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ORIGINAL ARTICLE

Galectin-3 in patients with chronic heart failure: association with oxidative stress, inflammation, renal dysfunction and prognosis

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ABSTRACT

BACKGROUND: Galectin-3 is a recently developed biomarker of fibrosis, which may play a role in cardiac remodeling and associated with both the progression and severity of heart failure (HF).
METHODS: A prospective cohort study of 190 patients with documented prior myocardial infarction and chronic HF (NYHA class II-IV) was conducted. Patients were divided into 3 groups based on their NYHA functional class. Levels of galectin-3, NT-proBNP, CRP, IL-6, oxidized-LDL, extracellular superoxide dismutase (EC-SOD), 3-nitrotyrosine, SH-groups, cystatin-C were determined. Follow-up period was 26 months, and all-cause mortality was determined as the primary endpoint. Statistical analysis was performed and statistical significance was set at $P<0.05$.
RESULTS: The cytokines hs-CRP, IL-6 and markers of oxidative stress had significant positive correlation with plasma galectin-3 levels in all groups of patients. The level of galectin-3 was significantly different between the groups ($P<0.05$). Galectin-3 was found to be the most sensitive and specific value in determination of 26 months mortality in patients with chronic HF. Logistic regression analysis showed that age, galectin-3 and cystatin-C were associated with death during the follow up period.
CONCLUSIONS: Galectin-3 levels are elevated in patients with chronic HF across all NYHA functional classes. Galectin-3 shows positive correlation with markers of oxidative stress, inflammation and kidney dysfunction. Galectin-3 levels and cystatin-C levels are independent predictors of 26-month mortality in patients with chronic HF. Patients with cystatin-C level >2800 pg/mL carry a worse prognosis. Galectin-3 level >21 ng/mL associated with increased mortality.

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Key words: Galectin 3 - Heart failure - Inflammation - Cystatin C.

Galectin-3 is a biomarker which has been associated with cardiac fibrosis in cardiovascular disease. Galectin-3 testing has been included in the most recent American College of Cardiology (ACC) and American Heart Association (AHA) Guidelines for the Management of Heart Failure for additive risk stratification.[1]

Galectin-3 is produced by activated macrophages, and is known to induce cardiac fibroblast proliferation.[2] Significant association between elevated levels of galectin-3 and poor prognosis in patients with chronic heart failure (HF) has been demonstrated in recent studies that examined galectin-3 as a potential diagnostic and prognostic marker for HF.[3-7] It has

been suggested that galectin-3 is involved in the pathogenesis of HF through mediation of myocardial fibrosis and inflammation.[8] However, only a few small studies have reported an association of galectin-3 levels with inflammatory markers in HF.[3,5]

We performed this study to further investigate the associations between galectin-3 and inflammatory markers as well as to examine plasma galectin-3 levels in relation to markers of neurohormonal activation, oxidative stress, renal function, and mortality in patients with chronic HF. It may help to identify the patients at high risk of severe HF development so an adequate biomarker-guided treatment could be initiated in a timely manner with an ultimate aim to reduce mortality, slow down disease progression, improve survival and quality of life.

Materials and methods

We conducted a prospective cohort study of patients from Samara State Medical University. Total of 190 patients with chronic HF (NYHA class II-IV) and documented prior myocardial infarction with LVEF<50%, who were admitted to the hospital due to worsening HF between January 2013 and December 2014 were enrolled. Patients were excluded if they had acute coronary syndrome within the last 6 months (N.=14) or stage IV kidney disease (N.=5). Those patients who underwent CRT (N.=9) were also excluded from the study.

Patients were divided into 3 groups based on their NYHA functional class. Group 1 (N.=54) comprised of patients with NYHA II, group 2 (N.=69) with NYHA III, and group 3 (N.=67) – NYHA IV. Data collected at the time of admission included age, sex, Body Mass Index, and smoking status, as well as clinical and laboratory data at the time of presentation.

All patients underwent a comprehensive clinical assessment following the enrolment in the study. Two-dimensional echocardiogram was performed for every patient; left ventricular ejection fraction (LVEF) was measured using the Simpson's biplane method. Levels of galectin-3, NT-proBNP, CRP, IL-6, and cystatin-C were obtained at the time of clinical assessment.

Galectin-3 levels were determined by enzyme-linked immunosorbent assay (BG Medicine, Waltham, MA, USA). NT-proBNP levels were determined by an immunoelectrochemiluminesence method (Elecsys, Roche Diagnostics, Basel, Switzerland). C-reactive protein (CRP), interleukin-6 (IL-6), cystatin-C were analyzed by immunoassay (BioVendor, Czech Republic). We evaluated the oxidative stress by level of oxidized low density lipoproteins (oxLDL) [9] and nitrosative stress — by level of 3-nitrotyrosine (3-NT), defined by immunoenzyme method. The antioxidative component was assessed by the activity of extracellular superoxide dismutase (EC-SOD) [10] and the concentration of SH-groups.

The estimated glomerular filtration rate (e-GFR) was calculated using the Modification of Diet in Renal Disease (MDRD) equation, which has been validated in patients with HF.[11]

All patients received standard treatment for HF and were prospectively followed for 26 months period. All-cause mortality was determined as the primary outcome.

Statistical analysis

All statistical analysis was performed with StatSoft Statistica 6.1, MedCalc 12.1.1, the open software R 2.12.0 statistical software packages. Continuous variables were described by median and interquartile ranges (IQRs). Comparisons of continuous variables were performed using Mann-Whitney, U-test and Kruskal-Wallis Test. Statistical significance was set at $p<0.05$. Spearman's rank correlation coefficient was calculated to measure dependence between two variables. ROC-analysis was performed to determine the predictive value of biomarkers and to define the cut-off points. Patient survival was assessed using the Kaplan-Meier method. Differential survival within the subgroups was assessed using the log-rank test. Cox-regression analysis was also performed. For the prediction of survival only statistically significant parameters ($P<0.05$) were taken into account. All investigations were in accordance

with the Declaration of Helsinki. This study was approved by the Samara State Medical University Institutional Review Board. Informed consent was obtained from every individual.

Results

Baseline characteristics

The baseline characteristics of patients are presented in Table I. Patients were of similar age and gender ratio. The frequencies of hypertension and beta-blocker use were similar across all three groups. The levels of NT-proBNP, galectin-3, hs-CRP, IL-6, and cystatin-C differed in all groups of patients. The level of galectin-3 in groups was 10, 19 and 38 ng/mL accordingly, representing significant difference between the groups (P<0.001). In patients with progressive chronic HF the increasing activity of oxidative processes in plasma was observed, resulting in higher oxidation of LDL, higher level of 3-NT and reduction of activity of antioxidant components (Table I).

Correlations between the studied parameters

The cytokines hs-CRP and IL-6 had significant positive correlation with plasma galectin-3 levels in all groups of patients. Strong correlations were also observed between galectin-3 - cystatin C and galectin-3 — e-GFR, but weak non-significant association was observed for galectin-3 — creatinine (Table II). Positive correlation between Galectin-3 — oxLDL, and Galectin-3 — 3-nitrotyrosine was observed in all groups of patients. We found that EC-SOD had a strong positive correlation with oxLDL and 3-NT in the group 1, whereas in the group 2 such correlation was less significant, and in the group 3 it was strong, but negative (Table II).

Follow-up on survival

During the follow up period, 102 out of 190 patients died. Group of died had significantly higher levels of Galectin-3, cystatin-C, and NT-proBNP compared to the group of survivors (P<0.01). (Table III).

The diagnostic value of Galectin-3, cystatin-C, and NT-proBNP for chronic HF was assessed by ROC curve analysis. AUC was 0.924 (P<0.0001) when plasma level of Galectin-3 was more than 21 ng/ml, (AUC) = 0,888, (P<0.0001) plasma level of cystatin-C more than 2800 pg/ml and level of NT-proBNP more than 1500 pg/mL (AUC)=0.851, P<0.0001) (Figure 1).

TABLE I.—*Baseline characteristics of patients.*

	NYHA II (N.=54)	NYHA III (N.=69)	NYHA IV (N.=67)	P-value
Age	58 (52-64)	62 (54-68)	60 (54-70)	>0.01
Male (%)	40	45	41.7	>0.01
6 MWT (m)	360 (342-392)	245 (200-289)	85 (64-115)	<0.01
LVEF (%)	46 (39-48)	40 (33-44)	34 (29-40)	<0.05
Hypertension (%)	26	20	17	>0.01
ACE inhibitors (%)	72	80	88	<0.01
Beta-blockers (%)	86	84	78	>0.01
NT-proBNP (pg/mL)	550 (250-850)	1275 (950-1750)	2500 (1900-2800)	<0.01
Galectin-3 (ng/mL)	10 (7-15)	19 (14-26)	38 (32-43)	<0.001
hs-CRP (mg/L)	1.8 (1.1-1.8)	3.3 (1.7-4.45)	6.5 (5-7.5)	<0.01
IL-6 (pg/L)	8 (4.5-15)	18 (11-30)	39 (31-52)	<0.01
e-GRF (mL/min/1.73 cm^2)	79 (66-90)	66 (57-78)	43 (34-60)	<0.01
Cystatin-C (pg/mL)	1800 (1300-2500)	2800 (2450-3600)	4600 (3700-5500)	<0.01
Creatinine (mkmol/L)	72 (60-90)	92.5 (83,5-112)	134 (98-150)	<0.05
3-NT (nmol/mL)	2.6 (2-3.0)	3.8 (2.9-4.2)	5.3 (4.4-6.6)	<0.01
Ox-LDL (nmol/mg protein)	45.5 (39-49)	60 (51-70)	79 (70-86,5)	<0.01
EC-SOD (u/mL)	109 (99-116)	124 (85-145)	65 (49-83)	<0.01
SH-groups	402 (390-423)	360 (321-387)	265 (220-320)	<0.01

Data presented as median and 25-75th percentile. P-value – NYHA II, III, IV.

TABLE II.—*Relation between galectin-3, inflammatory cytokines, and renal function.*

Groups	NYHA II (N.=54)		NYHA III (N.=69)		NYHA IV (N.=67)	
Pair correlation	Spearman·s correlation coefficient	P-value Spearman	Spearman·s correlation coefficient	P-value Spearman	Spearman·s correlation coefficient	P-value Spearman
Galectin-3-hsCRP	0.57	<0.0001	0.78	<0.0001	0.69	<0.00001
Galectin-3-IL-6	0.68	<0.0001	0.66	<0.0001	0.75	<0.00001
Galectin-3- eGFR	-0.497	<0.001	-0.588	<0.0001	-0.491	<0.0001
Galectin-3- cystatin C	0.615	<0.001	0.663	<0.001	0.745	<0.00001
Galectin-3-creatinine	0.194	>0.1	0.310	>0.05	0.359	>0.01
hs-CRP-cystatin C	0.52	<0.001	0.58	<0.0001	0.4	<0.001
hs-CRP-eGFR	-0.33	<0.001	-0.37	<0.001	-0.22	>0.05
IL-6-cystatin C	0.68	<0.0001	0.65	<0.0001	0.6	<0.0001
IL-6-eGFR	-0.54	<0.001	-0.56	<0.0001	-0.45	<0.001
Galectin-3-3NT	0.61	<0.01	0.65	<0.01	0.73	<0.01
Galectin-3-oxLDL	0.52	<0.01	0.59	<0.01	0.67	<0.01
oxLDL-NT-proBNP	0.48	<0.01	0.55	<0.01	-0.38	<0.01
3NT-EC-SOD	0.57	<0.01	0.21	>0.1	-0.59	<0.01
ox-LDL-C-SOD	0.451	0.00036	0.161	0.183	-0.605	0.00006
Galectin-3-EC-SOD	0.380	0.0015	0.184	0.095	-0.537	0.00017

TABLE III.—*Galectin-3, cystatin-C, and NT-proBNP levels in control group and study group.*

	Patients with CHF		P-value
	Group of survivors (N.=88)	Group of dead (N.=102)	
Galectin-3, ng/mL	12 (10; 18)	32.5 (26; 40)	<0.001
Cystatin C, pg/mL	2000 (1600; 2800)	4000 (3000; 5500)	<0.0001
NT-proBNP, pg/mL	800 (400; 1350)	2250 (1475; 2800)	<0.001

P-value: survivors vs. dead.

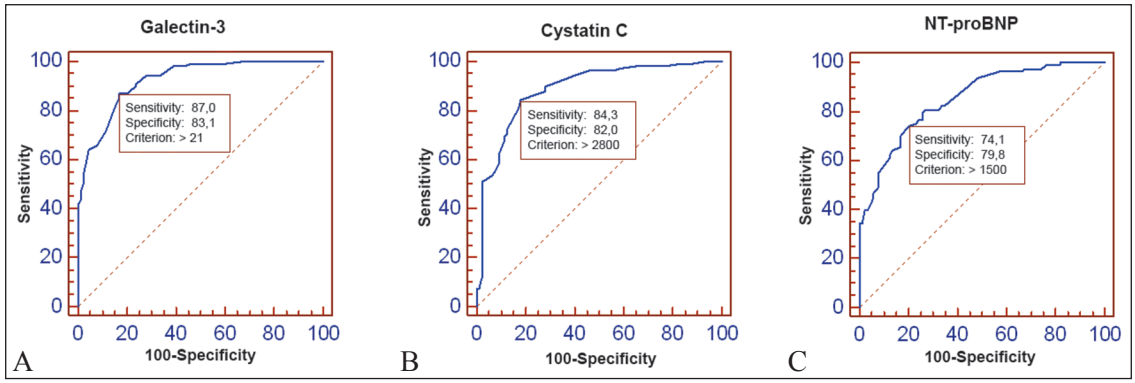

Figure 1.—Roc curve analysis of the diagnostic value of plasma A. Galectin-3 in patients with chronic HF. B. Cystatin-C in patients with CHF C. NT-proBNP in patients with chronic HF.

ROC analysis determined Galectin-3 to be the most sensitive and specific value in determination of 26 months all-cause mortality in patients with chronic HF, compared to cystatin-C and NT-proBNP.

Kaplan-Meier analysis showed that likelihood of death in patients with chronic HF during follow up period is significantly higher when Galectin-3 level >21 ng/mL (Log-rank, P=0.00009), cystatin-C level >2800 pg/ml (Log-rank, P=0.0001) and NT-proBNP>1500 pg/mL и<1500 pg/mL (Log-rank, P=0.006) (Figure 2).

Logistic regression analysis showed that

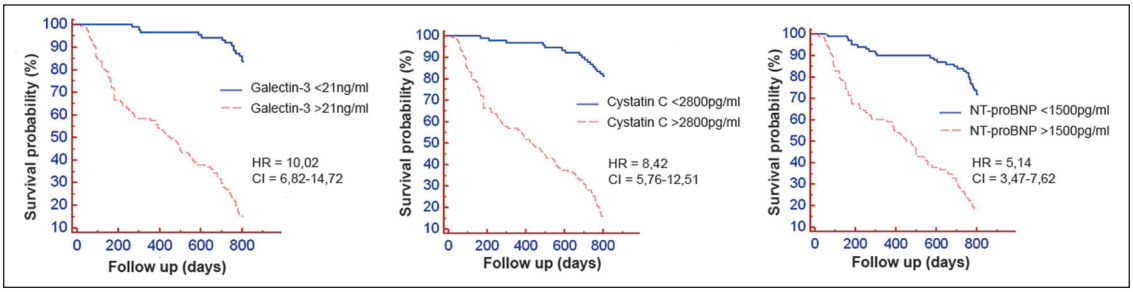

Figure 2.—Kaplan-Meier curves for time to death according to A) galectin-3 levels; B) cystatin C levels; and C) NT-proBNP levels.

TABLE IV.—*Cox proportional hazards regression coefficients for all-cause death during follow-up.*

Variable	B	SE	exp (B)	CI exp (B) 95%	P-value
Age	0.0328	0.0124	1.03	1.01 -1.06	0.0079
Galectin-3	0.0985	0.0101	1.10	1.08 -1.12	0.00001
Cystatin-C	0.0002	0.00008	1.0002	1.0001 - 1.0004	0.0039
NT-proBNP	0.0001	0.000123	1.0001	0.98 - 1.007	0.22

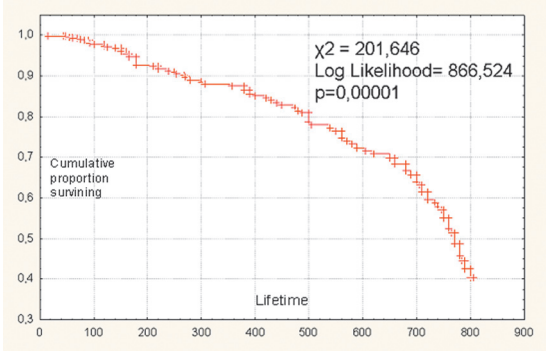

Figure 3.—Cox proportional hazard for the average values of predictors.

age (HR 1.059, CI 1.006-1.1140; P=0.02), galectin-3 (HR 1,1676, CI 1,0971-1,2426; P<0.0001) and cystatin-C (HR 1.004, CI 1.001-1.010; P=0.04) were significantly associated with death during the follow-up period. However, plasma level of NT-proBNP did not reach statistical significance. The sensitivity of the logistic regression model was 85%, specificity was 83% and AUC=0.922. The results of the Cox regression analysis are presented in Table IV.

For each indicator, we determined the coefficients of multiple regression (presented in column B). Survival function for the mean values of the independent variables is shown in Figure 3.

Discussion

Several studies have identified galectin-3 as a regulator of macrophage function, promoter of fibroblast proliferation, and regulator of collagen synthesis in kidney and liver fibrosis.[12, 13] Serial investigations found galectin-3 levels to be up-regulated in patients with decompensated HF, as well as in those with HF with preserved ejection fraction.[5, 14, 15] In our study we found that galectin-3 levels were elevated in all patients with chronic HF, and its levels were significantly different across all NYHA functional classes, with higher levels corresponding to the degree of functional impairment. Significantly higher levels of CRP, IL-6, and cystatin-C were also detected in the group with severe HF. We found very strong correlations between galectin-3 and markers of inflammation and renal dysfunction.

The progressive increase of oxidation of LDL in study groups was found. The significant correlation between oxLDL and NT-proBNP may suggest the important role of myocardial stress in the oxidation of LDL. It is known, that galectin-3 activates the receptor capture of oxidized LDL and increases their intracellular oxidation.[16] In this study we revealed a strong positive correlation between level of galectin-3 and oxidized LDL in all groups of

patients, which may indicate the involvement of galectin-3 in the oxidation of LDL, increasing with the disease severity.

Significant correlation between the levels of oxLDL, CRP, and IL-6 reinforces the role oxidized LDL plays in the inflammation process. Active forms of oxygen, which production is stimulated by galectin-3, activate Ras molecules Akt pathway, P13 kinase, MAP kinase, transcription factors AP-1, NFB and HIF-1, and initiate processes of inflammation, fibrosis and apoptosis of myocardium. In addition, galectin-3 induces nuclear factor kB, which activates endogenous inflammation.[17-19] At the same time, Toprak G *et al.* revealed significant differences in the concentration of galectin-3 between groups of patients with chronic HF of ischemic etiology and with dilated cardiomyopathy, furthermore the degree of activation of oxidative stress and inflammation were comparable.[20] In contrast, our data confirmed close connection between plasma concentration of galectin-3 and activity of plasma oxidative stress and inflammation.

In recent years, there has been an increasing interest in nitrosative stress and its role in pathogenesis of HF. Our data show that the activity of nitrosative stress and the level of peroxynitrite in heart cells is increased significantly in patients with severe chronic HF. The plasma level of galectin-3 has strong positive correlation with the level of 3-nitrotyrosine in all the groups of patients. It is belived that galectin-3 indirectly activates the processes of intracellular myocardial oxidative-nitrosative stress through the stimulation of NADP(h)-oxidase and its ability to release superoxide radical O_2^* from mitochondria.[21] Peroxynitrite has many adverse biochemical effects, however one of the most important in HF patients is activation of matrix metalloproteinase 2 and 9 and other nuclear enzymes poly (ADP-ribose) polymerase (PARP). As a result, the fibrous collagen breakdown is induced, which leads to ventricular dilatation and progressive systolic dysfunction. Activation of PARP has its own pathological effects — decreases the electron transport in mitochondria with ATP depletion, increases the expression of various proteins, including inducible NOS, ICAM-1, proinflammatory cytokines and hemokines, which eventually leads to activation of inflammation and myocardial dysfunction.[22]

It has been shown recently, that EC-SOD is an exceptionally important antioxidant, limiting the activity of oxidative-nitrosative stress and its distribution in tissue.[23] The strong positive correlation between EC-SOD and oxLDL in patients of group 1 can be associated with enzyme activation by moderate amount of superoxide radical. Not significant correlation between EC-SOD and markers of oxidative-nitrosative stress and the increase of the EC-SOD median in patients of group 2 can be the result of combination of high enzyme activity with low. And finally, a strong negative correlation of these factors in the group 3 may be explained by a partial inhibition of EC-SOD by oxidative-nitrosative stress metabolites. The same correlation was observed between the galectin-3 and EC-SOD, which confirms the relationship between increase in its synthesis and production of superoxide radical O_2 and EC-SOD in patients with chronic HF and associated with hypertrophy, dilatation and dysfunction of left ventricle, especially during haemodynamic stress.[23]

Galectin-3 has been shown to be associated with adverse outcomes in patients with HF.[24] Recent studies have demonstrated the correlation between galectin-3 level and hospital readmission rates for CHF,[5, 10] which implicates galectin-3 as a marker of disease severity and progression. In our study, we demonstrate that galectin-3, cystatin-C, and age are independent predictors of death. The baseline level of galectin-3 >21 ng/mL was associated with an increase in all-cause mortality within 26 months follow-up period. Patients with high circulating levels of galectin-3 had a substantially higher probability of deterioration of functional status or death, as compared with those with only moderately increased galectin-3 level. In this study we did not perform serial galectin-3 and inflammatory markers measures and can not comment on its role in disease progression.

In this study we demonstrated a statisti-

cally significant positive correlation between plasma galectin-3 level and cystatin-3 levels in patients with HF. Most of the recent studies utilized eGFR as an estimate of renal function, and failed to show correlation between galectin-3 level and eGFR.[11] This may suggest that cystatin-3 can be used as an alternate measure of renal impairment in HF.

The association of galectin-3 levels and inflammation in patients with HF is still debatable. Several studies showed weak correlations between individual cytokines and galectin-3 levels.[3, 5] However, some studies were able to demonstrate that inhibition of galectin-3 both in vitro and in vivo specifically blocks aldosterone-induced inflammation, type I collagen deposition, and vascular remodeling.[25] In our study we found strong statistically significant associations between galectin-3 and major inflammatory markers, CRP and IL-6. To our knowledge, these are considerably stronger than other analyses that were performed before. Moreover, the associations remains significant across all NYHA functional classes, which could imply a universal mechanism of pathogenesis.

The strongest positive correlation was seen between IL-6 and cystatin-C and CRP and cystatin-C. Those results further reinforce the role of inflammation in kidney damage in patients with chronic HF, however, additional investigation is required to delineate this hypothesis.

Cystatin-C level is a known independent risk factor for HF in older adults, and appears to provide a better measure of risk assessment than the serum creatinine concentration. However, data is lacking on the correlation between cystatin-C levels and severity of chronic HF, as well as the prognostic value of cystatin-C. In this study we were able to show that cystatin-C levels were 180% higher ($P<0.001$) in NYHA III and 360% higher ($P<0.001$) in NYHA IV compared to level in NYHA II. The cystatin-C level in NYHA III and IV patients was 50% higher than in the NYHA II group ($P<0.001$). Median cystatin-C level in our survival group was 2000 pg/mL, significantly different from those who died during the follow up period, who had a median level of 4000 pg/mL.

Limitations of the study

The main limitation of the current study is the small sample size, which precluded us from conducting quartile analyses and further more complex analyses examining the role of kidney function and inflammation in the association of galectin-3 and HF.

Galectin-3 level was measured at a single time point and thus we can only speculate on its importance over time. However, one of the recent studies by De Boer *et al.* was not able to show additive prognostic value of repeated measures of galectin-3 [5] thus it is still be very important to perform prospective study with serial measurements of the level of galectin-3 and markers of inflammation, oxidative stress and renal dysfunction during the follow-up period.

All patients in this study had prior myocardial infarction and our findings cannot be generalized to those with other etiologies of HF.

Conclusions

Galectin-3 levels are elevated in patients with HF across all NYHA functional classes. Galectin-3 has a strong positive correlation with inflammatory markers and markers of oxidative-nitrosative stress and kidney dysfunction. Galectin-3 levels and cystatin-C levels are independent predictors of mortality within 26 months in patients with chronic HF. Those patients with cystatin-C level >2800 pg/mL have worse prognosis. The level of galectin-3 >21 ng/mL is significantly associated with increased mortality. Galectin-3, cystatin C and age are independent predictors of death within 26 months.

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