*Original Article*

# Prognostic Values of Serum Tenascin-C in Patients with Ischaemic Heart Disease and Heart Failure

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*Objective:* **The aim of this study was to evaluate the prognostic values of serum tenascin-C in patients with heart failure and ischaemic heart disease.**

*Methods:* **Serum tenascin-C levels were assessed in 83 patients with heart failure and in 30 healthy subjects. The correlations between serum tenascin-C levels and left ventricular ejection fraction, serum B-type natriuretic peptide and procollagen III were analysed. Patients were followed up for 12 months, and the relations between the serum levels of tenascin-C and cardiac events (re-hospitalisation for worsening heart failure and mortality) were analysed.**

*Results:* **Serum tenascin-C levels in patients with heart failure were higher than in healthy volunteers ($72.24 \pm 11.02$ vs. $22.78 \pm 2.51$ μg/L, $p < 0.01$). Serum tenascin-C levels in patients of NYHA class IV were higher than in patients with NYHA class II ($88.56 \pm 3.73$ vs. $64.88 \pm 3.15$ μg/L, $p < 0.01$). The levels of tenascin-C were negatively correlated with the left ventricular ejection fraction ($r = -0.636$, $p < 0.01$), but were positively correlated with serum B-type natriuretic peptide ($r = 0.553$, $p < 0.01$) or procollagen III levels ($r = 0.665$, $p < 0.01$). An increased level of tenascin-C was an independent predictor for combined re-hospitalisation and mortality (OR 1.22, 95% CI: 0.86–2.14).**

*Conclusion:* **Serum tenascin-C levels were elevated in patients with heart failure. The levels of tenascin-C were associated with the severity of left ventricular dysfunction and 12-month major adverse cardiac events.**

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**Keywords. Heart failure; Tenascin-C; B-type natriuretic peptide; Procollagen**

## Introduction

Ischaemic heart disease describes a condition in which coronary artery disease results in severe myocardial dysfunction, which is mainly manifested by significant heart failure [1,2]. The prognosis of heart failure in patients with ischaemic heart disease has improved since the introduction of angiotensin converting enzyme inhibitors/angiotensin receptor blockers and coronary artery intervention therapy. However, heart failure remains a progressive condition with a higher morbidity and mortality. Tenascin-C, an extracellular matrix oligosaccharides protein, plays an important role in the development of the myocardium in early stage embryos, but it is not detected in adults [3]. Tenascin-C can re-express in some pathological conditions, such as athero-thrombosis [4], intimal hyperplasia [5], myocardial infarction [6], cardiomyopathy [7] and coronary valve calcification [8]. Studies have shown increased serum or plasma concentration of tenascin-C in patients with a range of cardiac problems, including acute myocardial infarction [6], pulmonary artery hypertension [9], and dilated cardiomyopathy [10,11]. Tenascin-C levels were found elevated and were correlated with New York heart association (NYHA) function classes in patients with dilated cardiomyopathy [11]. Increased levels of tenascin-C were predictive of major cardiac events in patients with dilated or hypertrophied cardiomyopathy [12,13]. However, the levels of tenascin-C and its relationship with heart function in patients with ischaemic heart disease were unclear, and the prognostic values of tenascin-C in ischaemic cardiomyopathy has not been fully investigated. The aim of this study was to evaluate the changes of tenascin-C levels and the relations with major adverse cardiac events in patients with ischaemic cardiomyopathy and decompensated heart failure.

## Materials and Methods

### *Patient Selection*

Eighty-three consecutive patients with chronic heart failure were enrolled in the study. The diagnosis of heart

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failure was according to the current guideline [14] and ischaemic aetiology of heart failure was confirmed by a history of myocardial infarction or coronary stenosis on coronary angiogram. Patients were eligible if their left ventricular ejection fraction (LVEF) < 45% on transthoracic echocardiography. Patients with infection or inflammatory diseases, autoimmune diseases, liver and kidney dysfunction, malignant cancer, severe trauma, surgical intervention within three months were excluded. Thirty healthy volunteers from people who presented to our hospital's health clinics for annual health check-ups were enrolled as the control group. Physical examination, ECG, chest X-ray and blood biochemistry studies in these subjects revealed no cardiovascular or other chronic diseases.

### *Transthoracic Echocardiography*

Echocardiography was conducted as previously described [15]. Imaging was performed using a HP 5500 system. Patients were imaged in the left lateral decubitus position, and the images of the parasternal and apical views (standard long axis, two- and four-chamber image) were obtained. LVEF was calculated from the conventional apical two- and four-chamber images, using the biplane Simpson's technique [16]. Echocardiographic examinations were conducted after the heart failure patients' admission and on the day of venous blood collection from tenascin-C studies. The cardiologist who performed the echocardiographic studies was not aware of patients tenascin-C or other biochemical test results.

### *Assay of Serum Tenascin-C Levels by ELISA*

Venous blood samples were obtained and serum samples were centrifuged. Serum aliquoted and stored at −80 until time of assay. The ELISA double antibody sandwich assay was used to determine the serum levels of tenascin-C as previously described [17]. Briefly, 100 μl of serum samples were added into plate wells, which were coated and incubated for 2 h at 37 °C. After discarding the liquid and washing, working fluid A (100 μl) was added to each well and incubated for 1 h at 37 °C. Working fluid B was then added to each well and incubated for 30 min at 37 °C. The optical density (OD) of each well was measured with a microplate reader at 450 nm wavelength, and the tenascin-C content of the sample was calculated.

### *Biochemical Analysis*

Serum B-type natriuretic peptide (BNP) was determined using radioimmunoassay. Serum procollagen type three (PC-III) content was measured as previously described by our laboratory [18]. The testing kits for BNP and PC-III were provided by the Jingmei Products Company, Shenzhen, China.

### *Follow-up*

Patients were followed-up in our clinics every two months with clinical examination and echocardiography for a total of 12 months. Major adverse cardiac events were defined as re-hospitalisation due to worsening of heart failure and death.

### *Statistics Analysis*

Continuous variables were presented as mean ± standard deviation, and were compared by two-tail student *t* test or one way analysis of variance (ANOVA) for multiple variables. Categorical data were presented as numbers and percentages, and were compared with chi-squire test or Fisher exact test. Cox regression analysis was used to assess the prognostic value of serum tenascin-C on major adverse cardiac events. All data were analysed by SPSS 11.0 software (SPSS, Inc. Chicago, Illinois). A two-sided *p* value of ≤0.05 was considered to be significant.

## Results

### *General Findings*

A total of 83 patients were included in the study (43 men and 40 women). NYHA function class II was found in 33; class III in 27 and class IV in 23 patients, respectively. Baseline characteristics of the patients in each group are summarised in Table 1. There were no statistically significant differences among the groups of cardiac function class II, III and IV in age, sex, history of hypertension, diabetics and myocardial infarction, and medication use of diuretics, ACE inhibitors, digoxin and statins (all $p > 0.05$). The mean LVEF in NYHA class IV patients was lower than in NYHA class II or III patients ($p < 0.01$, Table 1).

### *Serum BNP, PC III*

The mean values of serum BNP and PC III in heart failure patients were higher than in the healthy subjects ($p < 0.01$, Table 2). The mean values of serum BNP and PC III in NYHA IV patients were higher than in the NYHA II patients ($p < 0.01$, Table 2).

### *Serum Tenascin-C*

As shown in Table 2, serum tenascin-C levels in patients with heart failure were higher than in healthy volunteers ($p < 0.01$). Serum tenascin-C levels in patients of NYHA class IV were higher than in class II ($p < 0.01$).

### *Relations Between Serum Tenascin-C and Left Ventricular Function*

The levels of tenascin-C were negatively correlated with LVEF ($r = -0.636$, $p < 0.01$), and were positively correlated with serum BNP levels ($r = 0.553$, $p < 0.01$) and PCIII ($r = 0.665$, $p < 0.01$).

### *Prognostic Value of Tenascin-C on Major Adverse Cardiac Events*

During the 12-month follow-up, major adverse cardiac events were observed in 14 patients (16.9%), including 10 re-hospitalisations as a result of worsening heart failure, and four deaths. After adjustment for age, sex, baseline left ventricular ejection fraction, pharmacological therapies, the baseline tenascin-C levels were predictive of the major adverse cardiac events (OR 1.22, 95% CI: 0.86–2.14). Baseline BNP levels were also predictive of the major adverse cardiac events (OR 1.06, 95% CI: 0.66–1.98).