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Growth differentiation factor-15 combined with N-terminal prohormone of brain natriuretic peptide increase 1-year prognosis prediction value for patients with acute heart failure: a prospective cohort study

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Abstract

Background: Clinical assessment and treatment guidance for heart failure depends on a variety of biomarkers. The objective of this study was to investigate the prognostic predictive value of growth differentiation factor-15 (GDF-15) and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) in assessing hospitalized patients with acute heart failure (AHF).

Methods: In total, 260 patients who were admitted for AHF in the First Affiliated Hospital of Nanjing Medical University were enrolled from April 2012 to May 2016. Medical history and blood samples were collected within 24 h after the admission. The primary endpoint was the all-cause mortality within 1 year. The patients were divided into survival group and death group based on the endpoint. With established mortality risk factors and serum GDF-15 level, receiver-operator characteristic (ROC) analyses were performed. Cox regression analyses were used to further analyze the combination values of NT-proBNP and GDF-15.

Results: Baseline GDF-15 and NT-proBNP were significantly higher amongst deceased than those in survivors ($P < 0.001$). In ROC analyses, area under curve (AUC) for GDF-15 to predict 1-year mortality was 0.707 (95% confidence interval [CI]: 0.648–0.762, $P < 0.001$), and for NT-proBNP was 0.682 (95% CI: 0.622–0.738, $P < 0.001$). No statistically significant difference was found between the two markers ($P = 0.650$). Based on the optimal cut-offs (GDF-15: 4526.0 ng/L; NT-proBNP: 1978.0 ng/L), the combination of GDF-15 and NT-proBNP increased AUC for 1-year mortality prediction (AUC = 0.743, 95% CI: 0.685–0.795, $P < 0.001$).

Conclusions: GDF-15, as a prognostic marker in patients with AHF, is not inferior to NT-proBNP. Combining the two markers could provide an early recognition of high-risk patients and improve the prediction values of AHF long-term prognosis.

Clinical trial registration: ChiCTR-ONC-12001944, http://www.chictr.org.cn.

Keywords: Growth differentiation factor-15; Heart failure; N-terminal pro-B type natriuretic peptide; Prognosis

Introduction

Heart failure (HF) is the end stage of various cardiovascular diseases having a high mortality, hospitalization expenses, and disability rate. A large cohort registry study in China showed high in-hospital mortality (4.1% ± 0.3%) and revealed the need of improved care for acute HF (AHF).[1] Prompt diagnosis and proper risk stratification of HF rely on the use of biomarkers.

Brain natriuretic peptide (BNP) and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) are mainly secreted by ventricular cardiomyocytes with overload of volume and/or pressure.[2-4] BNP and NT-proBNP are the most widely used biomarkers in differential diagnosis, risk stratification, and prognostic evaluation of HF. NT-proBNP is effective in diagnosis and prognosis evaluation for both AHF and chronic HF (CHF).[5-11] Current guidelines of HF have incorporated with the usage of natriuretic peptide in establishing the severity and prognosis.[12-14] Clinical applications of NT-proBNP are limited by various conditions.[15-22] NT-proBNP can increase in coronary heart diseases, arterial fibrillation, sepsis, recent cancer treatment, etc. Additionally, for right HF caused solely by pulmonogenic disease, the elevated plasma BNP level may be misinterpreted since dyspnea is primarily from lung disease instead of left HF.

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On the other hand, a novel HF biomarker, growth differentiation factor-15 (GDF-15), is a stress response protein in different regulatory pathways. Studies showed a significant increase under different pathophysiological conditions such as inflammation, hypoxia, injury, and various tumors.[4,23-29] GDF-15 strongly expresses in cardiomyocyte in ischemia/reperfusion injury, pressure overload and HF. It antagonizes the hypertrophic response and loss of ventricular performance, hence reversing myocardial hypertrophy and apoptosis. Furthermore, the elevation of GDF-15 is implicated in the early diagnosis, risk stratification, and prognosis in CHF with the threshold of approximately 2000 ng/L.[30-33] Because of the short half-life and unique pathophysiology of GDF-15, GDF-15 level reflects myocardial re-modeling in the progression and prognosis of HF.[34-37] GDF-15 is affected by various conditions, which limits the use of GFP-15 in evaluating HF. GDF-15 elevates significantly with pulmonary pressure increases[38-42] due to acute pulmonary embolism, idiopathic pulmonary arterial hypertension, and congenital heart disease. The elevated GDF-15 might be associated with the anti-apoptotic effect of GDF-15 in pulmonary endothelial cell upon exposure to shear stress and hypoxia. Studies also showed increased expression of GDF-15 in metabolic diseases (such as diabetes mellitus [DM], cancer, pregnancy), and other cardiovascular diseases (such as coronary artery diseases, atrial fibrillation).[28,43-46]

Accurate assessment of HF with one single marker is complicated by its diverse etiology. The combinational use of multiple biomarkers is required to fulfill the gap in clinical practice. Therefore, this study aimed to further investigate the value of GDF-15 combined with NT-proBNP in AHF of the Chinese population.

Methods

Ethical approval

The study was approved by the independent Ethics Committee of the First Affiliated Hospital of Nanjing Medical University. All of the participants were over 18 years old and have given their informed consent before enrollment. The trial was registered at http://www.chictr.org.cn/ (ChiCTR-ONC-12001944).

Patients population

From April 2012 to December 2016, 260 patients hospitalized for AHF in the First Affiliated Hospital of Nanjing Medical University were enrolled (289 patients were initially enrolled, among which 29 patients [10.0%] were dropped out). AHF refers to the rapid onset or deterioration of symptoms and signs of HF which included new-onset AHF and acute decompensated HF. Patients were initially assessed in cardiology outpatient or emergency department by physicians and were diagnosed according to Chinese Guideline for Diagnosis and Treatment of AHF.[12] The diagnosis criteria of AHF were based on the history of the symptoms and a physical examination with confirmation by echocardiogram, which consisted with American College of Cardiology Foundation/American Heart Association & European Society of Cardiology guidelines.[13,14] In addition to the volume control, patients without specific contraindications received the standard medication for treatment, including angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB), beta-blocker, and mineralocorticoid receptor antagonist (MRA). Major events and complications occurring during hospitalization were documented. Renal dysfunction, hypertension, and DM were defined as comorbidities of AHF according to current guidelines at the time of hospitalization.[47-49] The patients who were diagnosed with malignant tumor, cognitive deficit, dementia, severe mental illness, and uncontrolled systemic disease (eg, unstable or uncompensated respiratory, hepatic disease) were excluded.

Data collection and follow-up

Variables including demographic characteristics, etiology of AHF, medical history and features, and accessory examinations were collected within 24 h after admission. Accessory examinations included electrocardiogram (ECG), transthoracic echocardiogram (TTE), and other evaluation tests of the comorbidities.

All patients received standard treatment without intervening with therapy at the follow-up. The primary endpoint was defined as all-cause mortality within 1 year. The follow-up data were obtained by the outpatient visit and telephone interview every 3 months after discharged. The endpoint events confirmed by reviewing of medical records or contacting with their families members and physicians.

Samples

Peripheral blood samples were collected at admission or in the following morning within 12 h. Samples were used for testing NT-proBNP, GDF-15, sodium (Na), and other biochemical markers. NT-proBNP was analyzed by electrochemical luminescence automatic immunoassay (Roche Elecsys® NT-proBNP Immunoassay, Switzerland). The serums for analyzing GDF-15 were separately stored at –40°C until assayed and were measured with the corresponding detection kit (Roche Elecsys® Diagnostics GmbH, Mannheim, Germany). Complete blood count and other biochemical indexes were measured by the according automated analyzers (Beckman Coulter® AU 5800, Brea, CA, USA). Normal reference ranges by the above methods for NT-proBNP is 0 to 300 ng/L and GDF-15 is 0 to 1200 ng/L. TTE parameters were taken by sonographers in our hospital when their symptoms subsided using Vivid E9 (GE Medical System, Wauwatosa, WI, USA). Left ventricular ejection fraction was measured by M-mode and two-dimensional echocardiographs.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) for normal distribution or median (Q1–Q3), while discrete variables as counts (percentage); and compared using *t* test or one-way analysis of variance for normally distributed continuous variables, and the Mann-Whitney *U* test for skewed distribution. The Chi-square test was used for categorical variables. Receiver-operator characteristic (ROC) analysis for predicting 1-year mortality

was also performed and Kaplan-Meier models were used to estimate the time-to-event for death. Youden index was used in evaluating the cut-off regarding two markers in further analysis. Cox regression analysis was used to further explore the predictors independently related to 1-year mortality. According to the cut-off points, multivariate Cox regression analysis using forward stepwise was performed to further analyze the predictive value of 1-year mortality in the study. All tests were two-sided, *P* values lower than 0.05 were considered statistically significant. All data analyses were performed using SPSS version 23.0 (SPSS Inc., Chicago, IL, USA) and Med-Calc version 15.0 (MedCalc Software, Mariakerke, Belgium).

Results

Baseline characteristics

In total 260 patients diagnosed with AHF participated in our study. Patients' mean age was 61.0 ± 15.8 years and a modest majority was male (65.0%). In admission, 58.5% patients were in New York Heart Association (NYHA) Functional Classification III. The median of NT-proBNP of all patients was 2100.5 ng/L (1132.0–4857.0) ng/L, and GDF-15 was 2449.0 ng/L (1465.8–4699.8) ng/L. Correlation analysis between the two markers demonstrated a statistical significance ($r = 0.475$, $P < 0.001$).

By the end of follow-up, 46 (17.7%) patients had died within 1 year. According to the primary end-point (1-year mortality), patients were divided into two groups as survival group and death group. In total 11 variables from the baseline characteristics were considered to be statistically significant between the two groups [Table 1]. The research targets, NT-proBNP and GDF-15 concentrations, were higher in death group than those in survival group ($P < 0.001$). Other variables included systolic blood pressure, diastolic blood pressure, serum Na, hemoglobin, red cell distribution width, blood urea nitrogen, aspartate aminotransferase, history of DM, and NYHA class were statistically significant (all $P < 0.050$).

In addition, there was no significant difference in the sex distribution, ECG parameters (QRS duration, corrected QT interval [QTc], left bundle branch block), admission oral medication regimen (loop diuretics, MRA, ACEI/ARB, beta-blocker, digoxin), or etiologies (coronary heart disease, valvular heart disease, cardiomyopathy) between groups (all $P > 0.050$).

ROC analyses

In order to analyze the predictive value of GDF-15 combined with NT-proBNP, ROC analysis was used to determine the cut-off values regarding the two indexes.

The area under the curves (AUC) for GDF-15 as a predictor of 1-year mortality was 0.707 (95% confidence interval [CI]: 0.648–0.762, $P < 0.001$), which was similar to that for NT-proBNP (AUC = 0.682, 95% CI: 0.622–0.738, $P < 0.001$) [Figure 1]. Compared between these two markers, there was no statistical difference ($P = 0.650$).

On the other hand, combining the two markers NT-proBNP and GDF-15 into the further analysis showed the AUC increased significantly (AUC = 0.743, 95% CI: 0.685–0.795, $P < 0.001$). But the combination of the two markers compared to the two parameters separately did not demonstrate significance (Combining *vs.* GDF-15, $P = 0.241$; Combining *vs.* NT-proBNP, $P = 0.059$). Therefore further analyses were made as below.

Kaplan-Meier analyses

The optimal cut-off value for NT-proBNP was 1978.0 ng/L having 76.0% sensitivity (95% CI: 0.610–0.840) and 52.0% specificity (95% CI: 0.450–0.590). Similarly, the optimal cut-off value for GDF-15 was 4526.0 ng/L, with 57.0% sensitivity (95% CI: 0.410–0.710) and 80.0% specificity (95% CI: 0.740–0.860). Kaplan-Meier curves (all dichotomized by cut-off point) showed that admission serum GDF-15 and NT-proBNP concentrations were related to the 1-year mortality (all log-rank test, $P < 0.001$) [Figure 2A and 2B]. Patients with elevated GDF-15 or NT-proBNP values were at higher risk of death (log-rank test, $P < 0.001$).

All-cause mortality

Based on the cut-off values, the population was separated into different groups [Table 2]. The mortality (38.2%) in the group with GDF-15 >4526.0 ng/L was over three-fold higher compared to the opposite group (10.4%, $P < 0.001$). The difference between two NT-proBNP groups was similar (25.5% for >1978.0 ng/L *vs.* 8.9% for ≤1978.0 ng/L, $P < 0.001$). With both markers elevated, it demonstrated a higher mortality (11.0% *vs.* 46.0%, $P < 0.001$) [Table 3].

A Cox regression analysis models including the significant variables were established to further explore and assess the predictive value. After univariate analysis, covariates selected based on clinical implication were used in the multivariate regression hazard models. As a result, with both GDF-15 and NT-proBNP exceeding cut-off values as a new variable incorporated into the model, the combination of GDF-15 and NT-proBNP remained as an independent predictor of 1-year mortality in patients with AHF (hazard ratio = 5.623, $P < 0.001$) [Table 4].

Discussion

BNP inhibits the renin-angiotensin system, endothelin secretion, and systemic and renal sympathetic activity. GDF-15 impacts on cardiac remodeling by participating in myocyte hypertrophy, apoptosis, and inflammatory reaction. Both of the markers, NT-proBNP and GDF-15, have a significant predictive value in long-term mortality for AHF. Higher levels of admission NT-proBNP or GDF-15 were associated with occurrence of adverse outcomes. In actual practice, using one single biomarker in HF evaluation has unavoidable limitations caused by the varieties characteristics of HF and comorbidities. Both of GDF-15 and NT-proBNP could be affected by different pathophysiological conditions due to their unique mechanism pathway.

Table 1: Baseline characteristics of patients hospitalized with acute heart failure.

Characteristics	Total ($n = 260$)	Survival ($n = 214$)	Death ($n = 46$)	$t/\chi^2/Z$	P
Age (years)	61.0 ± 15.8	60.1 ± 15.8	64.9 ± 15.6	−1.866	0.076*
Male	169 (65.0)	144 (67.3)	25 (54.3)	2.787	0.095†
SBP (mmHg)	124.8 ± 22.8	126.6 ± 23.2	116.6 ± 19.1	2.721	0.003*
DBP (mmHg)	77.6 ± 15.5	79.3 ± 15.7	70.0 ± 12.0	3.836	< 0.001*
Heart rate (beats/min)	85.5 ± 21.5	85.9 ± 21.2	83.4 ± 23.0	0.699	0.397*
BMI§ (kg/m^2)	24.4 ± 4.6	24.6 ± 4.6	23.9 ± 5.0	0.831	0.359*
Serum concentrations					
Sodium (mmol/L)	139.2 ± 4.1	139.7 ± 3.8	137.1 ± 4.6	3.994	< 0.001*
Potassium (mmol/L)	4.00 ± 0.48	4.01 ± 0.48	3.96 ± 0.47	0.566	0.638*
Calcium (mmol/L)	2.25 ± 0.14	2.25 ± 0.14	2.26 ± 0.15	−0.236	0.981*
Hemoglobin (g/L)	130.9 ± 22.6	133.5 ± 21.8	118.4 ± 22.4	4.197	< 0.001*
RDW (%)	14.3 (13.4–15.6)	14.2 (13.4–15.2)	15.4 (13.8–16.8)	−3.527	< 0.001‡
ALB (g/dL)	36.7 (33.8–39.9)	37.0 (33.7–40.1)	35.3 (33.8–39.0)	0.802	0.170*
BUN (mmol/L)	7.4 (5.8–9.2)	7.2 (5.7–8.9)	8.7 (6.4–10.8)	−2.816	0.005‡
Creatinine (μmol/L)	88.1 (70.5–109.9)	86.3 (70.6–107.8)	96.1 (69.6–115.8)	−1.192	0.233‡
Uric acid (μmol/L)	471.0 (391.0–582.5)	469.1 (388.5–574.1)	485.0 (402.5–668.1)	−1.586	0.113‡
Cystatin C§ (mg/L)	1.30 (1.15–1.60)	1.29 (1.13–1.55)	1.54 (1.16–1.80)	−1.788	0.074‡
ALT (U/L)	25.7 (16.4–43.1)	25.6 (16.6–39.6)	30.3 (15.9–57.5)	−0.917	0.359‡
AST (U/L)	28.3 (22.4–43.7)	27.6 (22.2–40.8)	34.6 (23.9–59.8)	−2.192	0.028‡
NT-proBNP (ng/L)	2100.5 (1132.0–4857.0)	1883.0 (1073.3–4217.8)	3550.5 (1916.8–7790.8)	−4.156	< 0.001‡
GDF-15 (ng/L)	2449.0 (1465.8–4699.8)	2272.0 (1397.3–3955.0)	5055.0 (2272.0–11891.3)	−4.403	< 0.001‡
Echo results					
LVEF (%)	39.3 (29.6–57.8)	38.8 (29.5–55.4)	43.8 (29.7–63.0)	−1.312	0.190‡
LVEDd (mm)	61.8 ± 12.6	62.0 ± 12.3	60.5 ± 14.2	−0.733	0.459‡
Comorbidities					
Hypertension	127 (49.0)	109 (51.2)	18 (39.1)	2.196	0.138†
Diabetes mellitus	61 (23.6)	44 (20.7)	17 (37.0)	5.582	0.018†
Renal insufficiency	22 (8.5)	16 (7.5)	6 (13.0)	0.863	0.353†
Atrial fibrillation	90 (34.7)	71 (33.3)	19 (41.3)	1.060	0.303†
Pulmonary infection	53 (20.5)	41 (19.3)	12 (26.1)	1.054	0.305†
Etiology					
Pulmonary heart disease	13 (5.0)	10 (4.7)	3 (6.5)	0.265	0.607†
CHD	30 (11.6)	25 (11.7)	5 (10.9)	0.028	0.868†
VHD	67 (25.9)	53 (24.9)	14 (30.4)	0.608	0.435†
Cardiomyopathy	101 (39.0)	85 (39.9)	16 (34.8)	0.417	0.518†
NYHA class				3.558	0.049†
II	29 (11.2)	25 (11.7)	4 (8.7)		
III	152 (58.5)	130 (60.7)	22 (47.8)		
IV	79 (30.4)	59 (27.6)	20 (43.5)		
ECG parameters					
QRS duration	118.0 (99.0–154.3)	116.0 (98.8–152.5)	133.0 (102.3–169.8)	−1.369	0.171‡
QTc interval	459.0 (429.0–486.0)	461.0 (432.0–485.5)	455.0 (396.3–487.5)	−0.689	0.491‡
LBBB, *n* (%)	65 (25.6)	56 (26.9)	9 (19.6)	0.526	0.301†
Oral medication at admission, *n* (%)					
Loop diuretics	242 (93.1)	197 (92.1)	45 (97.8)	1.163	0.281†
Aldosterone antagonists	233 (89.6)	189 (88.3)	44 (95.7)	1.471	0.225†
ACEI/ARB	213 (81.9)	175 (81.8)	38 (82.6)	0.018	0.894†
Beta-Blocker	205 (78.8)	167 (78.0)	38 (82.6)	0.474	0.491†
Digoxin	115 (44.2)	95 (44.4)	20 (43.5)	0.013	0.910†

Data are shown as mean ± standard deviation, median (Q1–Q3), or *n* (%). * Calculated by unpaired *t* test. † Calculated by Chi-square test. ‡ Calculated by rank-sum test. § BMI data was only available in 208 patients, and for Cystatin C was 176 patients. SBP: Systolic blood pressure; DBP: Diastolic blood pressure; BMI: Body mass index; RDW: Red cell distribution width; ALB: Albumin; BUN: Blood urea nitrogen; ALT: Alanine transaminase; AST: Aspartate aminotransferase; NT-proBNP: N-terminal-pro-brain natriuretic peptide; GDF-15: Growth differentiation factor-15; LVEF: Left ventricular ejection fraction; LVEDd: Left ventricular end-diastolic dimension; CHD: Coronary heart disease; VHD: Valvular heart disease; NYHA: New York Heart Association; ECG: Electrocardiogram; LBBB: Left bundle branch block; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker.

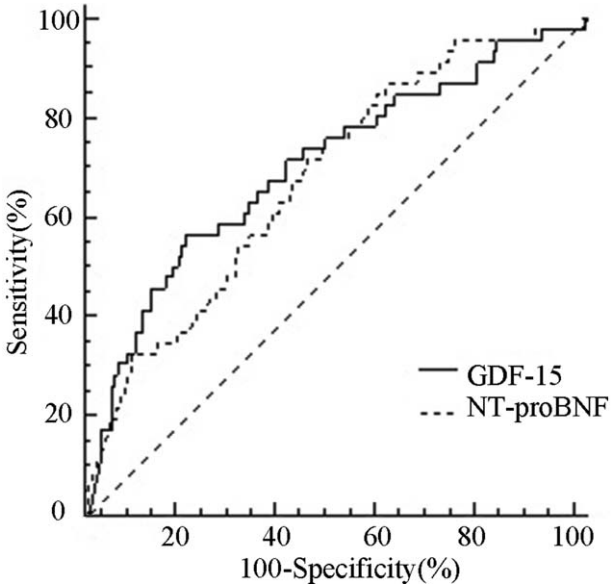

Figure 1: Receiver operator characteristic curves of GDF-15 (AUC = 0.707, 95% CI: 0.648–0.762) and NT-proBNP (AUC = 0.682, 95% CI: 0.622–0.738) for predicting 1-year morality in AHF. AUC: Area under curve; CI: Confidence interval; GDF-15: Growth differentiation factor-15; NT-proBNP: N-terminal-pro-brain natriuretic peptide.

With the worldwide promotion of personalized medicine and precision medicine, combination uses of the HF biomarkers are prompt to be explored. Thus, targeting multiple biomarkers based on their different pathophysiological mechanism, and combination uses with novel biomarkers for different physiological aspects could fulfill an effective clinical use.

Among the demographic characteristics, etiologies and blood results, NT-proBNP and GDF-15 were significantly different between survival and death groups. Comparing the two markers, no significant difference between NT-proBNP and GDF-15 was found regarding 1-year mortality assessment in AHF. Results suggested GDF-15 was no inferior as the benchmark HF marker NT-proBNP in long-term prognosis evaluation of AHF.

When GDF-15 and NT-proBNP were both above the cut-offs, the risk of 1-year mortality was significantly higher than those who had none or only either one elevated. The admission evaluation and prognostic utility for AHF patients with both markers were greater than either GDF-15 or NT-proBNP alone.

In acute settings of HF, the unbalance of homeostasis involved various pathophysiological aspects. The increased stress of myocardial cells, myocardial isocheimal injury, and remodeling of myocardial cells, can significantly increase the secretion in corresponding biomarker such as NT-proBNP and GDF-15. On the other hand, the shear stress of pulmonary vasculature might be the other potent stimulator for the increase expression of GDF-15. The signals of vessel remodeling can be identified in plexiform lesions, and also effects on proliferation and apoptosis of vascular endothelial cells. These two markers regarding different pathophysiology pathway might be given the addition prediction value in AHF evaluation.

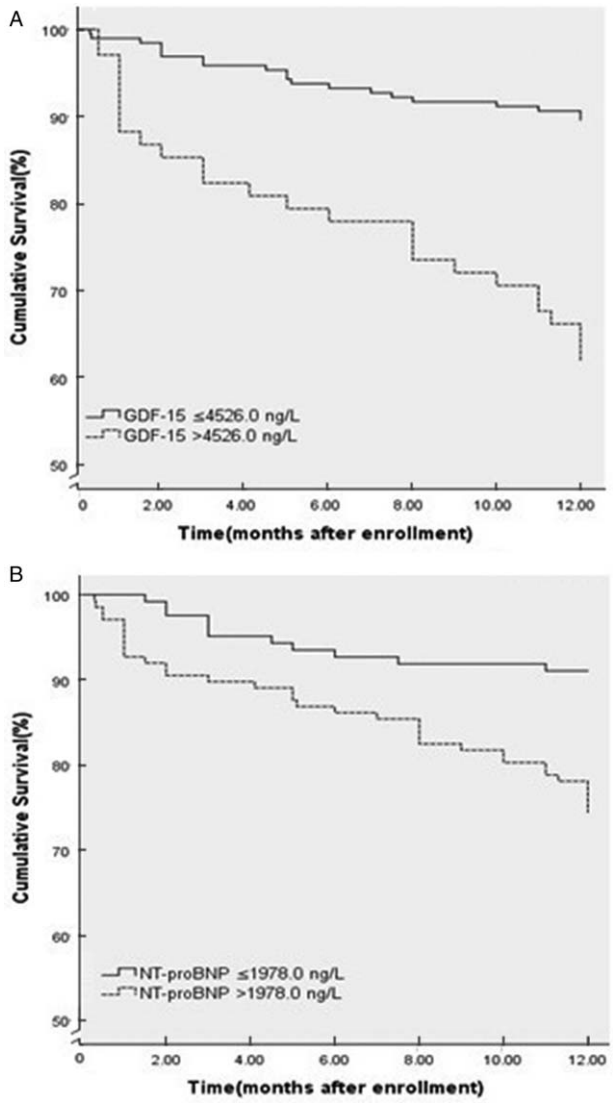

Figure 2: Kaplan-Meier survival curves for 1-year mortality. GDF-15 (A) and NT-proBNP (B) (all log rank test, $P < 0.001$). GDF-15: Growth differentiation factor-15; NT-proBNP: N-terminal-pro-brain natriuretic peptide.

However, there is a lack of studies in the signaling pathway and molecular mechanisms beneath. Further exploration could open the avenues in all aspects.

Moreover, our data provided the additional evidence for the thresholds of NT-proBNP and GDF-15 in risk-stratifying and early recognition of the high-risk patients. Further research should focus on serial measurements during the course of disease to guide optimal clinical management regarding the differences and similarities in the two markers. It could fulfill not only in assessing prognosis but also in guiding diagnosis and optimal regimen for actual clinical practice.

This study had a number of limitations. The results were derived from a single-center and relative small cohort. Larger sample size is needed to further assess the sensitivity and specificity of prognostic values. Besides, the underlying mechanisms and signal pathways between GDF-15 and NT-proBNP are remained unclear. In different phrase,

Table 2: Mortality analysis of the cut-off value with NT-proBNP and GDF-15.

Items	NT-proBNP		GDF-15	
	≤1978.0 ng/L	>1978.0 ng/L	≤4526.0 ng/L	>4526.0 ng/L
Death, *n*	11	35	20	26
Survival, *n*	112	102	172	42
Mortality (%)	8.9	25.5	10.4	38.2
P	<0.001		<0.001	

NT-proBNP: N-terminal-pro-brain natriuretic peptide; GDF-15: Growth differentiation factor-15.

Table 3: Mortality analysis with the combination of NT-proBNP and GDF-15.

GDF-15/NT-proBNP	Survival, *n*	Death, *n*	Mortality (%)	*P*
None/either elevated	187	23	11.0	<0.001
Both elevated	27	23	46.0	

NT-proBNP: N-terminal-pro-brain natriuretic peptide; GDF-15: Growth differentiation factor-15.

Table 4: Regression analysis and additional predictive value of combining GDF-15 and NT-proBNP.

Variables	Univariate			Multivariate		
	HR	95% CI	*P*	HR	95% CI	*P*
SBP	0.994	0.974–1.015	0.568			
DBP	0.973	0.940–1.006	0.105			
Sodium	0.931	0.868–0.999	0.048	0.920	0.862–0.983	0.013
AST	1.001	1.000–1.002	0.003			
Hemoglobin	0.987	0.973–1.002	0.084			
RDW	1.143	1.001–1.305	0.049	1.164	1.010–1.342	0.036
DM	2.010	1.022–3.950	0.043			
NYHA class	1.107	0.622–1.971	0.730			
Both above cut-off value*	2.707	1.415–5.179	0.003	5.623	2.784–11.356	<0.001

* Growth differentiation factor-15 >4526 ng/L, N-terminal-pro-brain natriuretic peptide >1978 ng/L. NT-proBNP: N-terminal-pro-brain natriuretic peptide; GDF-15: Growth differentiation factor-15; HR: Hazard ratio; CI: Confidence interval; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; AST: Aspartate aminotransferase; RDW: Red cell distribution width; DM: Diabetes mellitus; NYHA: New York Heart Association.

their roles and interaction in HF deserve further investigation.

In conclusion, our prospective analysis showed GDF-15 as an independent prognosticator for patients with AHF, is not inferior to NT-proBNP within 1 year of discharge. Also, the optimal cut-off value for NT-proBNP (1978.0 ng/L) and GDF-15 (4526.0 ng/L) provided additional evidences of thresholds for the two markers. Further analysis showed the combination of GDF-15 and NT-proBNP could assist in predicting long-term mortality and identifying high-risk for hospitalized patients with AHF.

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Conflicts of interest

None.

References

1. Zhang Y, Zhang J, Butler J, Yang X, Xie P, Guo D, *et al*. On behalf of the China-HF investigators. Contemporary epidemiology, management, and outcomes of patients hospitalized for heart failure in China: results from the China heart failure (China-HF) registry. J Card Fail 2017;23:868–875. doi: 10.1016/j.cardfail.2017.09.014.
2. Morrow DA, de-Lemos JA. Benchmarks for the assessment of novel cardiovascular biomarkers. Circulation 2007;115:949–952. doi: 10.1161/CIRCULATIONAHA.106.683110.
3. Hanna KG, James LJ Jr. Cardiac Biomarkers and Heart Failure. 2015;American College of Cardiology, [cited 2016 Oct 15]. Available from: http://www.acc.org/latest-in-cardiology/articles/2015/02/09/13/00/cardiac-biomarkers-and-heart-failure.
4. Bootcov MR, Bauskin AR, Valenzuela SM, Moore AG, Bansal M, He XY, *et al*. MIC-1, a novel macrophage inhibitory cytokine, is a divergent member of the TGF-beta superfamily. Proc Natl Acad Sci U S A 1997;94:11514–11519. doi: 10.1073/pnas.94.21.11514.
5. Lainchbury JG, Campbell E, Frampton CM, Yandle TG, Nicholls MG, Richards AM. Brain natriuretic peptide and n-terminal brain natriuretic peptide in the diagnosis of heart failure in patients with acute shortness of breath. J Am Coll Cardiol 2003;42:728–735. doi: 10.1016/S0735-1097(03)00787-3.
6. Bettencourt P, Azevedo A, Pimenta J, Friões F, Ferreira S, Ferreira A. N-terminal-pro-brain natriuretic peptide predicts outcome after hospital discharge in heart failure patients. Circulation 2004;110:2168–2174. doi: 10.1161/01.CIR.0000144310.04433.BE.
7. Hartmann F, Packer M, Coats AJ, Fowler MB, Krum H, Mohacsi P, *et al*. Prognostic impact of plasma N-terminal pro-brain natriuretic peptide in severe chronic congestive heart failure: a substudy of the carvedilol prospective randomized cumulative survival (COPERNICUS) trial. Circulation 2004;110:1780–1786. doi: 10.1161/01.CIR.0000143059.68996.A7.
8. Chen AA, Wood MJ, Krauser DG, Baggish AL, Tung R, Anwaruddin S, *et al*. NT-proBNP levels, echocardiographic findings, and outcomes in breathless patients: results from the ProBNP Investigation of Dyspnoea in the Emergency Department (PRIDE) echocardiographic substudy. Eur Heart J 2006;27:839–845. doi: 10.1093/eurheartj/ehi811.
9. Moe GW, Howlett J, Januzzi JL, Zowall H. Canadian Multicenter Improved Management of Patients With Congestive Heart Failure (IMPROVE-CHF) Study Investigators. N-terminal pro-B-type natriuretic peptide testing improves the management of patients with

suspected acute heart failure: primary results of the Canadian prospective randomized multicenter IMPROVE-CHF study. Circulation 2007;115:3103–3110. doi: 10.1161/CIRCULATIONAHA.106.666255.
10. Latini R, Masson S, Anand I, Judd D, Maggioni AP, Chiang YT, *et al*. Valsartan Heart Failure Trial Investigators. Effects of valsartan on circulating brain natriuretic peptide and norepinephrine in symptomatic chronic heart failure: the Valsartan Heart Failure Trial (Val-HeFT). Circulation 2002;106:2454–2458. doi: 10.1161/01.cir.0000036747.68104.ac.
11. McQuade CN, Mizus M, Wald JW, Goldberg L, Jessup M, Umscheid CA. Brain-type natriuretic peptide and amino-terminal pro-brain-type natriuretic peptide discharge thresholds for acute decompensated heart failure: a systematic review. Ann Intern Med 2017;166:180–190. doi: 10.7326/M16-1468.
12. Chinese Society of Cardiology of Chinese Medical Association, Editorial Board of Chinese Journal of Cardiology. Guideline for diagnosis and treatment of heart failure 2014 (in Chinese). Chin J Cardiol 2014;42:98–122. doi: 10.3760/cma.j.issn.0253-3758.2014.02.004.
13. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, *et al*. Authors/Task Force Members; Document Reviewers. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016;18:891–975. doi: 10.1002/ejhf.592.
14. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, *et al*. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines and the heart failure society of America. J Am Coll Cardiol 2017;70:776–803. doi: 10.1016/j.jacc.2017.04.025.
15. Takami Y, Horio T, Iwashima Y, Takiuchi S, Kamide K, Yoshihara F, *et al*. Diagnostic and prognostic value of plasma brain natriuretic peptide in non-dialysis-dependent CRF. Am J Kidney Dis 2004;44:420–428. doi: 10.1053/j.ajkd.2004.05.023.
16. Mair J, Gerda F, Renate H, Ulmer H, Andrea G, Pachinger O. Head-to-head comparison of B-type natriuretic peptide (BNP) and NT-proBNP in daily clinical practice. Int J Cardiol 2008;124:244–246. doi: 10.1016/j.ijcard.2006.11.230.
17. Kälsch H, Neumann T, Erbel R. Less increase of BNP and NT-proBNP levels in obese patient with decompensated heart failure: interpretation of natriuretic peptides in obesity. Int J Cardiol 2009;133:e22–e24. doi: 10.1016/j.ijcard.2007.08.098.
18. Raymond I, Groenning BA, Hildebrandt PR, Nilsson JC, Baumann M, Trawinski J, *et al*. The influence of age, sex and other variables on the plasma level of N-terminal pro brain natriuretic peptide in a large sample of the general population. Heart 2003;89:745–751. doi: 10.1136/heart.89.7.745.
19. Wieshammer S, Dreyhaupt J, Müller D, Momm F, Jakob A. Limitations of N-terminal pro-B-type natriuretic peptide in the diagnosis of heart disease among cancer patients who present with cardiac or pulmonary symptoms. Oncology 2016;90:143–150. doi: 10.1159/000443505.
20. Kragelund C, Gronning B, Kober L, Hildebrandt P, Steffensen R. N-terminal pro-B-type natriuretic peptide and long-term mortality in stable coronary heart disease. N Engl J Med 2005;352:666–675. doi: 10.1056/NEJMoa042330.
21. Varpula M, Pulkki K, Karlsson S, Ruokonen E, Pettilä V. FINNSEPSIS Study Group, FINNSEPSIS Study Group. . Predictive value of N-terminal pro-brain natriuretic peptide in severe sepsis and septic shock. Crit Care Med 2007;35:1277–1283. doi: 10.1097/01.CCM.0000261893.72811.0F.
22. Nagaya N, Nishikimi T, Okano Y, Uematsu M, Satoh T, *et al*. Plasma brain natriuretic peptide levels increase in proportion to the extent of right ventricular dysfunction in pulmonary hypertension. J Am Coll Cardiol 1998;31:202–208. doi: 10.1016/S0735-1097(97)00452-X.
23. Emdin M, Vittorini S, Passino C, Clerico A. Old and new biomarkers of heart failure. Eur J Heart Fail 2009;11:331–335. doi: 10.1093/eurjhf/hfp035.
24. Hsiao EC, Koniaris LG, Zimmers-Koniaris T, Sebald SM, Huynh TV, Lee SJ. Characterization of growth-differentiation factor 15, a transforming growth factor beta superfamily member induced following liver injury. Mol Cell Biol 2000;20:3742–3751. doi: 10.1128/mcb.20.10.3742-3751.2000.
25. Welsh JB, Sapinoso LM, Kern SG, Brown DA, Liu T, Bauskin AR, *et al*. Large-scale delineation of secreted protein biomarkers overexpressed in cancer tissue and serum. Proc Natl Acad Sci U S A 2003;100:3410–3415. doi: 10.1073/pnas.0530278100.
26. Danta M, Barber DA, Zhang HP, Lee-Ng M, Baumgart SWL, Tsai VWW, *et al*. Macrophage inhibitory cytokine-1/growth differentiation factor-15 as a predictor of colonic neoplasia. Aliment Pharmacol Ther 2017;46:347–354. doi: 10.1111/apt.14156.
27. Dong G, Zheng QD, Ma M, Wu SF, Zhang R, Yao RR, *et al*. Angiogenesis enhanced by treatment damage to hepatocellular carcinoma through the release of GDF15. Cancer Med 2018;7:820–830. doi: 10.1002/cam4.1330.
28. Koopmann J, Buckhaults P, Brown DA, Zahurak ML, Sato N, Fukushima N, *et al*. Serum macrophage inhibitory cytokine 1 as a marker of pancreatic and other periampullary cancers. Clin Cancer Res 2004;10:2386–2392. doi: 10.1158/1078-0432.CCR-03-0165.
29. Brown DA, Ward RL, Buckhaults P, Liu T, Romans KE, Hawkins NJ, *et al*. MIC-1 serum level and genotype: associations with progress and prognosis of colorectal carcinoma. Clin Cancer Res 2003;9:2642–2650. doi: 10.1159/000071148.
30. Gaggin HK, Szymonifka J, Bhardwaj A, Belcher A, De Berardinis B, Motiwala S, *et al*. Head-to-head comparsion of serial soluble ST2, growth differentiation factor-15, and highly-senitive troponin T measurements in patients with chronic heart failure. JACC Heart Fail 2014;2:65–72. doi: 10.1016/j.jchf.2013.10.005.
31. Anand IS, Kempf T, Rector TS, Tapken H, Allhoff T, Jantzen F, *et al*. Serial measurement of growth-differentiation factor-15 in heart failure: relation to disease severity and prognosis in the valsartan heart failure trial. Circulation 2010;122:1387–1395. doi: 10.1161/CIRCULATIONAHA.109.928846.
32. Lok DJ, Klip IT, Lok SI, Bruggink-André de la Porte PW, Badings E, van Wijngaarden J, *et al*. Incremental prognostic power of novel biomarkers (growth-differentiation factor-15, high-sensitivity C-reactive protein, galectin-3, and high-sensitivity troponin-T) in patients with advanced chronic heart failure. Am J Cardiol 2013;112:831–837. doi: 10.1016/j.amjcard.2013.05.013.
33. Sharma A, Stevens SR, Lucas J, Fiuzat M, Adams KF, Whellan DJ, *et al*. Utility of growth differentiation factor-15, a marker of oxidative stress and inflammation, in chronic heart failure: insights from the HF-ACTION study. JACC Heart Fail 2017;5:724–734. doi: 10.1016/j.jchf.2017.07.013.
34. Kempf T, Eden M, Strelau J, Naguib M, Willenbockel C, Tongers J, *et al*. The transforming growth factor-beta superfamily member growth-differentiation factor-15 protects the heart from ischemia/reperfusion injury. Circ Res 2006;98:351–360. doi: 10.1161/01.res.0000202805.73038.48.
35. Kempf T, von Haehling S, Peter T, Apostolovic S, Stanojevic D, Jovanovic I, *et al*. Prognostic utility of growth differentiation factor-15 in patients with chronic heart failure. J Am Coll Cardiol 2007;50:1054–1060. doi: 10.1016/j.jacc.2007.04.091.
36. Xu J, Kimball TR, Lorenz JN, Brown DA, Bauskin AR, Klevitsky R, *et al*. GDF15/MIC-1 functions as a protective and antihypertrophic factor released from the myocardium in association with SMAD protein activation. Circ Res 2006;98:342–350. doi: 10.1161/01.RES.0000202804.84885.d0.
37. Heger J, Schiegnitz E, von Waldthausen D, Anwar MM, Piper HM, Euler G. Growth differentiation factor 15 acts anti-apoptotic and pro-hypertrophic in adult cardiomyocyte. J Cell Physiol 2010;224:120–126. doi: 10.1002/jcp.22102.
38. Lankeit M, Kempf T, Dellas C, Cuny M, Tapken H, Peter T, *et al*. Growth differentiation factor-15 for prognostic assessment of patients with acute pulmonary embolism. Am J Respir Crit Care Med 2008;177:1018–1025. doi: 10.1164/rccm.200712-1786OC.
39. Nickel N, Jonigk D, Kempf T, Maegel L, Rische J, Laenger F, *et al*. GDF-15 is abundantly expressed in plexiform lesions in patients with pulmonary arterial hypertension and affects proliferation and apoptosis of pulmonary endothelial cells. Respir Res 2011;12:62. doi: 10.1186/1465-9921-12-62.
40. Meadows CA, Risbano MG, Zhang L, Geraci MW, Tuder RM, Collier DH, *et al*. Increased expression of growth differentiation factor-15 in systemic sclerosis-associated pulmonary arterial hypertension. Chest 2011;139:994–1002. doi: 10.1378/chest.10-0302.
41. Li G, Li Y, Tan XQ, Jia P, Zhao J, Liu D, *et al*. Plasma growth differentiation factor-15 is a potential biomarker for pediatric

pulmonary arterial hypertension associated with congenital heart disease. Pediatr Cardiol 2017;38:1620–1626. doi: 10.1007/s00246-017-1705-7.
42. Eindhoven JA, van den Bosch AE, Oemrawsingh RM, Baggen VJ, Kardys I, Cuypers JA, *et al*. Release of growth-differentiation factor 15 and associations with cardiac function in adult patients with congenital heart disease. Int J Cardiol 2016;202:246–251. doi: 10.1016/j.ijcard.2015.09.010.
43. Wollert KC, Kempf T, Peter T, Olofsson S, James S, Johnston N, *et al*. Prognostic value of growth-differentiation factor-15 in patients with non–ST-elevation acute coronary syndrome. Circulation 2007;115:962–971. doi: 10.1161/CIRCULATIONAHA.106.650846.
44. Adela R, Banerjee SK. GDF-15 as a target and biomarker for diabetes and cardiovascular diseases: a translational prospective journal of diabetes research. J Diabetes Res 2015;2015:490842. doi: 10.1155/2015/490842.
45. Foley PW, Stegemann B, Ng K, Ramachandran S, Proudler A, Frenneaux MP, *et al*. Growth differentiation factor-15 predicts mortality and morbidity after cardiac resynchronization therapy. Eur Heart J 2009;30:2749–2757. doi: 10.1093/eurheartj/ehp300.
46. Moore A, Brown DA, Fairlie WD, Pankhurst SL, Bauskin AR, Russell PK, *et al*. The transforming growth factor-beta superfamily cytokine macrophage inhibitory cytokine-1 is present in high concentrations in the serum of pregnant women. J Clin Endocrinol Metab 2000;85:4781–4788. doi: 10.1210/jcem.85.12.7007.
47. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. Am J Kidney Dis 2002;39:S1–266.
48. Liu LS. Writing Group of 2010 Chinese Guidelines for the Management of Hypertension. 2010 Chinese guidelines for the management of hypertension (in Chinese). Chin J Cardiol 2011;39:579–615. doi: 10.3760/cma.j.issn.0253-3758.2011.07.002.
49. American Diabetes Association. Diagnosis and classification of diabetes. Diabetes Care 2011;34:S62–S69. doi: 10.2337/dc11-S062.

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