

Clinical Implications of CA 125 Elevation in Patients with Cardiac Amyloidosis: An Observational Study

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Research

Keywords: Cardiac amyloidosis, CA 125, Clinical implications, prognostic predictor

Posted Date: February 10th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-202184/v1>

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Abstract

Aims: The level of serum carbohydrate antigen 125 (CA 125) elevated is a common finding in patients with cardiac amyloidosis in clinical practice. It is unclear whether CA 125 is correlated with cardiac amyloidosis. The aim of this study was to systematically evaluate the clinical implications of CA 125 elevation in patients with cardiac amyloidosis.

Methods and Results: We enrolled 101 patients diagnosed with cardiac amyloidosis at the Second Xiangya Hospital, 41 patients with acute decompensated heart failure (AHF) and 39 patients with multiple myeloma (MM) who were confirmed to have no cardiac amyloidosis served as control group, respectively. In 101 patients with cardiac amyloidosis, 58 (57%) patients had elevated serum CA 125 levels, which the mean age was 61.2 ± 11.4 years. Patients with high CA 125 were more likely to present with polyserositis (79.3% vs 60.5%, $p = 0.03$), higher levels of hemoglobin (117.22 ± 21.87 g/L vs. 106.07 ± 25.15 g/L, $p = 0.01$), serum potassium (4.17 ± 0.49 mmol/L vs. 3.98 ± 0.41 mmol/L, $p = 0.05$), low density lipoprotein-cholesterol (2.98 ± 1.65 mmol/L vs. 2.22 ± 1.10 mmol/L, $p = 0.01$), and cardiac troponin T (115 pg/mL vs. 59.52 pg/mL, $p = 0.005$). The serum CA 125 levels were significantly higher in cardiac amyloidosis than AHF and MM. The median overall survival for patients with elevated and normal serum CA125 were 5 and 20 months, respectively ($p = 0.012$). According to multivariate Cox hazard analysis, CA 125 (HR 1.002, 95%CI 1.000-1.004, $p = 0.020$) contributed to all-cause mortality. The time-dependent receiver operating characteristic was used to reflect the accuracy of different biomarkers in predicting overall survival at various time points by the area under the curve (AUC). CA 125 has no worse prediction accuracy than cardiac troponin T, NT-proBNP and LDH according to the AUC.

Conclusions: The prevalence of elevated serum CA 125 levels is more than 50% in patients with cardiac amyloidosis. As an independent prognostic predictor, highly serum CA 125 values indicated the lower overall survival and the accuracy of predicting prognosis was not inferior to the other biomarkers.

Background

Cardiac amyloidosis is a condition of systemic amyloidosis with myocardial involvement, which is caused by deposition of amyloid proteins derived from misfolded transthyretin or immunoglobulin light-chain in the myocardial interstitium, small vessels and conduction system, leading to increased ventricular wall thickness, diastolic dysfunction and arrhythmia. Although more than 30 types of amyloid are known to exist, there are three main types of cardiac amyloidosis, acquired monoclonal immunoglobulin light-chain amyloidosis (AL-CA), wild-type transthyretin amyloidosis (wtTTR-CA) and hereditary transthyretin amyloidosis (hTTR-CA) [1–3]. The natural course, treatment and prognosis of different types of cardiac amyloidosis are distinguishing [4, 5] and the diagnosis of cardiac amyloidosis is often delayed and missed. Although recent advances in noninvasive testing equipment and drug therapy have brought some new hope, it is still worth emphasizing that the exact pathophysiological mechanism of cardiac amyloidosis has not been elucidated, and its prognosis is still very poor. Therefore,

we need to make continuous efforts in the pathophysiology and clinical aspects of myocardial amyloidosis.

Previous studies indicated that several biomarkers have a demonstrated diagnostic and prognostic value in cardiac amyloidosis patients such as cardiac troponin T [6, 7], N-terminal pro-B-type natriuretic peptide (NT-proBNP) [7], D-dimer [8], and lactate dehydrogenase (LDH) [9]. However, these biomarkers are easily affected by other conditions such as end-stage liver dysfunction and renal failure. These biomarkers staging system can not accurately stratify the risk of subjects. Therefore, a better indicator is needed to evaluate patients' condition and predict the prognosis in clinical.

CA 125 is a tumour marker related to ovarian cancer [10, 11], which is a high-molecular-weight soluble glycoprotein produced by serosal epithelium. It is also reported that increased serum CA 125 levels have been connected with other malignancies such as haematological malignant tumours like leukaemia and non-Hodgkin's lymphoma, breast and lung cancers, melanoma and gastrointestinal carcinoma, as well as non-malignant situation including abdominal surgery, bacterial peritonitis and tuberculosis [12]. In recent years, some studies have revealed that elevated serum CA 125 values are associated with the clinical severity, hemodynamic status and short-term prognosis of heart failure patients [13–17].

The level of serum CA 125 increased is a common finding in patients with cardiac amyloidosis in clinical practice. Up to now, the prevalence and implications of increased CA 125 levels in cardiac amyloidosis is unknown, so in the present study, we investigated the associations between serum CA 125 levels and cardiac amyloidosis, and systematically evaluated the clinical implications of CA 125 elevation in patients with cardiac amyloidosis.

Methods

Patients

We conducted a retrospective analysis that enrolled 201 consecutive patients diagnosed as cardiac amyloidosis in the Second Xiangya Hospital of Central South University, from June 2012 to September 2020. The diagnosis of cardiac amyloidosis was based on symptoms of HF; echocardiography that indicated the interventricular septum and/or the posterior thickness of left ventricular ≥ 12 mm without any other causes of left ventricular hypertrophy; electrocardiogram that showed low voltage in the limb leads; positive findings on cardiac magnetic resonance (CMR), 99mTc-labelled pyrophosphate (99mTc-PYP) scintigraphy and tissue biopsies; with/without positive serum free light chain. The CA 125 test was completed in 135 patients and we excluded 13 patients with cancer history (except multiple myeloma) and 21 patients with incomplete information. Finally, we collected 101 patients including demographic and clinical characteristics, comorbidities, laboratory testing results, electrocardiogram and echocardiography data, and treatment as the test group. For the control group, on the one hand, we conducted 52 patients with acute decompensated heart failure (AHF, NYHA functional class IV) in the same period as one of the control group (control group 1). On the other hand, both AL-CA and multiple

myeloma (MM) are plasma cell diseases, and AL-CA is mostly associated with multiple myeloma [5], so we also included 48 patients who had confirmed multiple myeloma in the corresponding period as another control group (control group 2). Both of two control groups were eliminated history of cancer diseases and missed CA 125 level data with non-cardiac amyloidosis. Consequently, the population of final control groups consisted of 41 patients in control group 1 and 39 patients in control group 2 (Fig. 1).

All patients have underwent venous blood sample for serum levels of CA 125 on the day of admission. Serum CA 125 levels were determined by using electrochemiluminescence [Relia Biotechnology (Jiangsu, China) Co., Ltd] and the cutoff value was set at 35 KU/L.

Follow-up And Prognosis

Follow-up started at the time of diagnosis of cardiac amyloidosis. The primary endpoint for this study was death from any cause. The survival time (months) was defined as the duration between the diagnosis to the date of death; if it was more than 15 days then it would be calculated as 1 month. Data were obtained from medical records or from telephone interviews with patients or relatives by 4 trained physicians. The last date of follow-up was November 16, 2020. Patients were censored if they were still alive at the end of the research period or were lost to follow-up, on which occasion their last clinic visit or correspondence time was used.

Statistical analysis

Normally distributed parameters were expressed as mean $\pm$ standard deviation (SD), whereas non-normally distributed parameters were expressed as median with inter-quartile range (IQR). Categorical values were presented as numbers (percentages). Categorical variables were compared with either Chi-squared or Fisher's exact test. Comparison of continuous variables between two independent groups was performed using unpaired Student's t-test (if normally distributed) or Mann–Whitney U-test (non-normally distributed variables). One-way analysis of variance (ANOVA) or Kruskal–Wallis test was used for comparison of more than two groups. Prognostic factors with p values < 0.05 on the univariate Cox regression analysis were subjected to multivariate regression analysis to determine the independent factors of predicting survival according to the forward likelihood ratio method. All over survival was evaluated with Kaplan–Meier curves, and the log-rank test was used to assess the significance of differences between groups. The time-dependent receiver operating characteristic (t-ROC) was used to reflect the accuracy of different biomarkers in predicting overall survival at various time points by the area under the curve (AUC). All tests were 2-tailed and a p value of < 0.05 was considered to be statistically significant. Statistical analysis was performed using SPSS 26.0 (IBM Software Inc), EmpowerStats 3.0 software and R (version 3.3.2).

Results

Baseline characteristics

Clinical characteristics of cardiac amyloidosis

The characteristics of 101 patients in test group were presented in Table 1. Of these 101 patients, 58 (57%) and 43 (43%) were divided into high (CA 125 > 35 KU/L) and normal (CA 125 ≤ 35 KU/L) serum CA 125 groups, respectively. The mean age was 61.2 ± 11.4 years with 43 (74%) males in high serum CA 125 group, and 62.9 ± 9.5 years with 30 (70%) males in normal CA 125 levels group. Among all patients with elevated CA 125, 4 (6.9%) patients at NYHA class I, 10 (17.2%) patients at class II, 18 (31%) patients at class III, and 26 (44.8%) patients at class IV, compared with normal serum CA 125 group, there was no significant difference in NYHA classification ($p = 0.29$). Polyserositis was observed in 46 (79.3%) patients with high serum CA 125 group, compared to 26 (60.5%) patients with normal CA 125 group ($p = 0.03$). The use of aspirin and bortezomib was significantly different between normal and high serum CA 125 groups (30.2% vs. 12.1%, $p = 0.02$; 30.2% vs. 13.8%, $p = 0.04$, respectively). Patients with high serum CA 125 were more likely to present with higher median levels of hemoglobin (117.22 ± 21.87 g/L vs. 106.07 ± 25.15 g/L, $p = 0.01$), serum potassium (4.17 ± 0.49 mmol/L vs. 3.98 ± 0.41 mmol/L, $p = 0.05$), low density lipoprotein-cholesterol (2.98 ± 1.65 mmol/L vs. 2.22 ± 1.10 mmol/L, $p = 0.01$), total cholesterol (4.62 ± 2.46 mmol/L vs. 3.71 ± 1.51 mmol/L, $p = 0.04$), cardiac troponin T [115 pg/mL (IQR 60.84-173.55) vs. 59.52 pg/mL (IQR 31.60-90.43), $p = 0.005$] and serum CA 125 (215.91 ± 150.16 KU/L vs. 18.84 ± 8.80 KU/L, $p < 0.001$) compared to patients with normal serum CA 125. There were no statistically significant difference in the diameter of atriums and ventricles, the thickness of ventricular wall and the ejection fraction. In the electrocardiogram, low limb voltage seemed to be appeared more common in patients with elevated CA 125 than patients with normal CA 125 (75.0% vs. 51.1%, $p = 0.01$).

Table 1
Characteristics of 101 patients with cardiac amyloidosis

	CA 125 > 35 KU/L	CA 125 ≤ 35 KU/L	<i>p</i>
	(n = 58)	(n = 43)	value
Age, years	61.2 (11.4)	62.9 (9.5)	0.43
Male, n (%)	43 (74.1%)	30 (69.8%)	0.62
Body mass index, kg/m ²	22.08 (3.15)	22.11 (4.31)	0.97
SBP, mmHg	111.4 (25.1)	118.7 (26.1)	0.15
DBP, mmHg	70.6 (13.2)	73.2 (13.3)	0.33
Type of amyloidosis, n (%)			0.83
AL-CA	52 (89.7%)	38 (88.4%)	
TTR-CA	6 (10.3%)	5 (11.6%)	
NYHA, n (%)			0.29
Class I	4 (6.9%)	2 (4.7%)	
Class II	10 (17.2%)	11 (25.6%)	
Class III	18 (31.0%)	18 (41.9%)	
Class IV	26 (44.8%)	12 (27.9%)	
Comorbidities, n (%)			
Multiple myeloma	12 (20.7%)	15 (34.9%)	0.11
Hypertension	16 (27.6%)	17 (39.5%)	0.20
Hyperlipidaemia	15 (25.9%)	9 (20.9%)	0.56
Polyserositis	46 (79.3%)	26 (60.5%)	0.03

Data are (N) Mean (SD) or (N) n (%), Median (Q3-Q1), where N is the total number of patients with available data.

ACEI: Angiotensin-Converting Enzyme Inhibitor; AL-CA: Light-Chain amyloidosis; ALB: Albumin; ARB: Angiotensin Receptor Blocker; CA 125: Carbohydrate Antigen 125; CHD: Coronary Heart Disease; COPD: Chronic Obstructive Pulmonary Disease; CRP: C-Reactive Protein; DBP: Diastolic Blood Pressure; eGFR: estimated Glomerular Filtration Rate; ESR: Erythrocyte Sedimentation Rate; IVS: Interventricular Septum; LAESd: Left Atrium End Systolic diameter; LDH: Lactate Dehydrogenase; LDL-C: Low Density Lipoprotein-Cholesterol; LVEDd: Left Ventricular End Diastolic diameter; LVEF: Left Ventricular Ejection Fraction; LVPW: Left Ventricular Posterior Wall; NT-proBNP: N-terminal pro-B-type Natriuretic Peptide; NYHA: New York Heart Association; PCT: Procalcitonin; PRWP: Poor R-wave progression; RAESd: Right Atrium End Systolic diameter; RVEDd: Right Ventricular End Diastolic diameter; SBP: Systolic Blood Pressure; TC: Total Cholesterol; TTR-CA: Transthyretin amyloidosis

	CA 125 > 35 KU/L	CA 125 ≤ 35 KU/L	<i>p</i>
Hypothyroidism	22 (37.9%)	9 (20.9%)	0.06
Type 2 diabetes	8 (13.7%)	5 (11.6%)	0.74
COPD	8 (13.8%)	7 (16.3%)	0.72
CHD	12 (20.6%)	8 (18.7%)	0.86
Medications, n (%)			
Aspirin	7 (12.1%)	13 (30.2%)	0.02
ACEI or ARB	16 (27.6%)	12 (27.9%)	0.97
Beta-blockers	16 (27.6%)	19 (44.2%)	0.08
Spironolactone	43 (74.1%)	28 (65.1%)	0.32
Furosemide	55 (94.8%)	36 (83.7%)	0.06
Digitalis	10 (17.2%)	8 (18.6%)	0.85
Thalidomide	16 (27.6%)	19 (44.2%)	0.08
Bortezomib	8 (13.8%)	13 (30.2%)	0.04
Laboratory results			
Hemoglobin, g/L	117.22 (21.87)	106.07 (25.15)	0.01
ALB, g/L	28.6 (25.50–33.60)	30.7 (26.30-36.65)	0.26
LDH, U/L	268.7 (216.1–328.0)	260.8 (215.4-314.1)	0.34
Potassium, mmol/L	4.17 (0.49)	3.98 (0.41)	0.05
LDL-C, mmol/L	2.98 (1.65)	2.21 (1.10)	0.01
TC, mmol/L	4.62 (2.46)	3.71 (1.51)	0.04
CRP, mg/L	22.4 (35.6)	16.8 (24.5)	0.48

Data are (N) Mean (SD) or (N) n (%), Median (Q3-Q1), where N is the total number of patients with available data.

ACEI: Angiotensin-Converting Enzyme Inhibitor; AL-CA: Light-Chain amyloidosis; ALB: Albumin; ARB: Angiotensin Receptor Blocker; CA 125: Carbohydrate Antigen 125; CHD: Coronary Heart Disease; COPD: Chronic Obstructive Pulmonary Disease; CRP: C-Reactive Protein; DBP: Diastolic Blood Pressure; eGFR: estimated Glomerular Filtration Rate; ESR: Erythrocyte Sedimentation Rate; IVS: Interventricular Septum; LAESd: Left Atrium End Systolic diameter; LDH: Lactate Dehydrogenase; LDL-C: Low Density Lipoprotein-Cholesterol; LVEDd: Left Ventricular End Diastolic diameter; LVEF: Left Ventricular Ejection Fraction; LVPW: Left Ventricular Posterior Wall; NT-proBNP: N-terminal pro-B-type Natriuretic Peptide; NYHA: New York Heart Association; PCT: Procalcitonin; PRWP: Poor R-wave progression; RAESd: Right Atrium End Systolic diameter; RVEDd: Right Ventricular End Diastolic diameter; SBP: Systolic Blood Pressure; TC: Total Cholesterol; TTR-CA: Transthyretin amyloidosis

	CA 125 > 35 KU/L	CA 125 ≤ 35 KU/L	<i>p</i>
PCT, ng/mL	0.4 (0.8)	0.3 (0.9)	0.51
Cardiac troponin T, pg/mL	115 (60.84-173.55)	59.52 (31.60-90.43)	0.005
NT-proBNP, pg/mL	7678.5 (3626.25–11424.0)	4271.0 (2471.4-9898.5)	0.14
D-Dimer, ug/mL	2.15 (2.41)	1.50 (1.94)	0.16
CA 125, KU/L	215.91 (150.16)	18.84 (8.80)	< 0.001
eGFR, mL/(min×1.73m ²)	58.28 (29.33)	61.54 (34.49)	0.63
Echocardiography			
LVEDd, mm	43.68 (6.55)	45.62 (6.97)	0.16
RVEDd, mm	32.88 (5.43)	32.62 (5.76)	0.82
LAESd, mm	40.53 (7.93)	41.29 (8.09)	0.64
RAESd, mm	38.67 (10.27)	37.90 (8.71)	0.69
IVS, mm	14.23 (3.89)	13.21 (2.96)	0.16
LVPW, mm	13.75 (3.27)	12.93 (2.75)	0.19
LVEF, (%)	55.0 (46.0–61.0)	57.0 (50.0-61.5)	0.35
Electrocardiogram			
Atrial fibrillation, n (%)	11 (19.6%)	9 (20.9%)	0.87
Low limb voltage, n (%)	42 (75.0%)	22 (51.1%)	0.01
PRWP, n (%)	46 (82.1%)	31 (72.1%)	0.23
Data are (N) Mean (SD) or (N) n (%), Median (Q3-Q1), where N is the total number of patients with available data.			
ACEI: Angiotensin-Converting Enzyme Inhibitor; AL-CA: Light-Chain amyloidosis; ALB: Albumin; ARB: Angiotensin Receptor Blocker; CA 125: Carbohydrate Antigen 125; CHD: Coronary Heart Disease; COPD: Chronic Obstructive Pulmonary Disease; CRP: C-Reactive Protein; DBP: Diastolic Blood Pressure; eGFR: estimated Glomerular Filtration Rate; ESR: Erythrocyte Sedimentation Rate; IVS: Interventricular Septum; LAESd: Left Atrium End Systolic diameter; LDH: Lactate Dehydrogenase; LDL-C: Low Density Lipoprotein-Cholesterol; LVEDd: Left Ventricular End Diastolic diameter; LVEF: Left Ventricular Ejection Fraction; LVPW: Left Ventricular Posterior Wall; NT-proBNP: N-terminal pro-B-type Natriuretic Peptide; NYHA: New York Heart Association; PCT: Procalcitonin; PRWP: Poor R-wave progression; RAESd: Right Atrium End Systolic diameter; RVEDd: Right Ventricular End Diastolic diameter; SBP: Systolic Blood Pressure; TC: Total Cholesterol; TTR-CA: Transthyretin amyloidosis			

Comparison Of Clinical Characteristics Among Different Groups

In order to make a better comparison with two control groups, test group was classified into AL-CA (n = 90) and TTR-CA (n = 11) according to the type of cardiac amyloidosis. The clinical characteristics between test group and two control groups were shown in Table 2. The mean age of AL-CA was 61.1 ± 10.1 years with 67 (74.4%) males, 68.4 ± 13.2 years with 6 (54.5%) males in TTR-CA, 72.1 ± 13.4 years with 24 (58.5%) males in control group 1, and 61.5 ± 10.9 years with 23 males (59.0%) in control group 2 ($p < 0.01$ and $= 0.14$, respectively). The median value of cardiac troponin T was 83.8 pg/mL (IQR 40.1-157.4) in AL-CA, and 51.4 pg/mL (IQR 37.6–64.5) in TTR-CA. The median value of NT-proBNP was 7326.2 pg/mL (IQR 2969.8-11424) and 2825.5 pg/mL (IQR 2645.8-4751.7) in AL-CA and TTR-CA, respectively. Compared with patients who has suffered from AHF, the cardiac troponin T levels in patients with cardiac amyloidosis has not significant difference [51.4 pg/mL (IQR 27.9-123.1), $p = 0.20$], however, it was significant lower in the NT-proBNP levels [11423.0 pg/mL (IQR 4738.0-28715.0), $p < 0.01$]. Elevated serum CA 125 values were observed in 52 (57.8%) patients at AL-CA, with 134.4 ± 152.2 KU/L mean value, in 6 (54.5%) patients at TTR-CA with 112.4 ± 134.7 KU/L mean value, in 16 (39.0%) patients at AHF with 45.7 ± 44.9 KU/L mean value and in 3 (7.7%) patients at MM with 18.9 ± 20.9 KU/L mean value ($p < 0.01$, Fig. 2).

Table 2
Clinical characteristics between test group and two control groups.

	AL-CA	TTR-CA	AHF	MM	<i>p</i>
	(n = 90)	(n = 11)	(n = 41)	(n = 39)	Value
Age, years	61.1 (10.1)	68.4 (13.2)	72.1 (13.4)	61.5 (10.9)	< 0.01
Male, n (%)	67 (74.4%)	6 (54.5%)	24 (58.5%)	23 (59.0%)	0.14
NYHA, n (%)					-
Class I	6 (6.7%)	0 (%)	0 (%)	0 (%)	
Class II	20 (22.2%)	1 (9.1%)	0 (%)	0 (%)	
Class III	29 (32.2%)	7 (63.6%)	0 (%)	0 (%)	
Class IV	35 (38.9%)	3 (27.3%)	41 (100%)	0 (%)	
Cardiac troponin T, pg/mL	83.8 (40.1-157.4)	51.4 (37.6–64.5)	51.4 (27.9-123.1)	-	0.20
NT-proBNP, pg/mL	7326.2 (2969.8-11424)	2825.5 (2645.8-4751.7)	11423 (4738.0-28715)	-	< 0.01
CA 125 > 35 KU/L, n (%)	52 (57.8%)	6 (54.5%)	16 (39.0%)	3 (7.7%)	< 0.01
CA 125, KU/L	134.4 (152.2)	112.4 (134.7)	45.7 (44.9)	18.9 (20.9)	< 0.01
Data are (N) Mean (SD) or (N) n (%), Median (Q3-Q1), where N is the total number of patients with available data.					
AHF: Acute decompensated heart failure; AL-CA: Light-chain Amyloidosis; CA 125: Carbohydrate Antigen 125; MM: multiple myeloma; NT-proBNP: N-terminal pro-B-type Natriuretic Peptide; NYHA: New York Heart Association; TTR-CA: Transthyretin amyloidosis					

Univariate and multivariate analyses of patient survival

We investigated the prognostic factors for all-cause mortality using univariate and multivariate Cox hazard analyses in our study, as presented in Table 3. In the univariate model, systolic blood pressure (HR 0.986, 95%CI 0.977–0.995, $p = 0.002$), diastolic blood pressure (HR 0.983, 95%CI 0.967-1.000, $p = 0.046$), hyperlipidemia (HR 1.752, 95%CI 1.031–2.977, $p = 0.038$), treatment without chemotherapy (HR 1.443, 95%CI 1.023–2.035, $p = 0.037$), low density lipoprotein-cholesterol (HR 1.210, 95%CI 1.022–1.433, $p = 0.027$), total cholesterol (HR 1.151, 95%CI 1.021–1.096, $p = 0.021$), CA 125 (HR 1.002, 95%CI 1.001–1.004, $p = 0.003$), left ventricular posterior wall (HR 1.085, 95%CI 1.004–1.174, $p = 0.040$), and low limb voltage (HR 1.907, 95%CI 1.132–3.213, $p = 0.015$) were statistically significant predictors of overall

survival, however, when multivariate analysis was performed, there were only two factors remained as independent determinants: treatment without chemotherapy (HR 1.694, 95%CI 1.121–2.562, $p = 0.012$) and CA 125 (HR 1.002, 95%CI 1.000-1.004, $p = 0.020$).

Table 3
Univariate and multivariate Cox hazard analyses of predictors for all-cause mortality.

Variables	Univariate			Multivariate		
	HR	95% CI	<i>p</i> value	HR	95% CI	<i>p</i> value
Male	0.97	0.57–1.64	0.911	-	-	-
Age	1.01	0.99–1.03	0.345	-	-	-
BMI	0.93	0.87–1.01	0.097	-	-	-
NYHA	1.20	0.91–1.58	0.195	-	-	-
SBP	0.986	0.977–0.995	0.002	0.979	0.958–1.001	0.064
DBP	0.983	0.967–1.000	0.046	1.017	0.977–1.057	0.415
MM	1.041	0.618–1.753	0.880	-	-	-
Hyperlipidemia	1.752	1.031–2.977	0.038	1.915	0.898–4.083	0.093
Polyserositis	1.002	0.590–1.701	0.995	-	-	-
Beta-blockers	1.388	0.818–2.353	0.224	-	-	-
Hemoglobin	1.008	0.999–1.018	0.093	-	-	-
ALB	0.973	0.938–1.010	0.152	-	-	-
Potassium	0.907	0.529–1.554	0.722	-	-	-
eGFR	0.998	0.990–1.006	0.662	-	-	-
Non-Chemotherapy	1.443	1.023–2.035	0.037	1.694	1.121–2.562	0.012
LDL-C	1.210	1.022–1.433	0.027	0.573	0.287–1.144	0.114
TC	1.151	1.021–1.096	0.021	1.479	0.926–2.363	0.101
D-Dimer	1.098	0.995–1.210	0.062	-	-	-
CA 125	1.002	1.001–1.004	0.003	1.002	1.000–1.004	0.020
IVS	1.049	0.984–1.118	0.141	-	-	-
LVPW	1.085	1.004–1.174	0.040	1.094	0.999–1.200	0.055
LVEF	0.979	0.953–1.005	0.116	-	-	-
Low voltage	1.907	1.132–3.213	0.015	1.673	0.882–3.172	0.115
PRWP	1.527	0.814–2.862	0.187	-	-	-
HR, hazard ratio; CI: Confidence Interval.						
For other abbreviations, see Table 1.						

Kaplan-meier Analysis And T-roc Analysis

Patients with high levels of CA 125 were followed-up for a median period of 5 months (IQR 1.0-10.2) and those normal levels were 7 months (IQR 1.5–19.0, $p = 0.10$). The median overall survival in evaluated CA 125 patients was 5 months (95%CI 3.881–6.119) and 20 months (95%CI 0.602–39.398) in patients with normal CA 125 ($p = 0.012$, Fig. 3A). With regard to therapies, palliative patients had a median overall survival of only 6 months (95%CI 4.823–7.177). Compared to 13 months (95%CI 2.103–23.897) in patients receiving chemotherapy, the overall survival was significantly shorter for patients with non-chemotherapy ($p = 0.035$, Fig. 3B). Finally, we quantified the accuracy of four biomarkers to predict the overall survival by t-ROC analysis. The AUC of 3-month, 6-month, 12-month, 18-month, 24-month overall survival for CA 125 were 0.58, 0.7, 0.72, 0.72, and 0.73, respectively (Fig. 4A), compared with NT-proBNP (Fig. 4B), cardiac troponin T (Fig. 4C), LDH (Fig. 4D).

Discussion

Cardiac amyloidosis is the most common type of infiltrative cardiomyopathy, which represents various clinical manifestations such as congestive HF, arrhythmia, orthostatic hypotension, syncope or even other system expressions like gastro-intestinal symptoms, albuminuria, and carpal tunnel syndrome leading to a large increase in the rate of missed diagnosis [1]. In the present study, we analyzed serum CA125 levels in 101 consecutive cardiac amyloidosis patients at an expertise center in China. To the best of our knowledge, this is the first study to analyse the prevalence and evaluate the clinical significance of serum elevated CA 125 levels in patients with cardiac amyloidosis. The principal results of this study are as follows: 1) serum CA 125 levels were elevated in more than a half of cardiac amyloidosis patients, compared to those with normal CA 125 levels, patients who exhibited high serum CA 125 had higher levels of hemoglobin, potassium, low density lipoprotein-cholesterol, total cholesterol and cardiac troponin T, as well as more common with polyserositis and low limb voltage; 2) the values of CA 125 in cardiac amyloidosis patients were significantly higher than in patients with MM and AHF; 3) CA 125 was a significant independent predictor of survival, with higher levels being independently concerned with lower overall survival; 4) as a predictor of the prognosis, CA 125 has no worse prediction accuracy than cardiac troponin T, NT-proBNP and LDH according to the AUC, in addition, it does not seem to be affected by estimated Glomerular Filtration Rate (eGFR) of patients.

Serum CA 125 values are used in the diagnosis and follow-up of the patients with ovarian cancer and to evaluate the response to therapy [18, 19]. It is reported that elevation of serum CA 125 also has been observed in other malignancies [20–24] and non-malignant diseases [25–28]. The first study regarding the underlying influences between CA 125 and cardiovascular system investigated the association of serum CA 125 levels and pericardial effusion in 1993 [29]. Whereafter, Nägele et al. [17] showed for the first time a systematic relation to serum values of CA 125 and HF in 1999, concluded that CA 125 may be a valuable tool for the monitoring of the status and clinical course of patients with HF or even influence the drug therapy and decision for heart transplantation. A study analyzed [16] a series of tumor marker levels in patients with chronic HF (CHF) also demonstrated that only CA 125 levels correlated with

baseline clinical status in HF compared with CA 19 – 9, CA 15 – 3, carcinoembryonic antigen (CEA) and alpha-fetoprotein (AFP). D'Aloia et al. [14] and Kouris et al. [15] found that serum CA 125 levels of patients with CHF were significantly higher in NYHA class III/IV compared with those in NYHA class I/II. Furthermore, in addition to CHF, elevated CA 125 values were also observed in AHF and used to assess 6-month risk stratification in patients admitted with AHF [30]. At present, some studies have confirmed that cardiac troponin T and NT-proBNP have significant clinical values in determining the prognosis for newly diagnosed AL amyloidosis patients, accordingly, the Mayo Clinic established a staging system involving the two biomarkers (as well as free light chain) to predict patient outcomes [31, 32]. This risk stratification system is also the most commonly used in clinical practice.

The potential mechanism of serum CA 125 levels elevation in cardiac amyloidosis remains unclear. Seo et al. [29] found that among 57 patients with different etiologies of pericardial effusion, 65% had significantly higher serum CA 125 levels than normal, moreover, with the reduction or disappearance of effusion, the levels of CA 125 were reported to decrease or even normalize. In addition, they also used anti-CA 125 antibodies to stain the pericardial tissue obtained at autopsy of 17 patients and showed higher serum CA 125 levels in the CA 125-positive-stained pericardium than compared to those in negative for CA 125. Except for pericardial effusion, elevated serum CA 25 levels have also been reported in pleural and peritoneal effusions with non-malignant diseases and demonstrated that CA 125 might be produced from the mesothelial cells of pleura and peritoneum [33–35]. Consistent with the present study, polyserositis were observed in 79.3% of 58 cardiac amyloidosis patients with elevated CA 125 levels in our findings. On the other hand, some studies indicated that blood levels of cytokines and/or its receptors such as IL-6, IL-10 and TNF- α were more likely to be increased in patients with HF and the cytokine network activation is one of the main factors for serum CA 125 elevation in patients with CHF dependent on inflammation [36–38]. Compared to patients with AHF, serum CA 125 levels with cardiac amyloidosis were significantly higher in our study ($p < 0.01$), although the blood mean levels of CA 125 in AHF above normal. Meanwhile, we found that only 3 patients with MM had a mild elevated in serum CA 125 levels ($p < 0.01$), so we mainly excluded the effect of plasma cell diseases on CA 125. Based on the studies and our findings, it could be hypothesized that the reasons for the elevation of serum CA 125 levels in cardiac amyloidosis might be as follows: 1) abnormal deposition of amyloid in the serosal tissue and increased chronic left ventricular filling pressure caused by HF leading to tissue stretching and stimulate the secretion of mesothelial cells; 2) amyloid activates the cytokine network by inflammation excitation and stimulate the mesothelial cells to produce and secrete CA 125. However, the underlying mechanism linked between CA 125, cytokines, CA 125-producing cells and cardiac amyloidosis needs further study to illustrate.

Our study found that the levels of cardiac troponin T are associated with the serum CA 125 levels, as the higher cardiac troponin T levels in high serum CA 125 group compared to normal CA 125 group. We speculated that patients with elevated serum CA 125 could have more fluid accumulation leading to increased left ventricular filling pressure and polyserositis, which caused increased wall stress due to diastolic dysfunction and compressed myocardial capillaries, induced deficient myocardial blood supply and myocardial ischemia. Similarly, we also discovered that patients with high serum CA 125 values had

higher levels of hemoglobin, potassium, low density lipoprotein-cholesterol, total cholesterol. We conjectured that most of the cardiac amyloidosis patients with elevated CA 125 levels have involved the kidney, and combined with nephrotic syndrome [39], which caused body fluid to enter the interstitial space or serous cavity, leading to blood concentration and dyslipidemia. Of course, the significant difference between the serum CA 125 levels of low limb voltage could also be explained by serous effusion. Nevertheless, further pathophysiological mechanisms need to be confirmed by subsequent studies.

CA 125 was significantly contributed to prognosis after adjusting for systolic blood pressure, diastolic blood pressure, hyperlipidemia, treatment without chemotherapy, low-density lipoprotein-cholesterol, total cholesterol, left ventricular posterior wall, and low limb voltage. The median overall survival of high levels of CA 125 patients was only 5 months while there were 20 months of median overall survival in normal CA 125 levels. It means high levels of serum CA 125 are independently concerned with high mortality in patients with cardiac amyloidosis. The accuracy of CA 125 in predicting the overall survival was not inferior to the classical prognostic biomarkers including cardiac troponin T, NT-proBNP and LDH in this study. In addition, the possible preponderance of CA 125 in contrast with those biomarkers maybe its easily obtainable, repeatable, no preparations and inexpensive cost (less than 4 dollars per determination in China compared with more than 40 dollars about NT-proBNP). Meanwhile, it is reported that the CA 125-guided therapy (keeping CA 125 levels at 35 KU/L or less by optimizing the use of diuretic, enforcing the use of statins and increasing the frequency of monitoring visits) was superior to the standard of care for AHF by reducing the risk of one year death and the rate of rehospitalization [40]. Maybe in the future, we can also adjust the treatment strategy for patients with cardiac amyloidosis to reduce the myocardial injury, improve the clinical condition of patients, assist chemotherapy and decrease the rate of mortality and readmission based on serum CA 125 values.

Limitations

Several limitations of the study need to be addressed. First, the small population and information bias may affect the results of our study. Further research should increase the study population and minimize the information bias to let the results more reliable. Second, we have not investigated the effect of therapies including chemotherapy and palliative care on serum CA 125 levels, which may have a crucial influence on the evaluation of treatment outcome and short-term prognosis. Third, although our study found that there was no significant difference in eGFR between disparate serum CA 125 levels, we did not further research the comparison of CA125 in different renal function stage at cardiac amyloidosis patients. Besides, a nephrotic syndrome caused by renal involvement of cardiac amyloidosis leading to fluid retention and polyserositis is one of the reason for elevated serum CA 125 we suspected. Therefore, the following studies need to focus on the connection between CA 125 and nephrotic syndrome.

Conclusion

The prevalence of elevated serum CA 125 levels is more than 50% in patients with cardiac amyloidosis. As an independent prognostic predictor, highly serum CA 125 values indicated the lower overall survival

and the accuracy of predicting prognosis was not inferior to the other biomarkers.

Abbreviations

AFP: alpha-fetoprotein; AHF: acute decompensated heart failure; AL-CA: light-chain amyloidosis; ANOVA: One-way analysis of variance; AUC: area under the curve; CA 125: carbohydrate antigen 125; CEA: carcinoembryonic antigen; CHF: chronic heart failure; CI: confidence interval; CMR: cardiac magnetic resonance; eGFR: estimated Glomerular Filtration Rate; HR: hazard ratio; hTTR-CA: hereditary transthyretin amyloidosis; IQR: inter-quartile range; LDH: lactate dehydrogenase; MM: multiple myeloma; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association; SD: standard deviation; t-ROC: time-dependent receiver operating characteristic; wtTTR-CA: wild-type transthyretin amyloidosis; ^{99m}Tc-PYP: ^{99m}Tc-labelled pyrophosphate.

Declarations

Ethics approval and consent to participant

The study protocol conformed to the ethical guidelines of the Declaration of Helsinki as reflected by prior approval from the human research committee of the Second Xiangya Hospital of Central South University. Written informed consent was obtained from patients while the patient was in a clinically stable, non-congested condition or their family members who can give informed consent on behalf of patients after they were informed about the objectives and procedures of the study. Their rights to refuse participation any time they want were assured.

Consent for publication

All authors have participated in the work and have reviewed and agree with the content of the article.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors have no conflicts of interest to disclose.

Funding

Financial support was obtained from the National Natural Science Foundation of China (No.81770337 and No.81800302), China International Medical Foundation (Z-2016-23-2001-14) and Provincial Natural Science Foundation of Hunan (No.2019JJ50871).

Authors' Contributions

QM Liu and JJ Tang designed this study and performed quality control of data authenticity. MZ Li drafted the manuscript, ZJ Wu and MZ Li collected and analyzed these data. MZ Li, ZJ Wu, Ilyas and NH Qi performed follow-up visits. W Li, Qingyi Zhu provided study guidance and revised the paper. MX Chen, YQ Chen, QM Liu and JJ Tang revised the paper and all authors approved the final version.

Acknowledgements

Not application.

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Figures

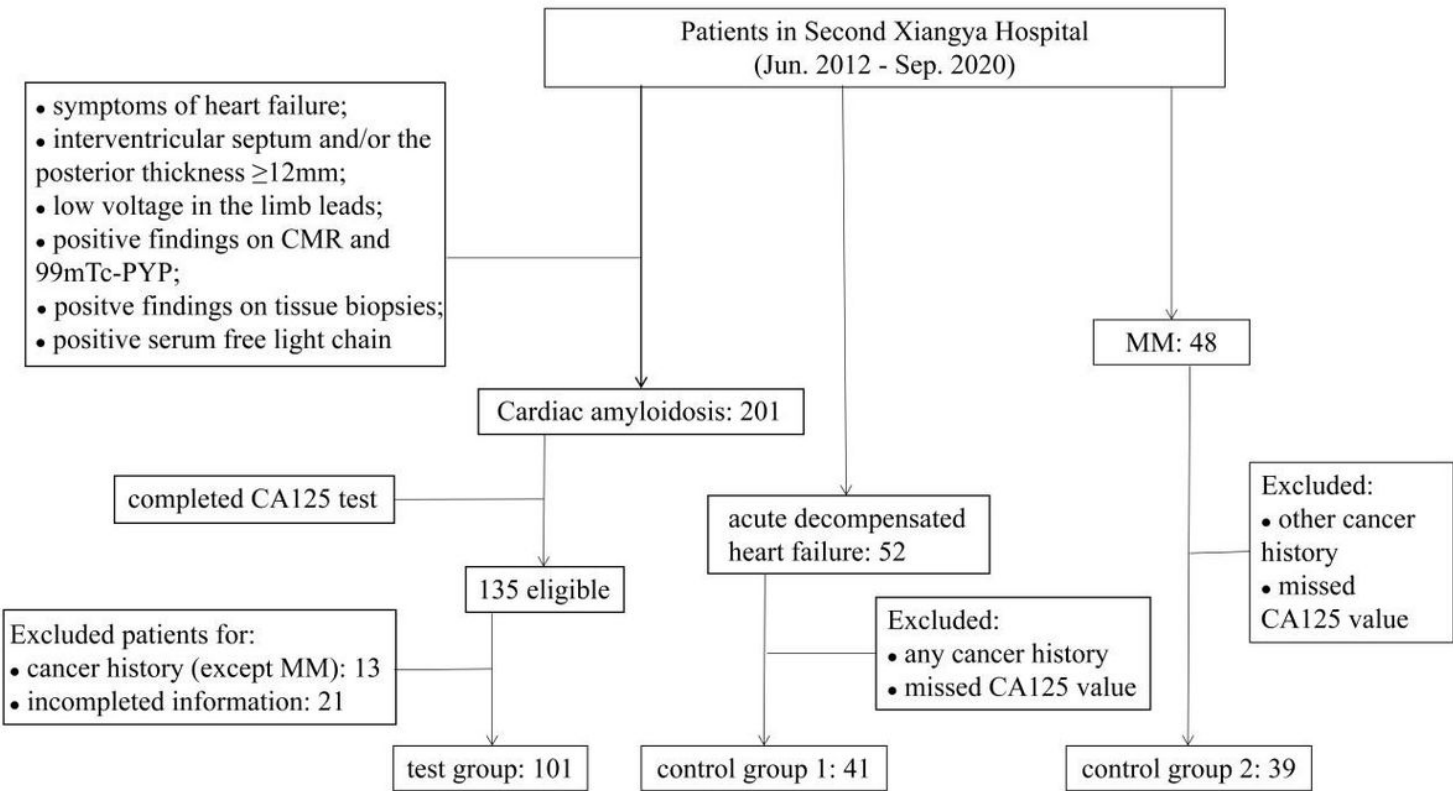


Figure 1

Flowchart of patients for the test group and other two control groups. CA125: Carbohydrate Antigen 125; CMR: Cardiac Magnetic Resonance; MM: Mutiple Myeloma; NYHA: New York Heart Association; 99mTc-PYP: 99mTc-labelled pyrophosphate

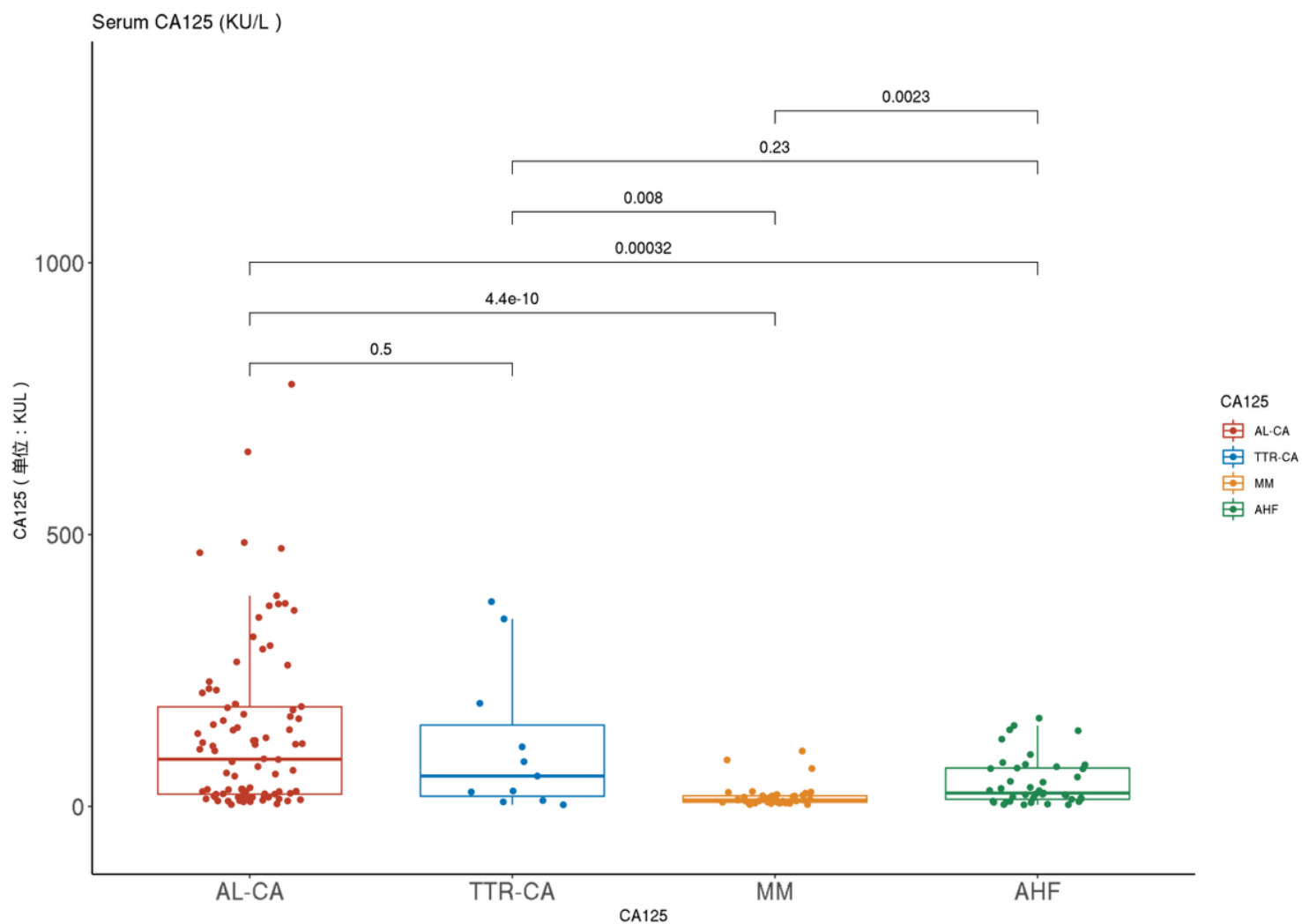


Figure 2

Comparison of serum CA 125 levels between different groups. AHF: acute decompensated heart failure; AL-CA: Light-chain Amyloidosis; TTR-CA: Transthyretin Amyloidosis; CA 125: Carbohydrate Antigen 125; MM: Mutiple Myeloma

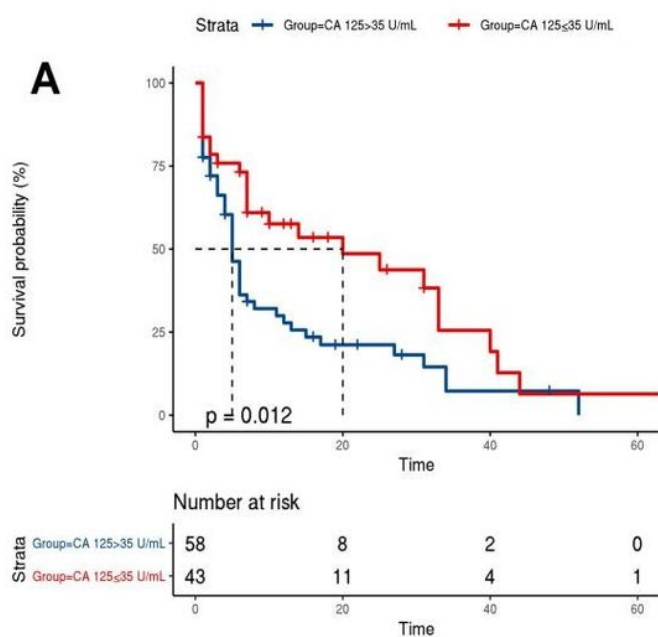
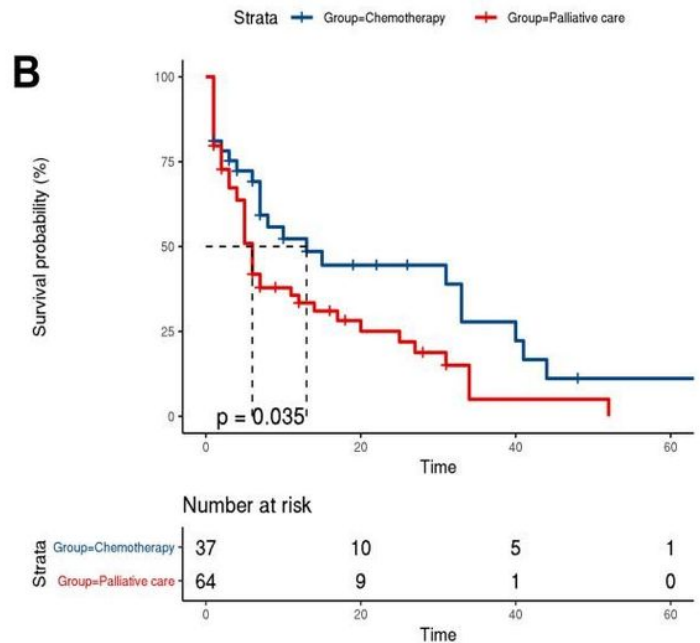


Figure 3

Kaplan-Meier analysis for 101 patients with cardiac amyloidosis classified according to serum levels of CA 125 (A) and treatment with/without chemotherapy(B). The median overall survival in elevated and normal CA 125 values were 5 months and 20months, respectively ($p = 0.012$). Palliative patients had a median overall survival of 6 months while the patients receiving chemotherapy had a median overall survival of 13 months ($p = 0.035$).

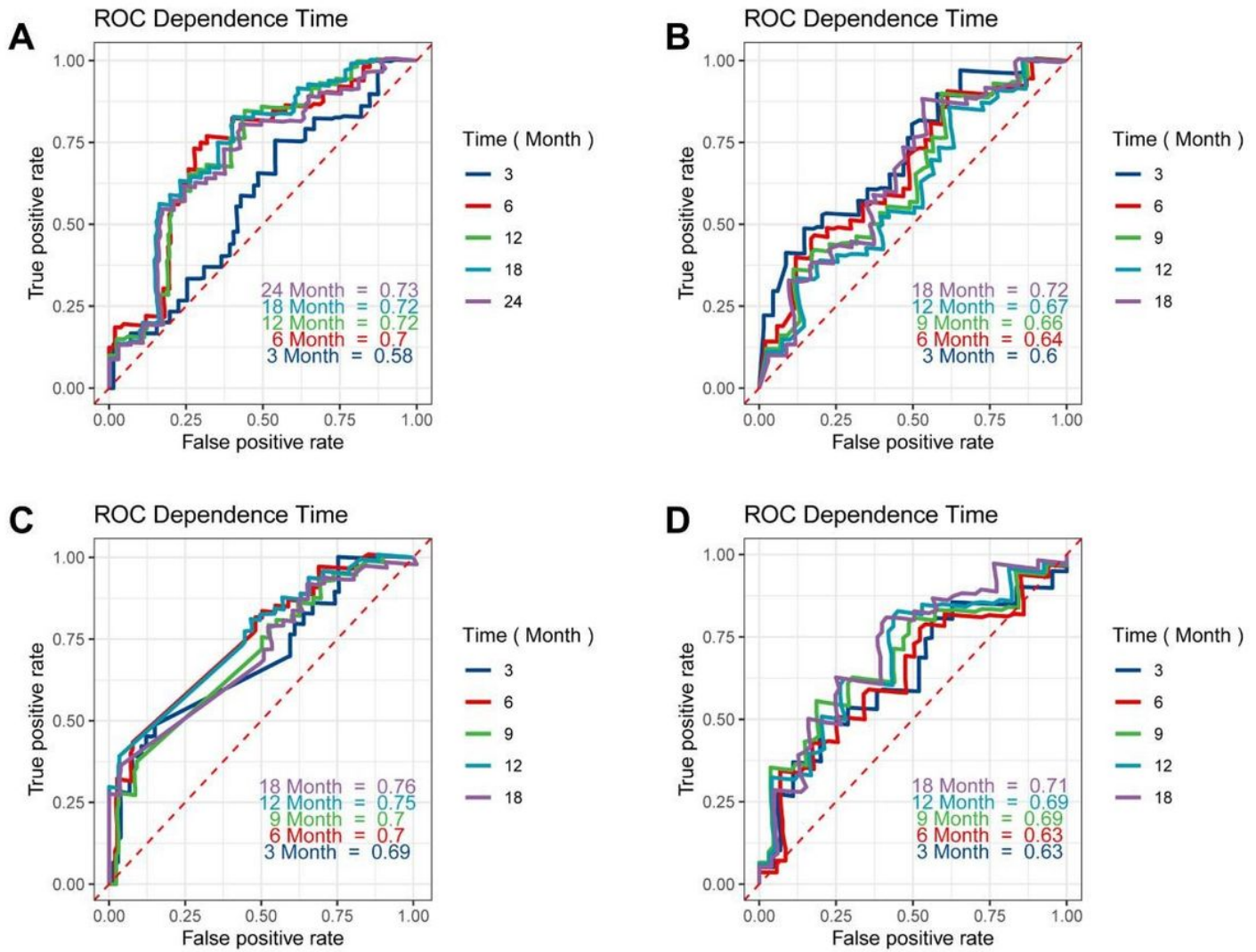


Figure 4

Time-dependent ROC (t-ROC) curves for CA 125 (A), NT-proBNP (B), cardiac troponin T (C), and LDH (D) models. The AUC presented the accuracy of predicting overall survival time (from diagnosis confirmed) for each biomarker at various time points.