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Additional Diagnostic Value of Growth Differentiation Factor-15 (GDF-15) to N-Terminal B-Type Natriuretic Peptide (NT-proBNP) in Patients with Different Stages of Heart Failure

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Background: Growth differentiation factor-15 (GDF-15) is a promising biomarker of cardiac remodeling. The purpose of this study was to explore the diagnostic value of plasma GDF-15 levels in different stages of heart failure (HF) and to assess the relationship with ventricular remodeling.

Material/Methods: We enrolled 219 HF patients from the Department of Cardiology in Tianjin Union Medical Center as the HF group and 32 healthy subjects as the control group. Circulating GDF-15, NT-proBNP, procollagen I C-terminal propeptide (PICP), and N-terminal procollagen III propeptide (PIIINP) levels were measured using ELISA. Associations between GDF-15 and clinical indicators in cardiac remodeling were assessed using receiver operating characteristic (ROC) curves and Spearman correlation. All the patients were followed up for 1 year.

Results: The level of plasma GDF-15 in HF patients was higher than in the control group (P<0.05) and increased with higher ACCF/AHA and NYHA classification (P<0.05). Patients with HFrEF had higher GDF-15 levels compared to patients with HFmrEF (P<0.05). GDF-15 and left ventricular mass index (LVMI) were significantly increased as early as the pre-clinical HF stage. Also, GDF-15 levels were positively correlated to LVMI (r=0.433, P<0.05), PICP (r=0.378, P<0.001) and PIIINP (r=0.382, P<0.001). ROC curves were constructed and GDF-15 plus NT-proBNP (AUC=0.905, 95%CI: 0.868–0.942, P<0.001) was superior to NT-proBNP (AUC=0.869, 95%CI: 0.825–0.913, P<0.001) in identifying HF. GDF-15 levels did not predict prognosis after a 1-year follow-up period.

Conclusions: GDF-15 combined with NT-proBNP significantly improves the accuracy of diagnosing HF. Plasma GDF-15 levels can indirectly reflect the degree of cardiac remodeling and fibrosis.

MeSH Keywords: Diagnosis • Growth Differentiation Factor 15 • Heart Failure • Ventricular Remodeling

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Background

Heart failure (HF), which is characterized by ventricular remodeling, neuroendocrine confusion, and abnormal peripheral blood distribution, is the terminal stage of cardiovascular disease [1]. Cardiovascular biomarkers exert an important role in diagnosis and assessment of HF [2]. Recently, several new biomarkers have been found that may add essential clinical information, such as atrial natriuretic peptide [3], brain natriuretic peptide (BNP) [2], N-terminal B-type natriuretic peptide (NT-proBNP) [4], N-terminal propeptide of type III procollagen [5], galectin-3 [6], suppression of tumorigenicity 2 [7], and growth differentiation factor 15 (GDF-15) [8]. In addition, N-terminal and C-terminal propeptides of collagen type I and III, the 2 major collagen types in the heart, including procollagen Type I C-terminal Peptide (PICP), procollagen 1 N-terminal peptide, procollagen 3 N-terminal peptide (PIIINP), and type I collagen telopeptide, can reflect collagen synthesis and degradation and serve as a serum biomarker of myocardial fibrosis [9].

GDF-15 was first reported in 1997 as a new member of the transforming growth factor-B family [10] and acts as a cardioprotective cytokine that inhibits cardiomyocyte hypertrophy, cell apoptosis, and myocardial remodeling. Plasma GDF-15 was found to have a close relationship with cardiovascular disease [11]. In cardiomyocytes, high expression of GDF-15 can be induced by a variety of cardiovascular diseases, such as ischemia-reperfusion injury, cardiac hypertrophic load, HF, and atherosclerosis, but it is not expressed in normal situations [12]. In subsequent studies, GDF-15 was found to have important clinical value in the pathophysiology of acute myocardial infarction [13], pulmonary embolism [14], tumor [15], heart failure [16], and other diseases. Moreover, recent studies have demonstrated that circulating GDF-15 is correlated with the severity of pulmonary fibrosis and myocardial fibrosis [17].

However, fewer studies have reports the relationships among HF staging, ejection fraction, ventricular remodeling, NT-proBNP, and GDF-15 in HF patients. Thus, we conducted a comprehensive study to evaluate the plasma GDF-15 levels in each stage of HF, and to provide useful information for diagnosis, prediction, and evaluation of HF patients.

Material and Methods

Study design

Our study enrolled 219 consecutive HF patients admitted to the Cardiology Department of Tianjin Union Medical Center from June 2014 to June 2016. Thirty-two subjects with cardiovascular risk factor (including age, smoking, obesity, dyslipidemia, hypertension, impaired glucose tolerance, and a family history of cardiovascular disease) selected from the physical examination center were enrolled during the same period as the control group. Baseline data, including demographic and clinical information, was recorded. The diagnosis of HF was based on the value of the biomarkers and validated by guidelines of the European Society of Cardiology (ESC) [18], and the HF classification was according to the functional NYHA classification and structural ABCD classification of the 2013 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) HF management guidelines [19]. Patients confirmed to have HF with an LVEF ≤40% were classified as having heart failure with reduced ejection fraction (HFrEF), and those with LVEF ≥50% were classified as having heart failure with preserved ejection fraction (HFpEF). HF with LVEF 40–49% was regarded as HF with mid-range ejection fraction (HFmrEF). Exclusion criteria included age less than 18 years, pregnancy or lactation, myocardiopathy, myocarditis, heart valve disease, acute myocardial infarction within the past 3 months, pulmonary emphysema, active infection or tumor, inflammatory disease or autoimmune disease, stroke, and severe renal insufficiency.

Biomarker measurement

Fasting venous blood was collected from the median cubital vein of the patients into a tube containing heparin and centrifuged at 3000 r/min for 10 min to separate plasma. The separated plasma was packed and stored at –80°C until analysis. Routine blood, total plasma cholesterol, low-density lipoprotein cholesterol, creatinine, and glycosylated hemoglobin were also assessed at baseline. GDF-15 was measured using ELISA kits from Elabscience Biotechnology Co., Ltd (Wuhan, China). NT-proBNP was measured by a Roche Diagnostics® electrochemiluminescent immunoassay (Roche Diagnostics, Mannheim, Germany). PICP and PIIINP concentrations were detected by the specific ELISA (Qiyi Biological Co., Shanghai, China) kits and performed according to the manufacturer's instructions. Detection of GDF-15 ranged from 23.44 to 1500 pg/ml, PICP ranged from 3.13 to 200 ng/ml, and PIIINP ranged from 0.1 to 10 ng/ml.

Echocardiography measurement

Echocardiography was performed for all enrolled patients (PhilipSonos5500; Phillips Healthcare, Amsterdam, Netherlands). Specialists trained in cardiac ultrasonography performed the examinations according to standard operating procedures in a quiet room at constant temperature. We recorded left atrium dimension (LAD), left ventricular end-diastolic dimension (LVEDD), left ventricular posterior wall thickness (LVPWT), interventricular septal thickness (IVST), and left ventricular ejection fraction (LVEF). Left ventricular mass (LVM) and left ventricular mass index (LVMI) were calculated using formulas recommended by Devereux [20].

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Table 1. General characteristics.

	Control group (n=32)	HF group (n=219)	*P*
Age (years)	66.94±6.04	69.95±11.91	0.160
Male (%)	50%	51.60%	0.866
HR (bpm)	71.72±6.69	78.84±13.87	0.005*
SBP (mmHg)	119.22±5.97	133.14±19.95	<0.001*
HGB (g/L)	149.56±14.98	128.26±23.84	<0.001*
HbAlc (%)	5.80 (5.60–6.00)	6.00 (5.80–7.15)	<0.001*
Cr (mg/L)	63.50 (55.25,72.75)	74 (61,99)	<0.001*
TG (mmol/L)	1.05 (0.86, 1.40)	1.18 (0.87, 1.55)	0.460
TC (mmol/L)	4.77±0.91	4.45±1.19	0.138
LDL-C (mmol/L)	3.05±0.57	2.73±0.76	0.023*
LVEDD (mm)	45.50 (44–47)	50 (45–58)	0.000*
LVMI (g/m^2)	75.82 (67.38–83.84)	110.86 (85.50–139.38)	<0.001*
LVEF (%)	60 (58.25–62)	50 (40–59)	<0.001*
NT-proBNP (pg/ml)	93.30 (69.49, 180.25)	1556.00 (302.35, 5239.50)	<0.001*
GDF-15 (pg/ml)	93.28 (78.50, 130.43)	188.12 (144.85, 262.54)	<0.001*
PICP (ng/ml)	45.86±23.86	184.05±79.56	<0.001*
PIIINP (ng/ml)	0.31±0.14	1.19±0.42	<0.001*
Adverse events (%)		50 (22.8)	

* Significant difference compared to the control group (P<0.05). HF – geart failure; HR – heart rate; SBP – systolic blood pressure; HbALc – hemoglobin A1c; Cr – creatinine; TG – triglyceride; TC – total cholesterol; LDL-C – low density lipoprotein cholesterol; LVEDD – left ventricular end diastolic dimension; LVMI – left ventricular mass index; LVEF – left ventricular ejection fraction; NT-proBNP – N-terminal pro-B-type natriuretic peptide; GDF-15 – growth differentiation factor-15; PICP – Procollagen Type I Cterminal Peptide; PIIINP – Procollagen III N-termi.

LVM (g)=1.04[(LVEDD+LVPWT+IVST)^3–LVEDD^3]–13.6. LVMI (g/m^2)=LVM/BSA.

Follow-up and outcomes

All the subjects were followed up regularly for 1 year (12±1 months). The regular schedule of visits included outpatient visits every 3 months, telephone interviews, and analysis of rehospitalization. The primary endpoint of study was all-cause mortality and rehospitalization due to HF.

Statistical analysis

All statistical analyses were performed using SPSS software (version 19.0; IBM SPSS, Armonk, NY, USA). The data are presented as percentage, means ± standard deviation, or median and interquartile ranges (25th to 75th percentile; IQR). The measurement data and count data are reported using means ± standard deviation and percentages, respectively. The *t* test and χ^2 test were used to analyze measurement data and count data, respectively. Spearman rank correlation analysis was used to estimate correlations between different variables. Statistical analysis of HF diagnosis was performed using the receiver operating characteristic (ROC) curve. The results are presented as area under the curve (AUC) and 95% confidence interval (CI). P values of <0.05 were considered statistically significant.

Results

General characteristics

The clinical details of patients are shown in Table 1. There were no significant differences in age, sex, TG, or TC between groups (P>0.05). The levels of SBP, HR, HGB, LVEDD, LVMI, PICP, and PIIINP in HF patients was significantly higher than in the control group (P<0.05). The level of LVEF and LDL-C in the HF group was lower than in the control group (P<0.05).

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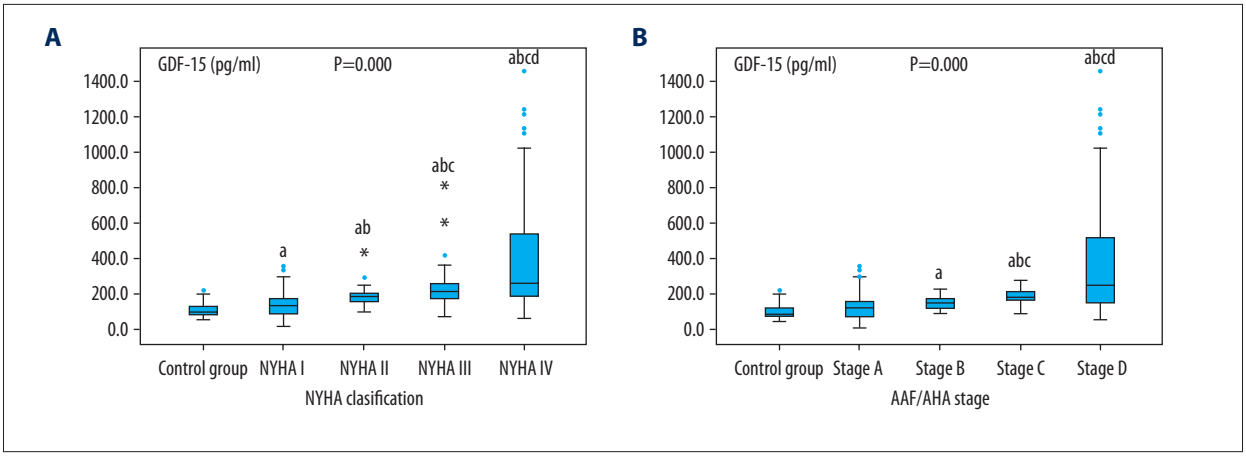

Figure 1. The plasma levels of GDF-15 in patients with HF categorized according to functional NYHA classification (**A**) and structural ACCF/AHA staging (**B**). a: compared with the control group; b: compared with NYHA I or stage A; c: compared with NYHA II or stage B; d: compared with NYHA III or stage C. Data are presented as medians with 25th and 75th percentiles. P<0.05 was considered statistically significant.

The concentration of GDF-15, NT-proBNP, PICP, and PIIINP in the HF group was significantly higher than in the control group (P<0.001). There were 50 adverse events in our study. The all-cause mortality rate was 3.2%, and the rate of rehospitalization for heart failure was 18.3%.

Levels of GDF-15 are associated with the progression of HF

The ACCF/AHA guideline points out that the GDF-15 levels are associated with NYHA classification and HF stages. In our study, the concentration of GDF-15 in patients classified to NYHA III [median 210.29, IQR (168.80-260.97) pg/mL, n=47] and NYHA IV [median 262.80, IQR (182.46–545.33) pg/mL, n=75] were significantly higher than those of NYHA I [median 131.65, IQR (84.34–172.72) pg/mL, n=58] and II [median 181.51, IQR (152.37–198.32) pg/mL, n=39] (P>0.05) (Figure 1A). Specifically, the GDF–15 levels started to rise from structural ACCF/AHA class B [median 154.56, IQR (121.35–181.70) pg/mL, n=20], which is the pre-clinical stage, compared to the control group. GDF-15 levels were significantly higher in patients classified as stage D [median 259.50, IQR (159.96–520.63) pg/mL, n=97] compared to those classified as stage C [median 187.79, IQR (168.85–220.47) pg/mL, n=62], stage B, and stage A [median 126.92, IQR (71.13–166.91) pg/mL, n=39] (P>0.05) (Figure 1B). In addition, LVMI showed a tendency to vary according to ACCF/AHA classification. The level of LVMI start to rise from stage B [median 99.29, IQR (81.87–124.35) g/m^2], and it was significantly higher compared to stage A [median 78.65, IQR (72.02–93.05) g/m^2] and the control group [median 75.82, IQR (67.38–83.84) g/m^2] (P>0.05), in keeping with GDF-15 (Figure 2).

GDF-15 levels were inversely proportional to LVEF. Patients with HFrEF [median 315.73, IQR (190.84–545.33) pg/mL, n=56] had

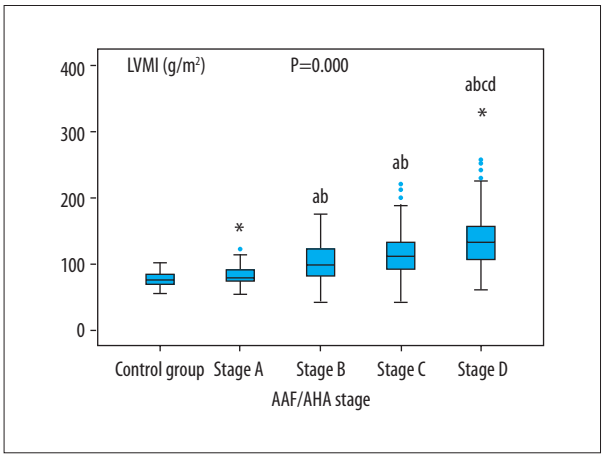

Figure 2. The levels of LVMI in patients categorized according to structural ACCF/AHA HF staging. LVMI – left ventricular mass index. a: compared with the control group; b: compared with stage A; c: compared with stage B; d: compared with stage C. Data are presented as medians with 25th and 75th percentiles. P<0.05 was considered statistically significant.

higher GDF-15 levels compared to patients with HFmrEF [median 209.00, IQR (164.93–266.92) pg/mL, n=53] and those with HFpEF [median 158.14, IQR (116.99-209.62) pg/mL, n=110]. The plasma levels of GDF-15 in all subgroups differed significantly (P<0.05) (Figure 3). These data indicate that the plasma level of GDF-15 is closely related to the progression of HF.

Diagnostic value of GDF-15 in association with NT-proBNP for HF

After we verified the closely relationship between GDF-15 and the progression of heart failure, we further explored the

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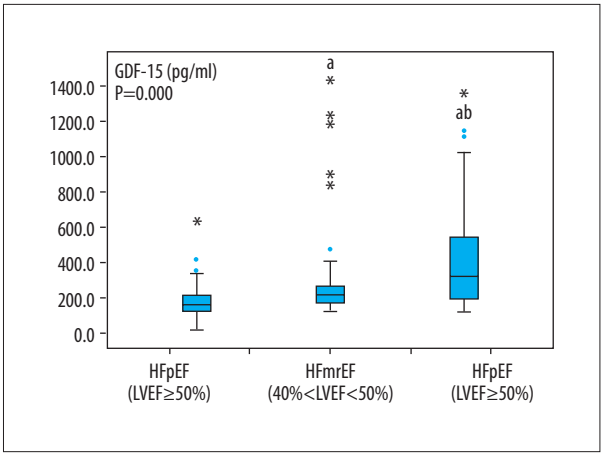

Figure 3. The plasma levels of GDF-15 in different LVEF groups. HFpEF – HF with reduced ejection fraction; HFmrEF – HF with mid-range ejection fraction; HFrEF – HF with reduced ejection fraction. a: compared with HFpEF; b: compared with HFmrEF. Data are presented as medians with 25th and 75th percentiles. P<0.05 was considered statistically significant.

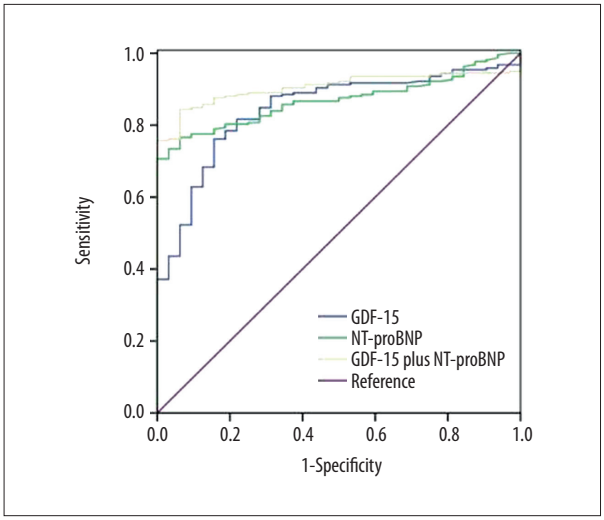

Figure 4. ROC curve of GDF-15 and NT-proBNP to diagnose HF. ROC – receiver operating characteristic curves.

diagnostic value when compared with NT-proBNP. The area under the curve (AUC) for GDF-15 and NT-proBNP was 0.844 (95%CI, 0.782–0.906, P<0.001) and 0.869 (95%CI, 0.825–0.913, P<0.001), respectively. An ROC curve for GDF-15 plus NT-proBNP was also constructed, and the AUC was 0.905 (95%CI, 0.868–0.942, P<0.001) (Figure 4). The AUC for the combined biomarkers was superior to the AUC of NT-proBNP alone in diagnosing HF. This result means that the combination of GDF-15 plus NT-proBNP had greater sensitivity and specificity in diagnosing HF (Table 2).

Association between GDF-15 and clinical indicators of HF

As shown in Table 3, GDF-15 were positively correlated with LVEDD (r= 0.391, P<0.001), LVMI (r=0.433, P<0.001), and NT-proBNP levels (r= 0.532, P<0.001), and was negatively correlated with LVEF (r=–0.543, P<0.001). However, GDF-15 levels did not correlate with age (r=0.086, P=0.173). As the biomarkers for the synthesis of type I collagen and type III collagen, both PICP and PIIINP levels were significantly elevated in HF patients and were positively correlated with GDF-15. These results suggest that GDF-15 is involved in the process of ventricular remodeling and cardiac fibrosis.

Table 2. Indicators of ROC curve for HF diagnosis.

	AUC	95% CI	Sensitivity	Specificity	*P*
GDF-15	0.844	0.782–0.906	0.761	0.844	<0.001
NT-proBNP	0.869	0.825–0.913	0.708	1.000	<0.001
GDF-15 plus NT-proBNP	0.905	0.868–0.942	0.844	0.938	<0.001

P<0.05 were considered statistically significant. HF – heart failure; ROC – receiver operating characteristic curves; AUC – area under the curve; CI – confidence interval; NT-proBNP – N-terminal pro-B-type natriuretic peptide; GDF-15– growth differentiation factor-15.

Table 3. Correlation between plasma GDF-15 level and clinical indicators in HF.

	Age	LVEDD	LVMI	LVEF	NT-proBNP	PICP	PIIINP
r	0.086	0.391	0.433	–0.543	0.532	0.378	0.382
P	0.173	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

P<0.05 were considered statistically significant. HF – heart failure; LVEDD – left ventricular end diastolic dimension; LVMI – left ventricular mass index; LVEF – left ventricular ejection fraction; NT-proBNP – N-terminal pro-B-type natriuretic peptide; GDF-15– growth differentiation factor-15; PICP – Procollagen Type I Cterminal Peptide; PIIINP – Procollagen III N-termi.

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Table 4. Indicators of ROC curve for prognostic outcomes after 1-year.

	AUC	95% CI	Sensitivity	Specificity	*P*
GDF-15	0.656	0.549–0.764	0.436	0.898	0.003
NT-proBNP	0.800	0.721–0.879	0.821	0.703	<0.001
GDF-15 plus NT-proBNP	0.816	0.740–0.893	0.744	0.781	<0.001

P<0.05 were considered statistically significant. ROC – receiver operating characteristic curves; AUC – area under the curve; CI – confidence interval; NT-proBNP – N-terminal pro-B-type natriuretic peptide; GDF-15– growth differentiation factor-15.

Prognostic value of GDF-15 and NT-proBNP in predicting 1-year adverse events

The ROC curve of GDF-15, NT-proBNP, and GDF-15 plus NT-proBNP was constructed to predicting 1-year adverse events (all-cause mortality and rehospitalization). The AUC for GDF-15 plus NT-proBNP (AUC 0.816 95%CI, 0.740-0.893, P<0.001) was superior to GDF-15 (AUC 0.656, 95%CI, 0.549–0.764, P=0.003) and NT-proBNP (AUC 0.800, 95%CI, 0.721–0.879, P<0.001) alone in forecasting adverse events (Figure 5). However, the predictive value of combined biomarkers compared to that of NT-proBNP alone increased by only a little in specificity, and no increase was found in sensitivity (Table 4). Therefore, GDF-15 levels did not completely reveal prognostic information with regard to outcomes.

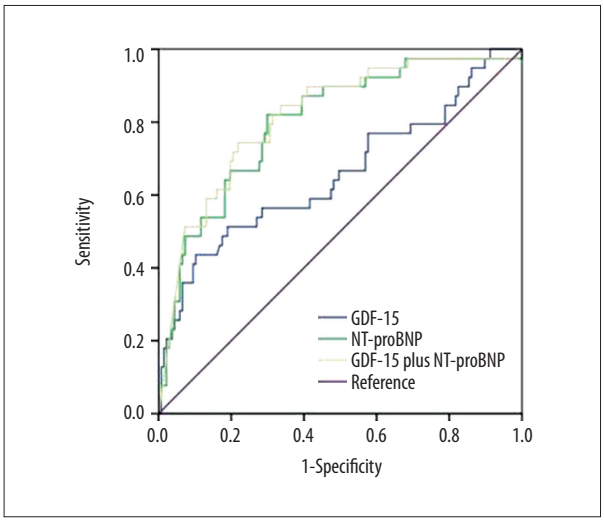

Figure 5. ROC curve of GDF-15 and NT-proBNP for predicting outcomes of 1-year follow-up. GDF-15 (blue), NT-proBNP (green), GDF-15 plus NT-proBNP (yellow), reference curve (purple). ROC – receiver operating characteristic curves.

Discussion

HF is a clinically irreversible disease, with ventricular remodeling occurring throughout its progression. Evaluation of cardiac function in HF patients is usually divided by NYHA classification. Although it is susceptible to subjective physician factors, it can clearly show exercise tolerance and evaluate cardiac function. Patients with pre-HF are not easily found and diagnosed, so treatment is often delayed. For a more comprehensive study of the cases, we also selected ACCF/AHA HF staging as inclusion criteria. With aggravated ventricular remodeling and deterioration of clinical symptoms, the process of HF is divided into stages A, B, C, and D (from the pre-HF stage to the refractory HF stage). The guidelines for acute and chronic HF were updated in 2016 by the European Society of Cardiology (ESC) with a new classification of HFpEF, HFmrEF, and HFrEF based on LVEF for diagnosis and treatment of HF. In our study, we performed a comparison and combination of plasma GDF-15 and NT-proBNP among these subgroups to evaluate the diagnosis of HF and prognosis of 1-year adverse events, including all-caused death and rehospitalization.

NT-proBNP is an independent factor for predicting clinical adverse events in patients with HF [21] and is recommended for use in diagnosis, risk stratification, and monitoring of HF. However, it does not have all the advantages of an ideal biomarker. NT-proBNP is affected by age, sex, obesity, and other factors [22]. It is also promoted by acute lung ligation, cardiomyopathy, arrhythmia, and other diseases [23], so NT-proBNP has some shortcomings in assessing the diagnosis of HF. It is absolutely essential to ascertain new biological indicators assisting BNP in diagnosis HF. In our study, the plasma level of GDF-15 was associated with worse stages of NYHA classification and ACCF/AHA classification of HF. In correlation analysis, GDF-15 levels were negatively correlated with LVEF. Furthermore, we found GDF-15 levels were increased significantly in HFrEF compared with HFpEF and HEmrEF, so higher GDF-15 levels discriminated patients with a predominant HFrEF from those with a normal left ventricular function. With the deterioration of heart function and the progress of staging, the difference between GDF-15 and the control group gradually increased. These results suggest that HF patients had significantly increased GDF-15 levels compared to the control group, indicating that GDF-15 can be used as a biomarker for assessing HF. To visually demonstrate the value of GDF-15, we performed

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ROC curve of diagnosis and prognosis. Combining GDF-15 with NT-proBNP revealed elevated AUC and a better overall sensitivity and specificity to diagnose HF compared to NT-proBNP alone. However, after 1 year of follow-up, plasma GDF-15 did not display prognostic outcomes (including all-caused death and rehospitalization), which is inconsistent with results of Chan et al. [24] showing that GDF-15 can function as an independent predictor of heart failure. This discrepancy may be related to the small sample size of our study.

Cardiac remodeling, which is the process of structural and functional changes in the left ventricle, is a precursor of clinical HF [25,26]. Clinically, cardiac remodeling is mainly characterized as the change of LVMI, LVPWT, and LVEDD. Because an effective means of reversing ventricular remodeling has not yet been found, it becomes critical to slow the rate of ventricular remodeling. Several studies had revealed that GDF-15 is associated with ventricular remodeling after myocardial infarction, such as unstable angina, non-ST-elevation myocardial infarction, and ST-elevation myocardial infarction [27–29]. Kempf et al. [30] concluded that GDF-15 had a cardiac-protective effect in the ischemia-reperfusion process. In our study, we found the plasma GDF-15 levels and LVMI were significantly increased beginning with stage B (pre-clinical HF stage) and there was a positive correlation between them. This further confirmed that ventricular remodeling had been quietly occurring in the pre-clinical stage, and GDF-15 had also been shown great value in this period. The changes of left ventricular structure and function elevated PICP and PIIINP, indicating that GDF-15 may have been related to the process of ventricular remodeling and cardiac fibrosis in HF. Overall, these results may provide a unique value for GDF-15 to judge and diagnosis HF combined with NT-proBNP.

Potential limitations of this study need to be acknowledged. The control group was relatively small because it was limited to our research center. However, the professor of statistics believes that the 2 sets of data are comparable (a sample size greater than 30 can be considered moderate size). Differences in kit sources and certain drugs may affect the test result of GDF-15. GDF-15 was measured only 1 time (at admission), so we did not know how it interacted with time and how it fluctuated over time during the progression of HF. This is also an issue that we will explore in future research.

Conclusions

Our study indicated that plasma GDF-15 levels were involved in higher stages of NYHA classification and ACCF/AHA classification as well as lower LVEF subgroup. Combined GDF-15 and NT-proBNP has a synergistic effect on diagnosis of HF. Moreover, GDF-15 may play a role in the pathophysiology of ventricular remodeling and myocardial fibrosis. However, GDF-15 levels did not show prognostic information with respect to prognostic outcomes after 1 year.

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