

## D-Dimer: A Novel Predictor of Survival in Patients with Cardiac Light-Chain Amyloidosis

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### Abstract

**Background:** To identify independent risk factors and predictors of survival in patients with cardiac light chain amyloidosis.

**Methods:** This study included 26 patients with cardiac AL amyloidosis who were diagnosed by biopsy between October 2009 and January 2016. All the patients were followed up until August 26th, 2016. Baseline clinical data including clinical symptoms, laboratory data, and echocardiographic findings were recorded. Univariate and multivariate Cox proportional hazard regression analyses were performed to identify risk factors for all-cause mortality. The Kaplan-Meier method and log-rank test were used to compare survival times.

**Results:** In univariate and multivariate analysis, N-terminal pro b-type natriuretic peptide (NT-proBNP) and D-dimer were independent risk factors for all-cause mortality in patients with cardiac AL amyloidosis ( $P < 0.05$ ). The cut-off value of NT-proBNP for 6-month all-cause mortality was 4509.5 ng/L (sensitivity 73.3%, specificity 77.8%, area under curve (AUC) 67%, 95% confidence interval (CI) 0.442-0.899). The cut-off value of D-dimer for 6-month all-cause mortality was 1.22 mg/L (sensitivity 60%, specificity 90%, AUC 70%, 95% CI: 0.489-0.911). Patients with NT-proBNP or D-dimer levels above the cut-off value had a higher all-cause mortality rate compared to patients below the cut-off value.

**Conclusion:** D-dimer may be an important biomarker of prognosis in cardiac AL amyloidosis patients.

**Keywords:** D-dimer; Cardiac light-chain amyloidosis; Survival analysis

### Introduction

Light-chain (AL) amyloidosis is a form of systemic amyloidosis that is characterized by extra-cellular deposition of pathologic insoluble  $\beta$ -fibrillar immunoglobulin light chains in virtually every organ except the central nervous system [1]. AL amyloidosis is usually associated with plasma cell dyscrasia [2], in which a malignant proliferation of plasma cells secretes an unstable light chain that is prone to misfolding. AL amyloidosis is a relatively rare disease, occurring with an incidence of approximately 10 patients per million per year; however, cardiac involvement has been reported in approximately 70% [3] of cases [4], resulting in rapidly progressive heart failure (HF) and a very poor prognosis, especially in untreated patients. The progression of cardiac AL amyloidosis involves myocardial hypertrophy and decreased myocardial compliance. Causes of death include congestive HF, ventricular tachyarrhythmia, bradyarrhythmia, and severe hypotension [5,6]. The median survival time from diagnosis of cardiac AL amyloidosis ranges from 6 to 24 months [5-8]. Prompt treatment is essential, as 25-30% of cardiac AL amyloidosis patients will die within the first year of diagnosis [3].

There remains an unmet need for non-invasive tools that allow early diagnosis of cardiac AL amyloidosis. Currently, diagnosis is

challenging, as the gold standard is endomyocardial biopsy (EMB), which is an invasive procedure with risks associated with sampling [5-10]. Biomarkers such as N-terminal pro b-type natriuretic peptide (NT-proBNP) and cardiac muscle troponin T have been shown to add clinically useful information for the management of patients with AL amyloidosis [11,12]. Therefore, the presence of clinical factors and/or biomarkers of cardiac pathology may play a critical role in identifying cardiac AL amyloidosis and determining the severity of cardiac involvement. The objective of this study was to identify independent risk factors and predictors of survival in patients with cardiac AL amyloidosis.

### Methods

#### Study design

Thirty-two consecutive patients (19 male, 13 female) with cardiac AL amyloidosis treated at our institution between December 1st, 2009 and February 26th, 2016 were included in this study. All patients had biopsy-proven AL amyloidosis confirmed by Congo red staining, serum/urine immunofixation electrophoresis, and serum free light-chain testing. Cardiac involvement was confirmed by cardiac magnetic resonance imaging or by a history of HF with myocardial wall thickening on cardiac ultrasound. Ethical approval for this study was provided by the medical ethics committee of Jiangsu Province Hospital, China.

## Laboratory measurements

Baseline clinical data including clinical manifestations, laboratory data, and echocardiographic findings were recorded. Clinical manifestations included an assessment of HF severity based on the New York Heart Association (NYHA) functional classification; the analysis of blood samples collected at the time of admission or the following morning, which were submitted for routine biochemistry and quantitative determinations of N-terminal pro b-type natriuretic peptide (NT-proBNP) (Roche Elecsys<sup>®</sup> proBNP Immunoassay, Switzerland) and D-dimer (Sysmex<sup>®</sup>CA-7000, Japan); and Glomerular Filtration Rate (eGFR) estimated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation. Laboratory data included quantitative estimations of muscle hemoglobin (Roche Elecsys<sup>®</sup>e411, Switzerland) and cardiac troponin T (cTnT, Roche Elecsys<sup>®</sup>e411, Switzerland). In addition, each patient underwent transthoracic echocardiography (Vivid 9 System, GE Medical System, USA). Left ventricular diameter (LVD), left atrial diameter (LAD), right atrial diameter (RAD), and left ventricular ejection fraction (LVEF) were measured. All patients were followed up through direct interviews or telephone calls until 26th August 2016.

## Statistical analysis

Statistical analyses were performed using STATA 12.0. Continuous variables are presented as mean  $\pm$  standard deviation (SD) and categorical variables are presented as median (interquartile range). Between-group differences for continuous variables were examined using the Student's t-test or Wilcoxon rank sum test. Between-group differences for categorical variables were examined using the  $\chi^2$  test. Survival time was calculated from the point of diagnosis until death or the last follow-up. Univariate and multivariate Cox proportional hazard regression analyses were performed to estimate hazard ratios (HRs). The Kaplan-Meier method and log-rank test were used to compare survival times. All tests were two-sided. Statistical significance was considered when  $P < 0.05$ .

## Results

### Study population

Of the 32 consecutive patients involved in this study, 26 were included in the analyses. Demographic and clinical characteristics of the study patients are shown in Table 1. Mean age was  $56.5 \pm 11.0$  years (range: 32 to 74 years), and 61.5% were men. In the majority of patients, plasma cell dyscrasia was documented by serum/urine immunofixation electrophoresis and the serum free light-chain test. The first diagnosis of AL amyloidosis was given between December 1st, 2009 and February 26th, 2016. Most patients ( $n=24/26$ , 92%) presented with HF; 73% ( $n=19$ ) of patients were NYHA Class III or IV. Three patients (11.5%) had renal failure. Four patients received chemotherapy for multiple myeloma. Four patients had coronary heart disease; two received percutaneous coronary intervention (PCI). Electrocardiogram (ECG) results showed that 84.6% ( $n=22/26$ ) of patients had low voltages of the QRS complexes in the limb leads, 8% ( $n=2/26$ ) of patients had atrial arrhythmias, and 4% ( $n=1/26$ ) of patients had premature ventricular beats.

Characteristic	Patients (n=26)
Age, years	$56.5 \pm 11.0$

Male/female	16 (62%)/10 (38%)
Systolic blood pressure, mmHg	$102.12 \pm 12.39$
Diastolic blood pressure, mmHg	$68.88 \pm 9.14$
Heart rate, beats per min	$77.92 \pm 16.30$
LAD, mm	$44.23 \pm 5.11$
RAD, mm	$40.77 \pm 4.47$
LVDd, mm	$44.35 \pm 6.92$
RVDd, mm	$35.10 \pm 5.34$
IVS thickness, mm	$13.71 \pm 2.64$
Ejection fraction, %	$55.18 \pm 11.12$
NYHA I or II	7 (27%)
NYHA III or IV	19 (73%)
NT-proBNP	5280.5 (6560)
Cardiac troponin T	<0.1 (53.85%)
	$\geq 0.1$ (30.77%)
	No data (15.38)
Muscle hemoglobin	$32.90 \pm 16.94$

**Table 1:** Demographic and clinical characteristics of the study patients. LAD: Left Atrial Diameter; RAD: Right Atrial Diameters; LVDd: Left Ventricular Diameters at Diastole; RVDd: Right Ventricular Diameters at Diastole; IVS: Interventricular Septal; NYHA: New York Heart Association; NT-proBNP: NT pro-B-type Natriuretic Peptide.

### Independent risk factors of cardiac AL amyloidosis

In univariate analyses, NT-proBNP ( $P=0.022$ ) and D-dimer ( $P=0.002$ ) were independent risk factors for cardiac AL amyloidosis. In multivariable analysis, NT-proBNP and D-dimer were also independent risk factors for cardiac AL amyloidosis (both  $p=0.002$ ) (Table 2).

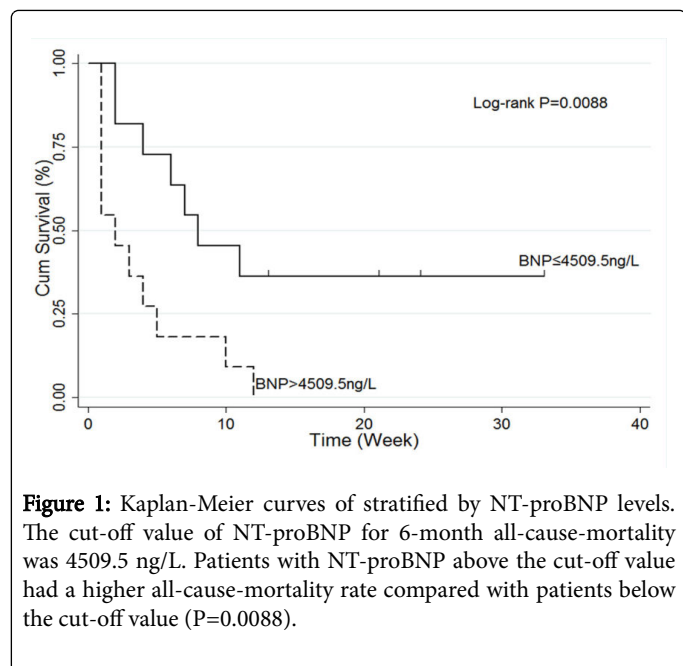
Variable	Hazard Ratio	95% CI	P	
Uni-variable analysis				
LAD	0.9675267	0.8902747	1.051482	0.437
RAD	1.031881	0.9319987	1.142467	0.546
NT-proBNP	1.000084	1.000012	1.000156	0.022
Heart rate	1.00147	0.9769903	1.026564	0.907
EF	1.016445	0.9724585	1.062422	0.47
Muscle hemoglobin	1.028632	0.9997121	1.058389	0.052
Cardiac troponin T	1.176077	0.4328801	3.19524	0.75
D-dimer	1.800821	1.243302	2.608342	0.002
eGFR	0.9832056	0.9654935	1.001243	0.068
Multivariable analysis				

D-dimer	2.365254	1.494378	3.74365	0.002
NT-proBNP	1.000164	1.000071	1.000258	0.002

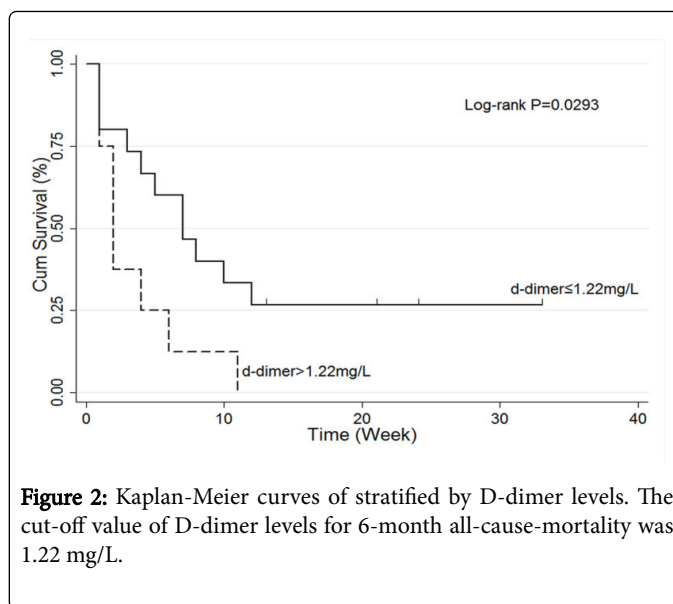
**Table 2:** Cox survival analysis. Data are expressed as mean ± SD. CI: Confidence Interval; SBP: Systolic Blood Pressure; LAD: Left Atrial Diameter; RAD: Right Atrial Diameter; eGFR: Estimated Glomerular Filtration; NT-proBNP: NT pro-B-type Natriuretic Peptide; EF: Ejection Fraction.

### Survival analysis

Twenty-two of the 26 patients died during follow-up. All patients were stratified according to NT-proBNP or D-dimer level. The cut-off value and discriminatory power of NT-proBNP for 6-month all-cause-mortality was 4509.5 ng/L (sensitivity 73.3%, specificity 77.8%, AUC 67%, 95% CI: 0.442-0.899). The cut-off value and discriminatory power of D-dimer for 6-month all-cause-mortality was 1.22 mg/L (sensitivity 60%, specificity 90%, AUC 70%, 95% CI: 0.489-0.911). Patients with NT-proBNP or D-dimer levels above the cut-off value had a higher all-cause-mortality rate compared with patients below the cut-off value (Figures 1 and 2). The highest all-cause-mortality rate was observed in patients with both NT-proBNP and D-dimer levels above the individual cut-off values.



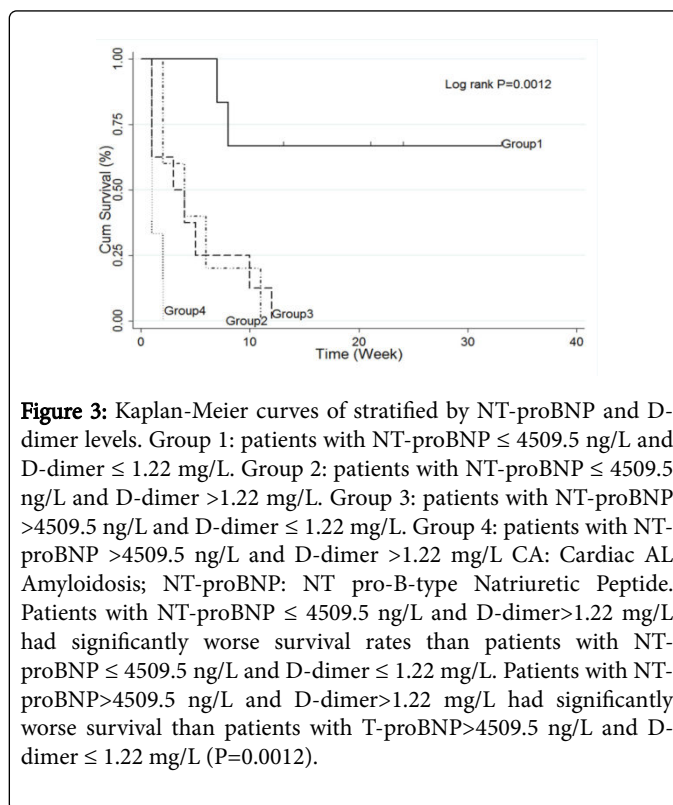
**Figure 1:** Kaplan-Meier curves of stratified by NT-proBNP levels. The cut-off value of NT-proBNP for 6-month all-cause-mortality was 4509.5 ng/L. Patients with NT-proBNP above the cut-off value had a higher all-cause-mortality rate compared with patients below the cut-off value (P=0.0088).



**Figure 2:** Kaplan-Meier curves of stratified by D-dimer levels. The cut-off value of D-dimer levels for 6-month all-cause-mortality was 1.22 mg/L.

Patients with D-dimer above the cut-off value had a higher all-cause-mortality rate compared with patients below the cut-off value (P=0.0293).

Patients with NT-proBNP ≤ 4509.5 ng/L and D-dimer >1.22 mg/L had significantly worse survival rates than patients with NT-proBNP ≤ 4509.5 ng/L and D-dimer ≤ 1.22 mg/L. Patients with NT-proBNP >4509.5 ng/L and D-dimer >1.22 mg/L had significantly worse survival than patients with T-proBNP >4509.5 ng/L and D-dimer ≤ 1.22 mg/L (Figure 3).



**Figure 3:** Kaplan-Meier curves of stratified by NT-proBNP and D-dimer levels. Group 1: patients with NT-proBNP ≤ 4509.5 ng/L and D-dimer ≤ 1.22 mg/L. Group 2: patients with NT-proBNP ≤ 4509.5 ng/L and D-dimer >1.22 mg/L. Group 3: patients with NT-proBNP >4509.5 ng/L and D-dimer ≤ 1.22 mg/L. Group 4: patients with NT-proBNP >4509.5 ng/L and D-dimer >1.22 mg/L CA: Cardiac AL Amyloidosis; NT-proBNP: NT pro-B-type Natriuretic Peptide. Patients with NT-proBNP ≤ 4509.5 ng/L and D-dimer >1.22 mg/L had significantly worse survival rates than patients with NT-proBNP ≤ 4509.5 ng/L and D-dimer ≤ 1.22 mg/L. Patients with NT-proBNP >4509.5 ng/L and D-dimer >1.22 mg/L had significantly worse survival than patients with T-proBNP >4509.5 ng/L and D-dimer ≤ 1.22 mg/L (P=0.0012).

## Discussion

The results of the current study indicate that N-terminal pro b-type natriuretic peptide (NT-proBNP) and D-dimer levels are independent risk factors for all-cause mortality in cardiac AL amyloidosis patients. Our data are in accordance with previous studies that show NT-proBNP has 100% sensitivity in detecting cardiac involvement in AL amyloidosis [13] and D-dimer is a potential biomarker in cardiovascular diseases. D-dimer is a product of fibrinolysis [14-17], and plasma levels of D-dimer may indicate disease severity and predict outcome in patients with heart failure [5,14]. In addition, D-dimer has been reported as a sensitive marker for early detection of acute myocardial infarction [18]. To the author's knowledge, the current study is the first to indicate that *D-dimer has a prognostic role for all-cause mortality in cardiac AL amyloidosis*.

## D-dimer and venous thrombosis/inflammatory

The presence of D-dimer has been shown to correlate with a hypercoagulable state, which can result in thrombosis [19]. D-dimer levels are widely used clinically to detect patients with suspected disseminated intravascular coagulation, thromboembolic events, and myocardial infarction [15]. Furthermore, D-dimer is an independent correlate of increased mortality and venous thrombosis across a variety of disease states [14,20]. D-dimer positively correlates with biomarkers of inflammation. Inflammatory responses increase fibrin formation and lysis, elevating D-dimer levels and promoting activation of the coagulation cascade. D-dimer and other fibrin degradation products modulate the production of IL-6 and other inflammatory mediators [20,21]. In the current study, D-dimer levels were likely elevated as most patients had been bed-ridden for an extended period of time, which increased the risk for venous thrombosis and secondary inflammation.

## D-dimer and prognosis of patients with AL

Therapeutic regimens for AL amyloidosis are evolving, and survival is improving. However, life expectancy is dependent on accurate and timely diagnosis. Clinical manifestations of AL amyloidosis are nonspecific; therefore, sensitive and specific biomarkers of end-organ injury represent a viable option for diagnosis and prognosis. NT-proBNP and troponins are used routinely in the assessment of heart dysfunction in AL amyloidosis [3]. Markers of renal involvement include albuminuria, cystatin C, and eGFR, while liver involvement may be detected by increases in alkaline phosphatase and transaminases [3]. The findings from the current study suggest D-dimer may be an emerging biomarker of prognosis and could contribute information that will improve AL amyloidosis patients' life expectancy and quality of life.

## Study limitation

This study is associated with several limitations. Firstly, it is a retrospective analysis from a single center. However, this study design was appropriate as cardiac AL amyloidosis is a rare condition. Secondly, troponin T was measured in only a few patients and was not found to be an independent risk factor for all-cause mortality. This requires further investigation, as previous studies indicate T troponin is an important prognostic factor in AL [12,22]. Thirdly, two thirds of the AL amyloidosis patients' NYHA functional class was III or IV, and the average systolic blood pressure was 102 mmHg. Therefore, both the systolic blood pressure and NYHA functional class had no statistical

significance in our study. Lastly, EMB is the gold standard for diagnosis of cardiac AL amyloidosis [9,10]. However, in the current study, most patients were diagnosed with AL by lingualis biopsy.

## Conclusion

D-dimer may be an important biomarker of prognosis in cardiac AL amyloidosis patients.

## Authors' Contributions

- Dongjie Xu designed the study.
- Xian Cheng and Liuyan Zhang acquire data and analyzed the data.
- Xian Cheng and Fei Xu drafted the manuscript.
- Dongjie Xu, Fang Zhou, Haifeng Zhang, and Xinli Li revised the manuscript critically.
- All authors read and approved the final manuscript.

## Ethical Approval

Ethical approval was given by the medical ethics committee of Jiangsu Province Hospital with the following reference number 2016-SR-169. We obtained verbal consent of the patients or their families of the deceased patients for the reason that only their clinical records before were involved.

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