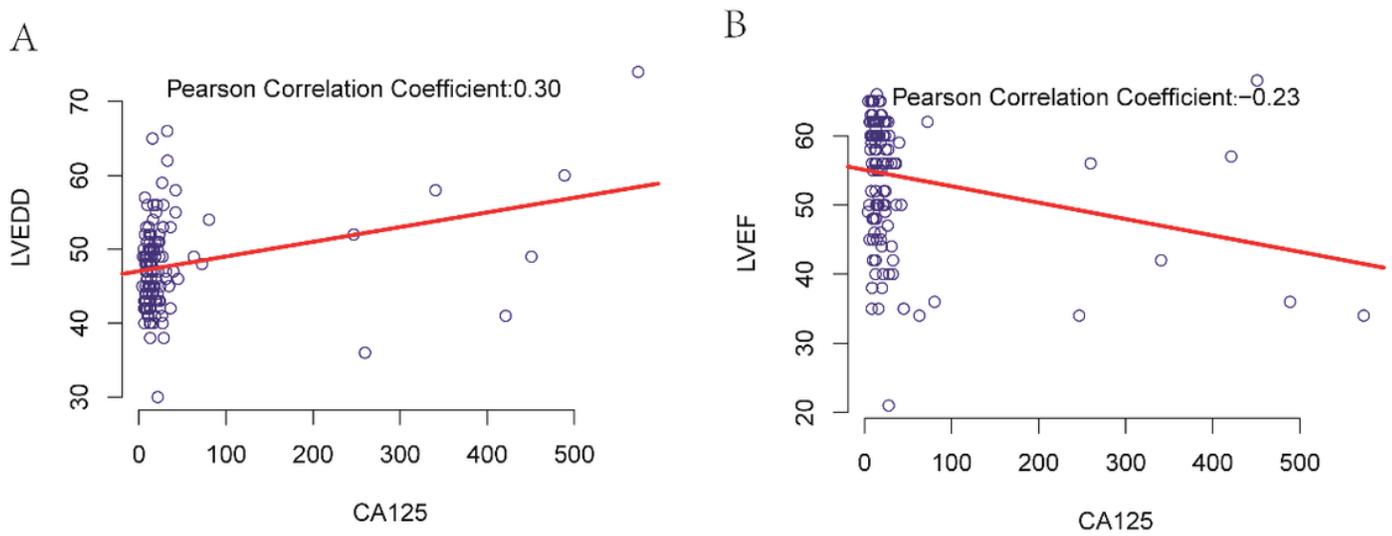


Figure 2

Correlation between CA125 and LVEDD (A); Correlation between CA125 and LVEF (B)

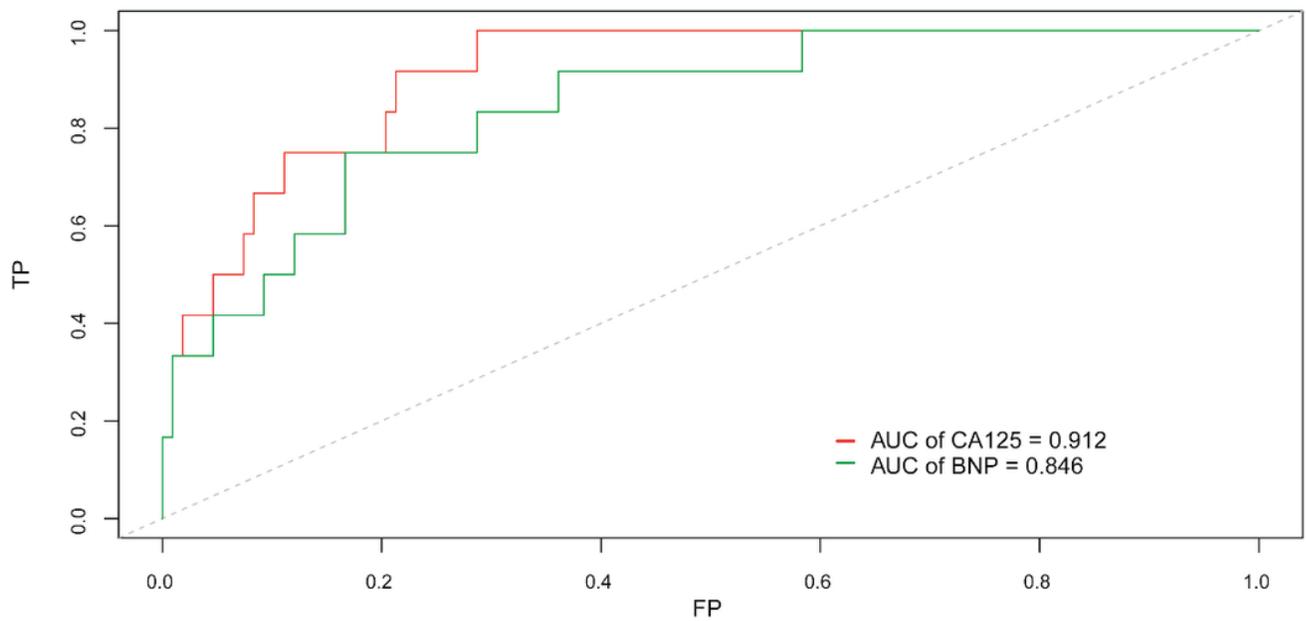


Figure 3

ROC curve comparing CA125 and BNP for predicting AHF in patients with ACS during hospitalization

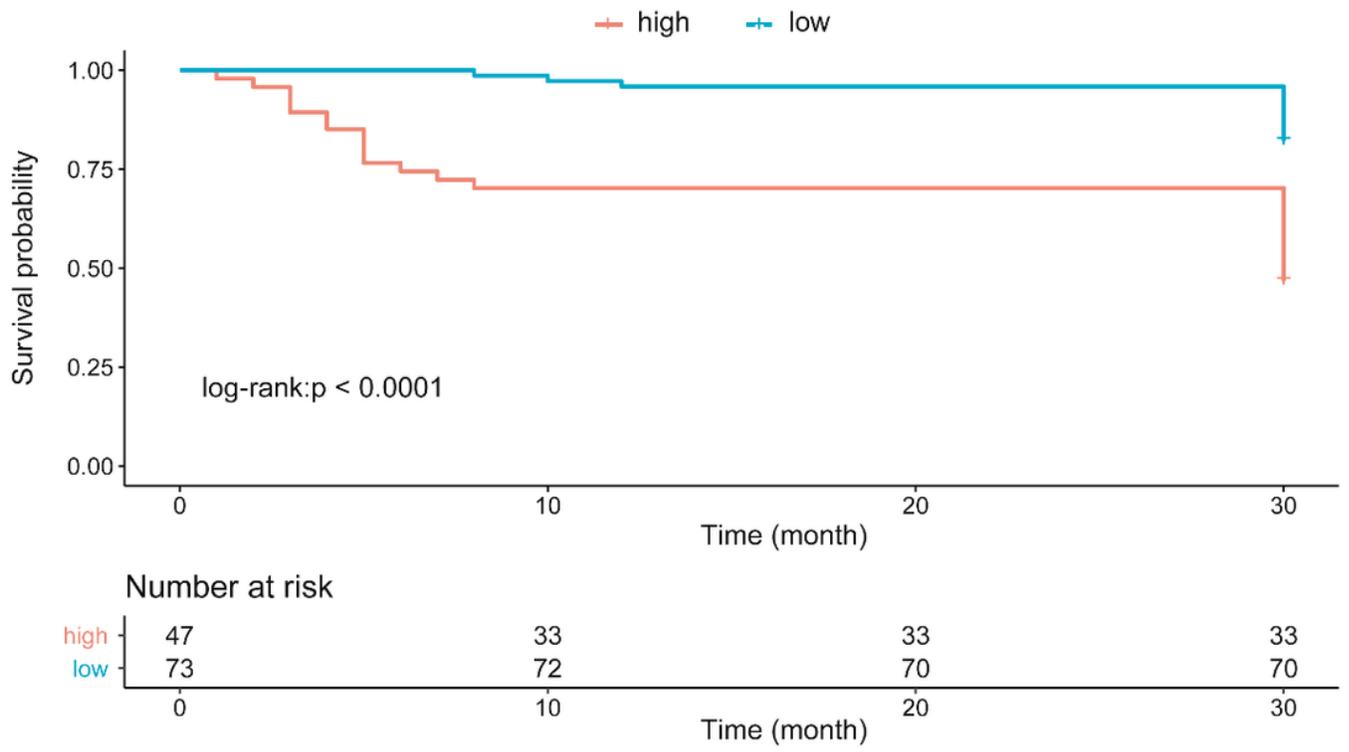


Figure 4

30 months of survival probability according to levels of CA125