European Review for Medical and Pharmacological Sciences 2017; 21: 4406-4410

Research on clinical value of galectin-3 in evaluating the prognosis of acute heart failure

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Abstract. – OBJECTIVE: To investigate the clinical value of galectin-3 in the prognosis evaluation of acute heart failure.

PATIENTS AND METHODS: A total of 316 patients treated in Suzhou Kowloon Hospital were enrolled into this study and followed up for 1 year. Venous blood during the onset was collected for examinations of blood routine, blood biochemistry, N-terminal B-type pro-brain natriuretic peptide (NT-proBNP), galectin-3 and other indexes. Cardiovascular events (CV events) include the re-admission or death due to the recent acute episode of chronic heart failure.

RESULTS: The concentrations of NT-proBNP and galectin-3 in the CV event group were significantly increased compared with those in non-CV event group ($p<0.001$). Receiver operating characteristic (ROC) curve analysis showed that the area under the curve (AUC) of NT-proBNP in predicting CV events of patients with acute heart failure within 1 year after discharge was 0.816 and that of galectin-3 was 0.847. Kaplan-Meier survival curve analysis showed that risks of CV events of patients with the NT-proBNP concentration >3013.21 pg/mL and galectin-3 concentration >17.15 ng/mL within 1 year after discharge were significantly higher than those in other groups ($p<0.001$).

CONCLUSIONS: Galectin-3 can be used as a biomarker for the prognosis evaluation of acute heart failure, and its combined analysis can increase the predictive value of NT-proBNP.

Key Words:
Acute heart failure, Prognosis evaluation, Galectin-3.

Introduction

Acute heart failure (AHF) is one of the leading causes of hospitalization in the world. According to statistics, there are 9 out of every 1000 patients with heart failure around the world; the total incidence rate of heart failure is 0.23-0.27% every year and about 60% patients will die within 5 years after being diagnosed as heart failure. With the aging of population and the prevalence of cardiovascular health risk factors, the prevalence rate of heart failure will continue to rise, becoming a heavy burden for the whole society and a serious challenge to the public health. Studies have shown that brain natriuretic peptide/N-terminal pro-brain natriuretic peptide (BNP/NT-proBNP) is of great value in the diagnosis, prognosis evaluation and clinical management of AHF, but it is influenced by multiple factors. Delaying ventricular remodeling is a main direction in the treatment of heart failure. A study has shown that galectin-3 plays an important role in the occurrence and development of ventricular remodeling[1]. In this study, the expression level of serum galectin-3 in patients with AHF was detected and patients were followed up for 1 year, so as to investigate the clinical value of galectin-3 in the diagnosis and prognosis evaluation of AHF.

Patients and Methods

General Materials

A total of 316 patients admitted into Suzhou Kowloon Hospital and initially diagnosed as AHF or chronic heart failure (CHF) were selected. This study was approved by the Ethics Committee of Suzhou Kowloon Hospital. Signed written informed consents were obtained from all participants before the study. The diagnostic criteria were recommended according to the American Heart Association (AHA) Guidelines. Exclusion criteria: patients with a history of malignant tumor, cognitive dysfunction or dementia, severe mental illness, uncontrollable systemic disease, pulmonary artery embolism and/or deep venous thrombosis, or who used to take anticoagulant drugs in the past three months or received blood transfusion recently. The study protocol was appro-

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ved by the Hospital Independent Committee, and patients were informed and signed the informed consent when enrolled. The study adhered to the principles of clinical practice and the Declaration of Helsinki. All patients were followed up for 1 year after discharge mainly through telephone or interview to understand the incidence of major adverse cardiac events within 1 year, including the new-onset cardiac insufficiency or deterioration of the original heart function, malignant arrhythmia, cardiogenic shock, recurrent acute myocardial infarction and sudden death, etc.

Blood Collection

Blood samples were collected on the day or the second day after admission of AHF patients, then immediately sent to the Center Laboratory of Suzhou Kowloon Hospital for detection, including blood routine, whole blood biochemistry and NT-proBNP; the serum of the other sample was retained and stored at -80°C for standby application. NT-proBNP was detected using the fully automated analyzer (Roche Elecsys®proBNP immunoassay, Basel, Switzerland). Serum galectin-3 was detected via enzyme-linked immunosorbent assay (ELISA) and the kit was purchased from BG (Sacramento, CA, USA). Red cell distribution width (RDW) was detected using the blood analyzer (Sysmex®xt-4000i, Kobe, Japan) and its range of normal value was 10.0-15.7%. Each patient received the cardiac ultrasonography (instrument model: Vivid E9, Horten, Norway) when enrolled.

Statistical Analysis

Statistical Product and Service Solutions (SPSS, Version X; IBM, Armonk, NY, USA) 20.0 software was used for statistical analysis. Measurement data were presented as mean ±standard deviation. t-test was performed. The predictive values of RDW, galectin-3 and NT-proBNP were analyzed using the receiver operating characteristic (ROC) curve. The survival rate was analyzed by Kaplan-Meier survival curve, and Log-rank test was performed for intergroup comparison. $p<0.05$ suggested that the difference was statistically significant.

Results

Analysis of General Materials of Patients Enrolled

A total of 316 patients were enrolled, including 185 males (58.54%) and 131 females with an average age of (62±17) years old. During the 1-year follow-up, there were 21 cases of death and 25 cases of re-admission due to the acute episode of CHF (Table I).

Table I. Analysis of demographic data and clinical indexes of the population enrolled.

	CV events within 1 year		
	Yes (n=41)	No (n=275)	*p*-value
Demographic data			
Age (years old)	63.48±15.17	61.01±15.74	0.46
Clinical parameter			
Systolic pressure (mmHg)	115.56±12.75	124.65±11.75	0.16
Diastolic pressure (mmHg)	70.12±10.58	75.15±12.65	0.27
Heart rate (times/min)	80.62±19.17	81.84±17.74	0.46
Left ventricular ejection fraction (%)	41.72±16.14	45.94±11.28	0.26
Left ventricular end diastolic diameter (mm)	56.11±14.19	59.60±11.98	0.79
Laboratory index			
ALT (U/L)	146.26±23.39	29.95±31.99	0.16
AST (U/L)	156.27±49.92	49.99±58.80	0.10
Serum sodium (mmol/L)	137.64±3.79	138.11±12.84	0.35
Serum potassium (mmol/L)	4.22±0.61	3.75±0.68	0.02*
Blood urea nitrogen (mmol/L)	12.38±6.87	7.19±4.10	0.03*
Serum creatinine (umol/L)	146.87±78.89	108.49±62.10	0.28
Uric acid (μmol/L)	568.18±218.49	499.78±179.64	0.08
Cystatin C (mg/L)	1.71±0.41	1.58±0.57	0.18
Hemoglobin (g/L)	121.34±28.92	135.65±19.95	0.01*
RDW (%)	17.11±2.44	14.54±1.10	<0.01**
Galectin-3 (ng/mL)	22.96±2.17	16.79±1.09	<0.01**
NT-proBNP (pg/mL)	6662.27±2529.07	2429.64±2148.57	<0.01**

*$p<0.05$; **$p<0.001$.

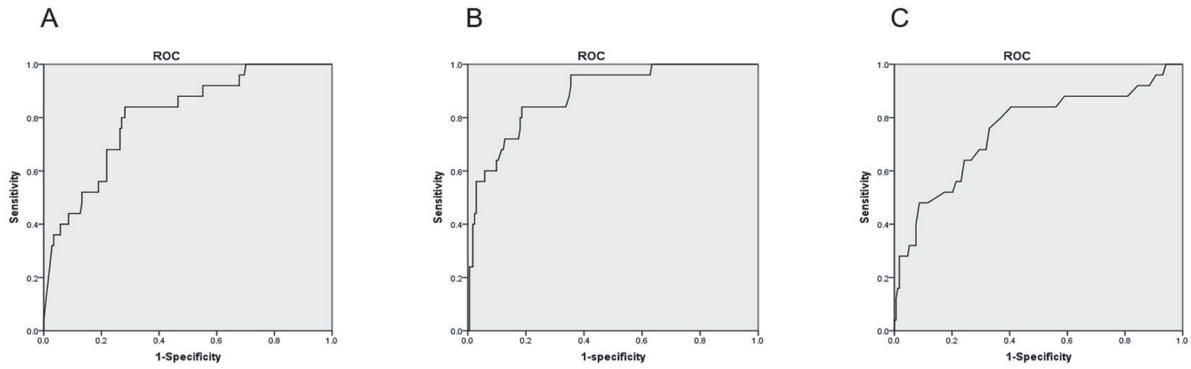

Figure 1. Receiver operating characteristic curve of NT-proBNP (A: AUC = 0.816 95% CI: 0.764 - 0.861), galectin-3 (B: AUC = 0.847 95% CI: 0.794 - 0.901) and RDW (C: AUC = 0.714 95% CI: 0.688 - 0.792) for prediction of cardiovascular events at 1 year.

Analysis of Laboratory Indexes in Event Group and Non-Event Group

The levels of hemoglobin, serum potassium, blood urea nitrogen, galectin-3, RDW and NT-proBNP in CV event group within 1 year after discharge were different from those in non-CV event group, and the concentrations of RDW, galectin-3 and NT-proBNP were significantly increased compared with those in non-CV event group (p<0.001) (Table II).

Comparisons of Values of Galectin-3, NT-proBNP and RDW in Predicting AHF Prognosis

ROC curve analysis was performed to compare the event-predicting specificities of the three biological indexes. The area under the curve (AUC) of NT-proBNP in predicting CV events of patients with AHF within 1 year after discharge was 0.816, that of galectin-3 was 0.847 and that of RDW was 0.714 (Figure 1). According to the higher sensibility and higher specificity, the optimal cutoff point of NT-proBNP in predicting the risks of CV events of patients with AHF within 1 year after discharge was 3013.21 pg/mL (sensitivity: 82.1%, specificity: 81.8%), while the optimal cutoff point of galectin-3 was 17.15 ng/mL (sensitivity: 86.0%, specificity: 71.4%). The pairwise comparisons of the ROC curves of the three biological indexes showed that galectin-3 was more valuable than RDW; galectin-3 had a higher sensitivity, while NT-proBNP had a higher specificity (Table II).

Combined Analysis of Galectin-3 and NT-proBNP

According to the optimal cutoff points of NT-proBNP and galectin-3, 316 patients were divided into four groups: Group 1: NT-proBNP>3013.21 pg/mL + galectin-3 >17.15 ng/mL (n=40); Group 2: NT-proBNP>3013.21 pg/mL + galectin-3 <17.15 ng/mL (n=121); Group 3: NT-proBNP<3013.21 pg/mL + galectin-3 >17.15 ng/mL (n=31); Group 4: NT-proBNP<3013.21 pg/mL + galectin-3 <17.15 ng/mL (n=124). Kaplan-Meier survival curve analysis showed that the risks of CV events of patients with the NT-proBNP concentration >3013.21 pg/mL and galectin-3 concentration >17.15 ng/mL within 1 year after discharge were significantly higher than those in other groups (p<0.001) (Figure 2).

Discussion

With the development of research on the pathophysiological mechanism of heart failure, people have had increasingly more interest in biomarkers of heart failure, and biomarkers have

Table II. Pairwise comparison of ROC curves.

	Z	95% confidence interval	*p*-value
NT-proBNP vs. galectin-3	1.13	-0.032,0.172	0.109
NT-proBNP vs. RDW	1.22	-0.059,0.184	0.384
Galectin-3 vs. RDW	2.22	0.026,0.248	0.024*

*p<0.05.

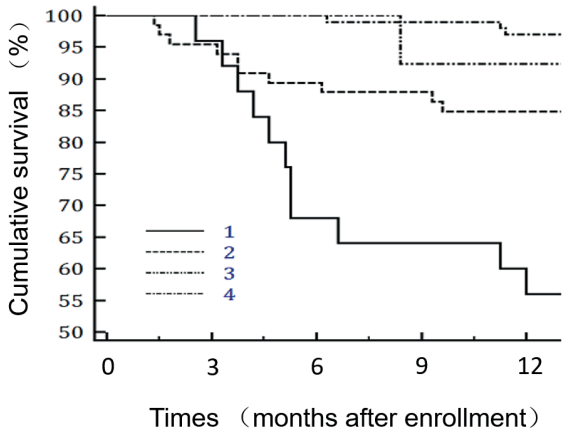

Figure 2. Kaplan-Meier survival curve analysis of CV events within 1 year (p<0.001). Group 1: NT-proBNP>3013.21 pg/mL + galectin-3 >17.15 ng/mL (n=40); Group 2: NT-proBNP>3013.21 pg/mL + galectin-3<17.15 ng/mL (n=121); Group 3: NT-proBNP<3013.21 pg/mL + galectin-3 >17.15 ng/mL (n=31); Group 4: NT-proBNP<3013.21 pg/mL + galectin-3 <17.15 ng/mL (n=124).

been widely used in the diagnosis and evaluation of heart failure. Studies have shown that the secretion of NT-proBNP is increased significantly under the increased myocardial cell stress, myocardial ischemic injury and cardiac remodeling, which has been proven to be helpful in assessing the severity and prognosis of AHF[2,3]. Although NT-proBNP has important values in the diagnosis, risk stratification, efficacy evaluation, prognosis and management inside and outside hospital of acute and chronic heart failure, it is affected by many factors, such as age, gender, renal function, and obesity[4]. New biomarkers reflecting different pathological and physiological mechanisms are still needed to improve the diagnosis, risk stratification and prognosis of heart failure and guide the individualized treatment. Studies have suggested that the elevated RDW may be associated with the inflammation, erythropoietin, renal function and nutritional status[5-7], which may explain the mechanism of poor prognosis of patients with AHF. The roles of RDW in predicting the severity and prognosis of heart failure (HF) have attracted more and more attention. At present, the research on the application value of RDW in HF in China and foreign countries mostly focuses on the CHF. The results suggest that RDW is closely associated with the prognosis, re-admission rate and CV all-cause mortality of HF patients; but there are few studies on the value of RDW in predicting prognosis of AHF patients. In recent years, He et al8 studied and compared the values of RDW and NT-ProBNP in predicting the prognosis of AHF patients, and found that RDW is superior to NT-ProBNP in predicting the mid-term prognosis (90 days), and the combined analysis can increase the value of NT-ProBNP in predicting the short-term prognosis (30 days). This study confirmed that the increased RDW is parallel to the increased NT-proBNP concentration, and it can be used as a new biomarker for predicting CV events in AHF patients. Galectin-3 is an important member of galectin family and an inflammatory signaling molecule, which is expressed in macrophages, eosinophils, neutrophils and mastocytes. Galectin-3 plays an important role in a variety of physiological and pathological processes, especially in the process of tissues fibrosis[9,10]. Previous studies found that galectin-3 is directly related to the cardiac fibrosis and cardiac remodeling, and it can accelerate the occurrence and development of heart failure, which is a potent predictor of the acute and chronic heart failure, especially for those AHF patients with normal left ventricular ejection fraction (LVEF)[11-13]. It was found in an experimental study on the short-term follow-up mortality of Fermann et al[14] that galectin-3 is associated with the incidence of 30-day adverse events in AHF patients, but not associated with the 5-day short-term event. Galectin-3 in some patients is higher than the level predicted by their own BNP, and these patients are mostly complicated with acute renal failure, low heart rate and high occurrence of 30-day adverse events; high galectin-3 is also accompanied by high incidence of 30-day adverse events regardless of BNP. BNP is a kind of neurohormone secreted by the heart when the heart is overloaded, which has important value in regulating the vascular homeostasis. Galectin-3 is an inflammatory signaling molecule that can promote the myocardial fibrosis and myocardial apoptosis[15]. It is, thus, inferred that galectin-3 may be a bridge between the inflammation and the neurohormonal system in heart failure.

Conclusions

This study aimed to investigate whether there are some common biomarkers that are easily detectable and can provide additional information for the prognosis of AHF. Common clinical indexes, RDW and galectin-3, have a certain predictive value, and their increased concentrations are related to the poor prognosis of heart

failure. The pairwise comparison of galectin-3 and RDW showed that galectin-3 is more valuable than RDW in predicting CV events of AHF and the combined analysis of galectin-3 and NT-proBNP can increase the predictive value of NT-proBNP.

Acknowledgements

This study was supported by Suzhou Industrial Park technology project program (SYSD2012061).

Conflict of interest

The authors declare no conflicts of interest.

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