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Are Plasma ST2 and Galectin-3 Predictors for Clinical Outcomes After Myectomy in Patients With Obstructive Hypertrophic Cardiomyopathy?

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Introduction

ST2 is a member of the interleukin-1 receptor family, which is expressed in a trans membrane form (ST2L) as well as in a soluble secreted form [1]. Recently, soluble ST2(sST2) was found to be elevated in patients with chronic heart failure with reduced ejection fraction (HFrEF) and regarded as a promising novel biomarkers that can improve risk stratification [2, 3]. In 2012, Broch K et al. showed that baseline sST2 was associated with death due to worsening heart failure (HF), hospitalization due to worsening HF, and all cardiovascular hospitalization in older patients with ischemic HF[4]. In a multicenter study enrolled 447 patients with acutely decompensated heart failure, sST2 was an independent predictor of mortality for 1 year follow-up, regardless of the left ventricular ejection fraction[5].

As a β-galactoside-binding lectin secreted by activated macrophages, galectin-3 (Gal-3) exists in the cytoplasm and in a secreted form, and is involved in several physiological and pathological processes that contribute to HF, including myocardial fibrosis, inflammation and cardiac remodeling [6-8]. Sub study of RELAX trial suggested that Gal-3 levels were associated with severity of renal dysfunction. De Boer et al. found that Gal-3 is an independent marker for composite end of all-cause mortality and HF hospitalization in HF and appears to be more powerful in patients with heart failure with preserved ejection fraction (HFpEF)[9]. According to results from the Aldo-DHF trial, plasma Gal-3 in HFpEF was associated with adverse outcome, independent of treatment or NT-proBNP [10].

Fibrosis of myocardial interstitium and impaired left ventricular diastolic function commonly exist in patients with hypertrophic cardiomyopathy [11]. Until so far, the relationships of other biomarkers like miR-29a and NT-proBNP with the degree of left ventricular hypertrophy and fibrosis or clinical outcomes of hypertrophic cardiomyopathy have been evaluated [12, 13]. However, the relationship between outcomes after myectomy and soluble ST2 and Gal-3 remains unknown in patients

with obstructive hypertrophic cardiomyopathy (HCM). The objective of this study was to determine whether plasma ST2 and Gal-3 levels are increased in obstructive HCM patients; to evaluate the relationship between ST2 and Gal-3 levels and patient characteristics in obstructive HCM; and to assess the association between the two biomarkers and clinical outcomes for patients after myectomy.

Methods

Study population

This observational cohort study enrolled obstructive HCM patients with refractory symptoms despite medical therapy who underwent surgical myectomy in Fuwai Hospital between March 2011 and February 2016. Transaortic extended septal myectomy was performed by a single surgeon (SYW) .The diagnosis of HCM was determined by two -imensional transthoracic echocardiographic examination of asymmetric left ventricular hypertrophy without any other cardiac or systemic disease [14]. Peak gradient ≥50 mmHg at rest or during physiological provocation such as Valsalva manoeuvre, standing and exercise, is regarded as haemodynamically important and an indication for surgery among obstructive HCM patients in our study [11]. Patients with a prior history of septal ablation or surgical myectomy, those who had severe renal or hepatic insufficiency, and those who have tumor were excluded. In total, two hundred and two patients were available for blood sampling, but only two hundred patients underwent a successful surgery and formed the final study cohort. Forty two volunteers without cardiac disease were included in control group. Circulating Gal-3 and sST2 levels of 42 obstructive HCM patients were compared with those of 42 both age- and sex-matched controls.

Then obstructive HCM patients were divided into two groups according to sST2 and Gal-3 levels, respectively. The primary endpoint was defined as a composite of all-cause mortality and cardiovascular hospitalization, including hospitalization for onset of atrial fibrillation, hospitalization for recurrence of symptoms like angina and suffocation, and hospitalization for worsening HF. Thirteen patients (6.5%) lost to follow up during the study. The study protocol was approved by the Ethics Committee of Fuwai Hospital and all patients gave informed consent to participate.

Laboratory methods

Concentrations of blood lipids like total cholesterol (TC)、triglyceride (TG) and low-density lipoprotein (LDL), plasma NT pro-BNP and serum cTnI were assessed at the core laboratory of Fuwai Hospital by standard methods after admission of every patient. Peripheral blood samples were obtained on the morning of the day for surgery . After separated by centrifugation, plasma was then stored at −80°C for the detection of sST2 and Gal-3 with a single freeze-thaw cycle. Soluble ST2 was measured using a commercial enzyme immunoassay (R&D Systems , Minneapolis, USA). The inter-assay coefficient of variation was 5.4-7.1% and the intra-assay coefficient of variation was 4.4-5.6%, with a mean minimum detectable dose of 5.1 pg/mL. Similarly, Gal-3 was also measured using a commercial enzyme immunoassay (R&D Systems, Minneapolis, USA). The inter-assay coefficient of variation was 5.8-6.3% and the intra-assay coefficient of variation was 3.5-3.8%, with a mean minimum detectable dose of 16 pg/mL.

Echocardiography

Doppler transthoracic echocardiogr aphy was performed using an E9 ultrasound system (GE Healthcare, Horten, Norway). Peak instantaneous left ventricular outflow tract or midventricular gradient was estimated using continuous wave Doppler echocardiography. Two-dimensional measurements for left ventricular diastolic dimension, ventricular septum, posterior wall thickness, and left ventricular ejection fraction were assessed as recommended by American Society of Echocardiography before [15]. M-mode of left atrial end-diastolic dimension (LAD) was measured from the parasternal long-axis view. Left

ventricular mass (LVM) was calculated in a standard fashion and was indexed to body surface area.

Statistical analysis

Data are presented as mean ± SD, medians (intra-quartile ranges) or frequencies (proportions) as appropriate. Logarithmic transformation was performed for the analysis of ST2 and Gal-3. Differences of continuous variables were evaluated with the independent Student's t test or Mann-Whitney U test. While categorical variables were compared using the chi-square test or Fisher's exact test. Survival curves were estimated using the Kaplan-Meier method, and the log-rank test was used to compare the survival distributions of the groups. To evaluate predictors of the end point, both univariate and multivariate Cox proportional hazard regression models were used to calculate relative risks and 95% confidence intervals. Calculations were performed using the statistical package SPSS 21.0 (SPSS Inc, Chicago, Illinois).

Results

Baseline demographic and clinical characteristics according to different groups of circulating ST2 and Gal-3

Plasma sST2 and Gal-3 levels of 42 obstructive HCM patients were compared with those of 42 both age- and sex-matched controls. Enzyme immunoassay results revealed that soluble ST2 and Gal-3concentrations were significantly higher in obstructive HCM patients than in control subjects [12.7(8.8, 18.8) vs. 8.1(5.8, 11.8) ng/mL, 7.5(6.4, 8.9) vs. 6.5(4.6, 7.9) ng/mL, both P< 0.01].

Two hundred patients with obstructive HCM were included in the cohort study (male 64% ; mean age 43.7 ± 13.9 years). Baseline characteristics are presented in (Table 1) according to sST2 and Gal-3 levels. After stratification by ST2 levels, there were more patients with syncope symptoms (P <0.05) and more patients receiving calcium channel antagonists (P=0.02) in the group with high sST2 (≥ 12.83ng/mL). Medical history and laboratory data did not differ significantly between different ST2 groups. On the other hand, the results stratified by Gal-3 levels showed that the group patients with high Gal-3 (≥7.23ng/mL) were older and had less male patients (both P<0.01) . Except for hypertension history, which was significantly different amongst the two Gal-3 groups (both P<0.05), no other significant differences were observed concerning clinical symptoms, history of syncope or atrial fibrillation.

Relationship between levels of circulating ST2 and Gal-3 and the echocardiographic parameters

Baseline echocardiographic characteristics of the obstructive HCM cohort are listed in (Table 1) Peak gradient at rest and moderate/severe mitral regurgitation were comparable between different ST2 groups (P =0.64 and 0.72, respectively). Similarly, after stratification according to Gal-3 levels, all the echocardiographic parameters of high Gal-3 group were not significantly different from that of low Gal-3 group (all P >0.05).

Table (1): Comparative baseline data in patients across the circulating sST2 and galectin-3 levels

Variables	Entire cohort (n=200)	ST2			Gal-3		
		Low ST2 < 12.8ng/mL (n=100)	High ST2 ≥ 12.8ng/mL (n=100)	*P value*	Low Gal-3 < 7.23ng/mL (n=100)	High Gal-3 ≥ 7.23ng/mL (n=100)	*P* value
Age (yrs)	43.7±13.9	43.7 ± 13.5	43.8 ± 14.3	0.96	39.9±14.3	47.6 ± 12.4	<0.01
Male	128(64)	61(61)	67(67)	0.38	73(73)	55(55)	<0.01
Hypertension	44(22)	18(18)	26(26)	0.17	16(16)	28(28)	0.04
Atrial Fibrillation	33(16.5)	14(14)	19(19)	0.34	15(15)	18(18)	0.57
Angina pectoris	79(39.5)	40(40)	39(39)	0.89	38(38)	41(41)	0.66
Suffocation	174(87)	86(86)	88(88)	0.67	83(83)	91(91)	0.09
Palpitation	54(27)	28(28)	26(26)	0.75	27(27)	27(27)	1.00
Syncope	48(24)	18(18)	30(30)	<0.05	23(23)	25(25)	0.74
NYHA functional class	2.7 ± 0.5	2.8 ± 0.5	2.7± 0.5	0.67	2.7 ± 0.5	2.8 ± 0.5	0.09
FH HCM	34(17)	21(21)	13(13)	0.13	22(22)	12(12)	0.06
FH SCD	18(9)	10(10)	8(8)	0.62	7(7)	11(11)	0.32
Medications							
β blocker	185(92.5)	90(90)	95(95)	0.18	92(92)	93(93)	0.79
ACEI/ARB	16(8)	11(11)	5(5)	0.12	6(6)	10(10)	0.30
CCB	44(22)	15(15)	29(29)	0.02	18(18)	26(26)	0.17
Laboratory data							
TC (mmol/L)	4.46±0.90	4.43± 0.89	4.50± 0.91	0.60	4.41±0.84	4.51± 0.96	0.41
LDL-C（mmol/L）	2.87±0.80	2.82± 0.80	2.91± 0.81	0.42	2.87±0.72	2.87± 0.88	0.99
cTnI (ng/ml)*	0.029(0.046)	0.026(0.034)	0.032(0.051)	0.52	0.020(0.049)	0.031(0.042)	0.08
NT-	1670.3(1884.9)	1622.0(1749.0	1707.2(180	0.73	1596.7(1885.6)	1897.4(1986.7)	0.38

proBNP(pmol/L)*		)	9.4)				
Echo characteristics							
Peak gradients (mmHg)	86± 33	86± 33	86± 33	0.64	83± 27	89± 38	0.23
Left atrial diameter(mm)	43.1± 7.4	42.6± 7.1	43.7± 7.6	0.28	43.4± 7.2	42.8± 7.5	0.58
LVEDD (mm)	42.6± 5.1	42.7± 5.1	42.5± 5.1	0.75	42.4± 5.3	42.8± 4.9	0.52
MWT	23.4± 5.4	23.2± 5.2	23.7± 5.6	0.56	24.3± 5.7	22.6± 4.9	0.56
LVEF (%)	71.9± 8.5	72.8± 7.0	71.0± 9.8	0.12	72.0± 9.7	71.8± 7.2	0.12
MR (moderate to severe)	38(19)	20(20)	18(18)	0.72	16(16)	22(22)	0.28
LVM (g)	286.0± 80.5	284.5± 73.7	287.5± 87.1	0.79	288.4± 74.2	283.6± 86.6	0.67
LVMI (g/m2)	164.3± 43.7	86± 33	86± 33	0.64	167.2± 45.0	161.5± 46.1	0.38

Abbreviations : NYHA ,New York Heart Association; FH HCM, family history of hypertrophic cardiomyopathy; FH SCD, family history of sudden cardiac death; ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blockers; CCB, Calcium antagonists; LAD, left atrial diameter; MWT, maximum wall thickness; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; LVMI, Left ventricular mass index; Data are presented as mean ± SD for the continuous variables and N (%) for the categorical variables.

*cTnI and NT-proBNP data were o btained in 130 of 200 study patients.

Outcomes and predictors of the end point

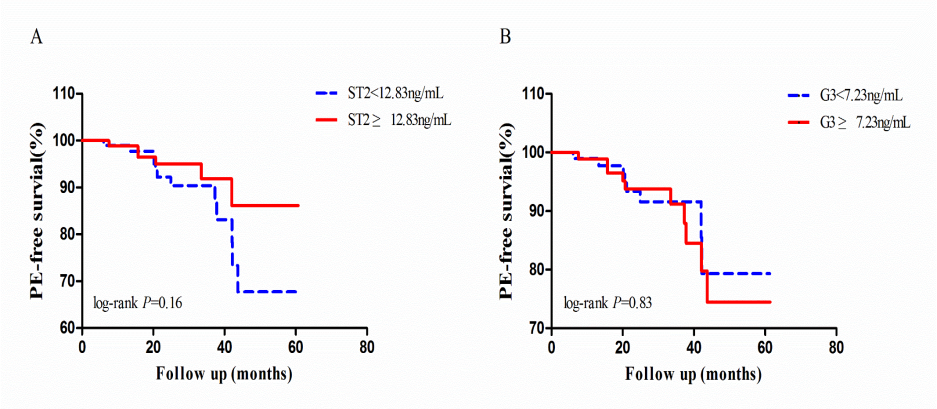
Major adverse events for a median follow-up of 26 months are depicted in (Table 2). The patients in the low ST2 group didn't have a favorable outcome of composite of all-cause mortality and cardiovascular hospitalization (12% vs. 6%; log-rank *P*=0.16; (Figure 1A)) compared with that in high ST2 group. Likewise, there was no significant difference in composite of all-cause mortality and cardiovascular hospitalization between two Gal-3 groups (8% vs.10%; log-rank *P* = 0.83; (Figure 1B)).

Table (2): Comparison of major adverse events among ST2 and G3 tertiles

Study end point	ST2				Gal-3		
	Overall	Low ST2 < 12.83ng/mL (n=100)	High ST2 ≥ 12.83ng/mL (n=100)	*P*	Low Gal-3 < 7.23ng/mL (n=100)	High Gal-3 ≥ 7.23ng/mL (n=100)	*P*
All-cause mortality, n (%)	3 (1.5)	1 (1)	2 (2)	1	0 (0)	3 (3)	0.25
Stroke, n (%)	5 (2.5)	2 (2)	3 (3)	1	2 (2)	3 (3)	1
All-cause hospitalization, n (%)	29 (14.5)	16 (16)	13 (13)	0.55	12 (12)	17 (17)	0.32
CVD hospitalization, n(%)	15 (7.5)	11 (11)	4 (4)	0.06	5 (5)	10 (10)	0.18
Other-cause hospitalization, n(%)	14 (7)	5 (5)	9 (9)	0.69	7 (7)	7 (7)	1

Abbreviations: CVD, cardiovascular disease.

Figure (1): (**A**) Survival free from the primary end point (PE; a composite of all-cause mortality and cardiovascular hospitalization) stratified by sST2 levels. During the follow-up, no differences were found in the rates of the primary end point (log-rank *P*=0.16) .(**B**) Survival free from the primary end point (PE; a composite of all-cause mortality and cardiovascular hospitalization) stratified by Gal-3 levels. Similarly, no differences were found in the rates of the primary end point (log-rank *P*=0.83).



On univariate analysis, patients with higher ST2 (adjusted HR, 0.67; 95% CI: 0.33- 1.39, *P*=0.29) or higher Gal-3 (adjusted HR, 1.24; 95% CI: 0.41-3.72, *P*=0.70) had no significantly greater likelihood of reaching primary endpoint (Table 3). But age (adjusted HR, 1.09; 95% CI: 1.03-1.14, *P*<0.01) and male (adjusted HR, 5.32; 95% CI: 1.42–19.91, *P*=0.01) were identified as independent determinant of primary endpoint (Table 3).

Table (3): Univariate and multivariate predictors of the primary end point (PE)

Variable	Univariate			Multivariate		
	HR	95%CI	*P* Value	HR	95%CI	*P* Value
Age	1.06	1.02-1.11	0.01	1.09	1.03-1.14	<0.01
Male	2.6	0.75-8.97	0.13	5.32	1.42-19.91	0.01
NYHA function class	1.99	0.83-4.75	0.12			
Maximum wall thickness	1.02	0.94-1.10	0.68			
Peak gradient	1	0.99-1.02	0.74			
LVMI	1.01	1.00-1.02	0.17			
AF	3.05	1.18-7.88	0.02	1.96	0.74-5.23	0.18
Angina	1.82	0.72-4.62	0.21			
Syncope history	0.44	0.05-3.58	0.44			
Log ST2*	0.67	0.33-1.39	0.29			
Log G3*	1.24	0.41-3.72	0.7			

Abbreviations: NYHA ,New York Heart Association; LVMI, Left ventricular mass index; FH HCM, family history of hypertrophic cardiomyopathy; FH SCD, family history of sudden cardiac death. *adjusted for age, male and NYHA class.

Discussion

As we know, myocardial fibrosis was already identified by biopsy in hypertrophic cardiomyopathy, and interstitial expansion due to fibrosis assessed by late gadolinium enhancement is suggested to be an independent predictor of major clinical events for these patients[16]. Recently, soluble ST2 and Gal-3 are emerging as novel biomarkers involved in myocardial remodeling and fibrosis. In present study, we are the first to show that plasma sST2 and Gal-3 concentrations are elevated in patients with obstructive HCM. However, the association between ST2 and Gal-3 levels and clinical outcomes were not statistically significant during a median 26 months follow-up. On the other hand, our data suggested that after adjustment for other clinical features, advanced age, male gender and preoperative AF were independent risk factors for all-cause hospitalization after myectomy surgery for patients with obstructive HCM.

For patients with medically refractory obstructive hypertrophic cardiomyopathy (HCM), surgical myectomy is a safe treatment and functional class and symptoms can be relieved in nearly all patients[17]. According to a retrospective

study, long-term survival of septal myectomy was equivalent to that of the general population, and superior to obstructive HCM without operation[18]. Identification for risk factors of adverse outcomes after myectomy may help to improve the management of obstructive HCM patients undergoing the operation. Few researches concerning predictive biomarkers for outcomes post myectomy have been conducted in obstructive HCM. Interestingly, we found that plasma sST2 and Gal-3 levels are elevated in the obstructive HCM patients in present study. Therefore, we would like to investigate the role of sST2 and Gal-3 in obstructive HCM patients.

The transmembrane form of ST2 protein (ST2L) acts as receptor of IL-33, which has anti-remodeling effects on the myocardium by preventing hypertrophy, fibrosis and apoptosis[1]. Soluble ST2 acts as a decoy receptor for IL-33and results in interruption of the interaction between IL-33/ST2L signaling . Soluble ST2 protein is produced not only in cardiomyocytes and fibroblasts, but also in human macrovascular and heart microvascular endothelial cells as response to mechanical stimulation or injury[19]. Bartunek et al found that serum ST2 correlated with the diastolic load in human hypertrophy and fai lure.[20]. In a model with acute myocardial infarction, the myocardial expression of sST2 was unregulated and correlated with inflammatory and fibrosis markers[21]. In the PROTECT study, baseline sST2 added independent prognostic value to NT-proBNP, and serial measurement of sST2 seemed to add prognostic information to baseline concentrations for cardiovascular outcomes in patients with chronic systolic dysfunction[22]. Patients with type 2 diabetes whether or not accompanied by left ventricular diastolic dysfunction, exhibited higher sST2 levels compared to healthy controls, with mean soluble ST2 ranged from 11.31 to 14.97 ng/ml[23]. In present study, the sST2 level of obstructive HCM patients was among that spectrum, but we found no significant differences in clinical and echocardiographic profiles between low ST2 group and high ST2 group. It seems that increased sST2 level could not reflect severity and left ventricular remolding for obstructive HCM patients.

Galectin-3 is expressed in many tissues, and interacts with a variety of intracellular and extracellular proteins to regulate several biological processes including cardiac fibrosis[3, 24]. Meijers et al. demonstrated that HF patients with Gal-3 concentrations exceeding 17.8 ng/mL were significantly more likely to be rehospitalized for HF[25]. Analysis of 27 selected original studies showed that Gal-3 was not superior to NT-proBNP and sST2 as a predictor of mortality in HF. But the combination of NT-proBNP and Gal-3 was superior in risk prediction compared with either of the biomarkers alone[26]. In CORONA and COACH trial, increasing Gal-3 levels over time were associated with significantly more HF hospitalization and mortality compared with stable or decreasing Gal-3 levels independent of age, sex and left ventricular ejection fraction[27]. When patients were stratified to Gal-3 levels, we found that the patients in high Gal-3 group (≥7.23ng/mL) were older and had less male patients, which consistent with prior studies. In sub study of RELAX Trial, both age and sex accounted for the variability in Gal-3 levels in HFpEF[28]. Patients in 3 cohorts with HF had greater Gal-3 levels than that in our study[25], but the median age of their participants was between 61.6 and 72.9 years across the cohorts, much older than 43.7 years in present study. It can be explained by that Gal-3 level increases with age. Moreover, the mean left ventricular ejection fraction of patients in above clinical trials was much lower compared to that of this HCM cohort.

Prior study demonstrated that preoperative hemoglobin A1c levels were associated with major cardiovascular event after coronary artery bypass grafting among patients with diabetes[29]. Fousteris et al showed that HbA1c positively and independently correlated with sST2[23]. Specially, plasma Gal-3 level independently predicted atrial fibrillation recurrence after ablation for persistent AF patients[30]. In

our study, multivariate analysis identified that older age, male and AF predict all-cause hospitalization after myectomy surgery for patients with obstructive HCM. A cohort study about obstructive HCM also suggested that age older than 50 years and AF could predict long-term outcome after myectomy[31]. However, plasma sST2 or Gal-3 levels were not found to be risk factors for all-cause hospitalization post myectomy according to our follow-up results. In fact, prior data regarding sST2 or Gal-3in cardiovascular disease are conflicting, too. A cohort study implied that none novel biomarkers detected including sST2 improved risk stratification of incident AF beyond standard clinical AF risk factors in participants from Framingham Heart Study[32]. Likewise, results from another cohort involved 3,306 participants from the Framingham Offspring did not support a role for Gal-3 in AF risk prediction[32]. Similarly, though elevated sST2 was associated with increased risk of the endpoint in acute heart failure with HFrEF, sST2 alone did not predict readmission within 6 months in acute heart failure with HFpEF[33]. Until now, no conclusive data were provided regarding the association between sST2 or Gal-3 and histologically assessed myocardial fibrosis[34] Furthermore, long term follow-up and serial measurement of sST2 and Gal-3 instead of relying on baseline concentrations might make a difference compared to present study.

The present study had several limitations. At first, this was a single-center study with a relatively small size of participants, which may limit the power of the study. However, the prevalence of HCM is much lower compared to common cardiovascular disease like heart failure, and obstructive HCM only accounts part of HCM. Secondly, patients were unable to pay a return visit at uniform follow-up time intervals, so the repeated measures analyses post surgery were not performed. In conclusion, our results suggested sST2 and Gal-3 may not be able to predict short-term outcomes after myetomy. On the other hand, advanced age and male gender were identified to be independent risk factors for composite of all-cause mortality and cardiovascular hospitalization post myectomy.

Conflict of interests

None declared.

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