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Original Article

Level and clinical significance of serum bFGF in patients with ischemic cardiomyopathy

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Abstract: Objective: To detect the level of serum basic fibroblast growth factor (bFGF) in patients with ischemic cardiomyopathy (ICM) and analyze its clinical significance. Methods: This is a prospective study. From June 2018 to June 2021, 244 patients diagnosed with ICM in the department of cardiology of Tianyou Hospital Affiliated to Wuhan University of Science and Technology and 244 healthy people who underwent physical examination in the physical examination center of our hospital during the same period were enrolled as the research subjects. Serum bFGF level was measured by ELISA kit, and the ICM patients were divided into a high bFGF group (180 cases) and a low bFGF group (64 cases) according to the cut-off value 56.83 obtained from X-tile software analysis, and the clinical data of the two groups were compared. In addition, according to the 12-month survival, the patients were grouped into a poor prognosis group (56 cases) and a good prognosis group (188 cases). Then, univariate and multivariate proportional hazards model (COX regression) analyses were applied to analyze the influencing factors of poor prognosis in ICM patients. Results: In the ICM group, there were more patients with hypertension and diabetes, and patients had higher levels of HbA1c, blood urea nitrogen, creatinine and uric acid, and lower levels of eGFR and bFGF than patients in the control group ($P<0.05$). The 12-month endpoint event rate in the low bFGF group was 54.69%, which was significantly higher than 11.67% in the high bFGF group ($P<0.05$). The left ventricular ejection fraction (LVEF) in the low bFGF group was significantly lower than that in the high bFGF group, and the bFGF group also had more patients with cardiac function grade IV ($P<0.05$). Multivariate COX regression analysis showed that age, diabetes, LVEF and low bFGF were independent influencing factors of poor prognosis in patients with ICM ($P<0.05$). After adjusting for age, diabetes and LVEF, patients with low bFGF had a higher risk of poor prognosis than those with high bFGF (HR=4.416, 95 CI%: 1.977-9.863, $P<0.05$). Conclusion: The serum expression of bFGF in ICM patients is low, and the risk of poor prognosis is higher in patients with low bFGF, suggesting that serum bFGF level has a certain value in the prognosis evaluation of ICM patients.

Keywords: Ischemic cardiomyopathy, basic fibroblast growth factor, prognosis, left ventricular ejection fraction

Introduction

With the continuous acceleration of urbanization, human lifestyles have undergone tremendous changes, and the morbidity and mortality of cardiovascular diseases have continued to increase. Attention must be paid to the prevention and control of cardiovascular diseases [1]. Ischemic cardiomyopathy (ICM), caused by severe stenosis of coronary atherosclerotic lesions, is the terminal stage of coronary atherosclerotic heart disease [2], and because most of the patients are elderly, with declined physical function, plus complex clinical manifestations, it is difficult to evaluate the disease condition. Chronic and long-term myocardial ischemia and hypoxia in patients with ICM can cause cell damage, apoptosis, necrosis and diffuse fibrosis, resulting in changes in cardiac structure and decreased cardiac function, with cardiac enlargement, arrhythmia and heart failure as the main clinical manifestations [3]. Multi-vessel disease, hyperstenosis and complete occlusion are challenges in advanced coronary heart diseases that endanger patients with ICM [4].

A survey shows that the incidence of coronary heart diseases in people over 40 years old is 10%, most of which can be treated, but some of them progress to ICM. ICM progresses slowly in the early stage, but develops rapidly once heart failure occurs. The 5-year mortality is high, which seriously endangers the life of the patients [5, 6]. Some metabolic markers such as enzymes [7], serum inflammatory factors [8] and microRNA [9] are abnormally expressed in the serum of ICM patients. However, there are few studies on the effect of serum protein factors on ICM patients. Basic fibroblast growth factor (bFGF or FGF-2), a member of the fibroblast growth factor family, regulates multiple behaviors during cell development, including proliferation and morphogenesis, through a complex signal transduction system and apoptosis [10]. bFGF is highly expressed in the nervous system and heart, and is a growth factor with cardioprotective effects, which is beneficial to the survival and growth of cardiomyocytes. As a highly active biological factor, bFGF can induce endothelial and smooth muscle cell proliferation and angiogenesis in vivo, including endothelial cell migration and proliferation, vascularization and connection to pre-existing vascular networks [11]. bFGF can also reduce cardiomyocyte apoptosis, improve neovascularization and reduce the deposition of interstitial fibrosis [12]. Brief infusion of bFGF in the myocardial ischemia/reperfusion (I/R) model may promote the recovery of cardiovascular function [13, 14]. So, it is speculated that serum bFGF levels may have a certain value in the prognosis evaluation of ICM patients. In this study, the serum level of bFGF in ICM patients was measured by enzyme-linked immunosorbent assay (ELISA), to compare the differences in serum bFGF levels in patients with different prognosis and analyze its clinical value.

Materials and methods

General data

In this study, 244 patients diagnosed with ICM in the Department of Cardiology of Tianyou Hospital Affiliated to Wuhan University of Science and Technology from June 2018 to June 2021 were prospectively selected as subjects, including 142 males and 102 females, aged 31-91 years, with an average age of (62.95± 9.93) years. Another 244 healthy people who underwent physical examination in the physical examination center were enrolled as controls, including 138 males and 106 females, aged 36-82 years, with an average age of (61.35± 8.76) years.

After admission, we collected the basic information of all research subjects, such as height, weight, history of hypertension, history of diabetes, smoking history, recent history of major surgery, severe trauma, stroke and recent drug use. All the patients received laboratory tests including routine blood, routine urine, liver function, renal function, electrolytes, blood lipids, blood sugar and myocardial injury indicators. In addition, imaging examinations such as cardiac function classification (New York Heart Association (NYHA) Functional Classification) echocardiography, cervical vascular ultrasound, electrocardiogram and coronary angiography were performed. This study was approved by Tianyou Hospital Affiliated to Wuhan University of Science and Technology Ethics Committee (201805534).

Inclusion criteria

(1) Diagnostic criteria of ICM [15]: There was clear evidence of myocardial ischemia or myocardial necrosis, including previous myocardial infarction or acute coronary syndrome, previous history of vascular reconstruction such as percutaneous coronary intervention or coronary artery bypass grafting surgery, clinical symptoms of angina pectoris, objective evidence of myocardial ischemia (electrocardiogram indicated myocardial necrosis, echocardiography indicated signs of ventricular wall motion weakening or disappearance) or coronary stenosis indicated by coronary computed tomography angiography. Cardiac enlargement was indicated by echocardiography or physical examination. There were clinical symptoms or laboratory evidence of cardiac insufficiency. Coronary heart disease complications such as ventricular septal perforation, ventricular aneurysm, mitral regurgitation due to papillary muscle insufficiency, and other heart diseases or other causes of heart enlargement and heart failure were excluded. (2) The health examinees were those who underwent regular physical examination, and had no history of tumor, cardio cerebrovascular disease, and no positive

symptoms or signs. (3) Patients and their families signed an informed consent.

Exclusion criteria

(1) Patients with acute myocardial infarction, myocarditis, pericarditis, moderate to severe coronary myocardial bridge and other causes of cardiomyopathy; (2) Patients with malignant tumor, blood system disease, pulmonary embolism, history of lower extremity venous thrombosis, abnormal thyroid function, connective tissue disease, malnutrition or severe infection; (3) Patients with pacemaker implantation; (4) Patients with a recent history of severe trauma, gastrointestinal bleeding, major surgery or stroke; (5) Patients with severe abnormal liver function: alanine aminotransferase and aspartate aminotransferase more than 3 times the upper limit of normal; (6) Patients who were taking drugs such as carbamazepine, phenytoin, methotrexate; (7) Patients with incomplete data.

Serum collection

The cubital venous blood was collected from the healthy subjects and ICM patients with dilated cardiomyopathy in the morning after 12-h fasting. The blood samples were put into the EDTA anticoagulant blood collection tubes and sent to laboratory for relevant examinations. The EDTA anticoagulation blood collection tubes were then retrieved from the laboratory, and the remaining blood was centrifuged at 3000 r/min for 15 minutes to collect the supernatant. After the supernatant was sealed in a 1.5 mL EP tube and marked, it was stored in a -80°C refrigerator until testing.

Echocardiography

All patients underwent echocardiography (ultrasound diagnostic equipment: Philips, IE33 and CX50), with probe frequency of 2 MHz and 4 MHz. During the examination, the patients were in left lateral decubitus or supine position, and they were instructed to breathe calmly. The long-axis, short-axis, five-chamber and four-chamber views of the left ventricle were scanned. The structure and thickness of the ventricular wall were observed, and the left ventricular end-systolic diameter (LVESD), left ventricular end-diastolic diameter (LVEDD), left ventricular ejection fraction (LVEF), left atrial diameter (LAD) were measured.

Measuring serum bFGF level

Level of bFGF in serum samples were measured using bFGF detection ELISA kits (R&D Systems, Minneapolis, MN, United States). The procedures were according to the instructions of the kit. Purified human bFGF coated microplates were used to make a solid phase carrier. Specimens or standard products and bFGF specific antibodies were added to the microplates coated with human bFGF successively, and then incubated after mixing. After thorough washing, substrate TMB was used for color rendering. TMB was finally yellow, and the color depth was negatively correlated with the bFGF in the sample. Then, the absorbance (OD) value was measured with an enzyme marker at the wavelength of 450 nm to calculate the sample concentration. All operations were performed by the same researcher according to the kit instructions to minimize errors.

Prognosis

Patients were divided into a poor prognosis group (n=56) and a good prognosis group (n=188) according to whether the end point event occurred within 1 year (the end point event was all-cause death, including non-sudden cardiac death and sudden cardiac death). There were 34 males and 22 females in the poor prognosis group, and 108 males and 80 females in the good prognosis group.

Statistical processing

Statistical analysis was performed using SPSS 25.0 software (IBM). Continuous variables that met a normal distribution were expressed as mean ± standard deviation, and an independent-sample t-test was used for comparisons. Categorical variables were expressed as cases (percentages) and expressed as n (%), and Chi-square (χ^2) test were used for comparison between groups. The bFGF levels of patients were stratified by X-tile software. COX regression analysis was used to evaluate the influencing factors of poor prognosis in patients with ICM. $P<0.05$ was considered statistically significant.

Table 1. Comparison of general data between the ICM group and the control group

Index	Control group (n=244)	ICM group (n=244)	t/χ^2	*P*
Age (years)	61.35±8.76	62.95±9.93	1.887	0.060
Sex	138 (56.55)	142 (58.20)	0.134	0.714
BMI (kg/m^2)	24.92±5.33	25.22±4.92	0.646	0.519
Smoking	102 (41.80)	118 (48.36)	2.119	0.145
Hypertension	84 (34.42)	146 (59.84)	31.612	<0.001
Diabetes	18 (7.38)	74 (30.33)	42.006	<0.001
Albumin (g/L)	38.65±10.11	37.25±12.42	1.366	0.173
TC (mm/Hg)	4.32±0.83	4.36±1.31	0.403	0.687
TG (mm/Hg)	1.43±0.50	1.45±0.26	0.554	0.580
LDL-C (mmol/L)	2.54±0.71	2.57±0.75	0.454	0.650
HDL-C (mmol/L)	1.15±0.33	1.13±0.34	0.659	0.510
HbA1c (%)	5.97±1.12	6.54±1.84	4.133	<0.001
Urea nitrogen (mmol/L)	5.09±1.09	8.87±2.92	18.944	<0.001
Creatinine (μmol/L)	77.55±11.36	107.81±26.58	16.352	<0.001
Uric acid (μmol/L)	332.95±74.54	440.22±143.86	10.342	<0.001
eGFR (mL/(min·1.73m^2))	84.32±19.95	72.55±21.11	6.330	<0.001
bFGF (pg/mL)	205.63±55.18	71.77±21.14	35.385	<0.001

Note: ICM, ischemic cardiomyopathy; BMI, body mass index; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate; bFGF, basic fibroblast growth factor.

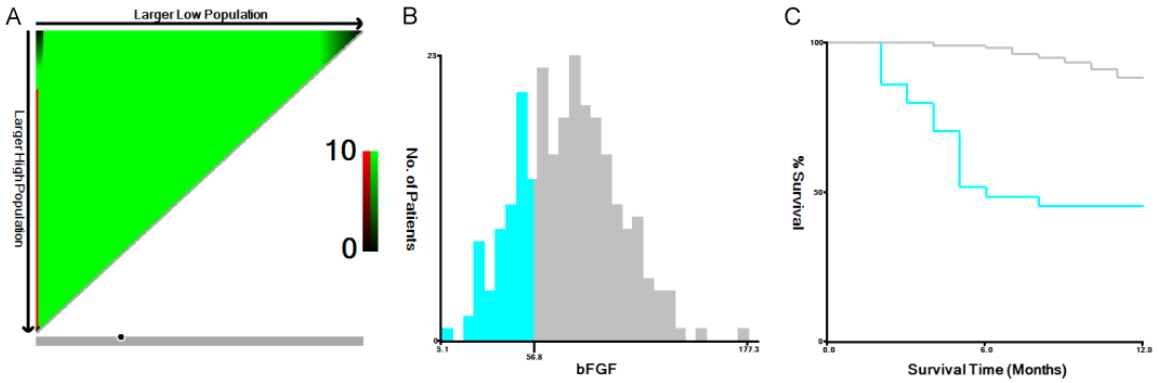

Figure 1. Identification of optimal cutoff value of bFGF at diagnosis using the X-tile program. (A) The cutoff value of bFGF at diagnosis was determined using the software with the black dots. Histograms (B) and K-M curves (C) were established based on the cutoff value determined. The optimal diagnostic cutoff value was 56.83 pg/mL. bFGF, basic fibroblast growth factor.

Results

Comparison of general data between the ICM group and the control group

In the ICM group, there were more patients with hypertension and diabetes, and the patients had higher levels of HbA1c, blood urea nitrogen, creatinine and uric acid than patients in the control group (P<0.05), but the levels of eGFR and bFGF were significantly lower in the ICM group than those in the control group (P<0.05) (**Table 1**).

Identification of bFGF cutoff value

The bFGF data of the ICM patients were analyzed using X-tile software. As shown in **Figure 1**, 56.83 pg/mL was the optimal cut-off value for the diagnosis of bFGF. Therefore, patients were subsequently divided into a high bFGF group (bFGF>56.83 pg/mL, n=180) and a low bFGF group (bFGF≤56.83 pg/mL, n=64). The 12-month endpoint event rate in the low bFGF group was 54.69%, which was significantly higher than 11.67% in the high bFGF group (*P*<0.05).

Table 2. Relationship between serum bFGF level and clinical data of ICM patients

Index	High bFGF group (n=180)	Low bFGF group (n=64)	t/χ^2	*P*
Age (years)	62.08±9.14	65.41±11.59	2.326	0.021
Sex	105 (43.03)	37 (15.16)	0.005	0.942
BMI (kg/m^2)	24.98±4.90	25.89±4.93	1.274	0.204
Smoking	88 (36.07)	30 (12.30)	0.077	0.782
Hypertension	110 (45.08)	36 (14.75)	0.464	0.496
Diabetes	72 (29.51)	20 (8.20)	1.539	0.215
Albumin (g/L)	37.26±12.51	37.20±12.26	0.033	0.974
TC (mm/Hg)	4.36±1.37	4.36±1.10	0.000	1.000
TG (mm/Hg)	1.45±0.20	1.44±0.38	0.265	0.791
LDL-C (mmol/L)	2.55±0.75	2.63±0.76	0.730	0.466
HDL-C (mmol/L)	1.15±0.36	1.07±0.30	1.592	0.113
HbA1c (%)	6.39±1.83	6.67±1.82	1.053	0.293
Urea nitrogen (mmol/L)	8.94±2.90	8.66±2.98	0.659	0.511
Creatinine (μmol/L)	108.46±27.13	105.99±25.09	0.638	0.524
Uric acid (μmol/L)	440.24±145.45	440.15±140.42	0.004	0.997
eGFR [mL/(min·1.73 m^2)]	73.25±20.43	70.59±22.95	0.866	0.388
LVEF (%)	37.68±8.56	25.10±7.80	10.329	<0.001
LVEDD (mm)	59.01±16.62	63.90±20.88	1.885	0.061
LVESD (mm)	45.56±13.45	48.10±16.93	1.209	0.228
LAD (mm)	44.17±12.73	42.80±13.16	0.733	0.464
NYHA class				
II-III	171 (95.00)	41 (64.06)	39.658	<0.001
IV	9 (5.00)	23 (35.94)		

Note: ICM, ischemic cardiomyopathy; BMI, body mass index; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate; bFGF, basic fibroblast growth factor; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LAD, left atrial diameter; NYHA, New York Heart Association Functional Classification.

The relationship between serum bFGF level and clinical data of ICM patients

The LVEF in the low bFGF group was significantly lower than that in the high bFGF group (P<0.05), and patients in the low bFGF group had older age and higher NYHA class than those in the high bFGF group (P<0.05) (**Table 2**). LVEF and bFGF levels were positively correlated (r=0.816, P<0.05).

Univariate analysis of poor prognosis in patients with ICM

The clinical indicators that may affect the poor prognosis of the ICM patients and the indicators with P<0.05 in **Table 2** were used as exposure factors to analyze their relationship with the poor prognosis of ICM. As shown in **Table 3**, age, hypertension, diabetes, LVEF and bFGF were associated with poor prognosis of ICM (P<0.05).

Multivariate analysis of poor prognosis in patients with ICM

The factors with P<0.05 in **Table 3** were used as independent variables (age, LVEF were entered with specific values; hypertension: no =0, yes =1; diabetes: no =0, yes =1; bFGF: >56.83=0, ≤56.83=1) to perform multivariate COX regression analysis. As shown in **Table 4**, age, diabetes, LVEF and low bFGF were independent risk factors for poor prognosis in patients with ICM (P<0.05). After adjusting for age, diabetes, and LVEF, patients with low bFGF had a higher risk of poor prognosis than those with high bFGF (HR =4.416, 95 CI%: 1.977-9.863, P<0.05).

Discussion

Despite the continuous development of medical technology, the prognosis of ICM has not improved significantly. Therefore, it is urgent to

Table 3. Univariate analysis of poor prognosis in patients with ICM

Index	Poor prognosis (n=56)	Good prognosis (n=188)	t/χ^2	*P*
Age (years)	70.50±10.32	60.70±8.64	7.114	<0.001
Hypertension	22 (9.02)	124 (50.82)	12.772	<0.001
Diabetes	32 (13.11)	42 (17.21)	24.733	<0.001
Albumin (g/L)	36.68±10.61	37.41±12.94	0.385	0.700
TC (mm/Hg)	4.38±1.14	4.36±1.36	0.100	0.920
TG (mm/Hg)	1.46±0.50	1.44±0.12	0.504	0.615
LDL-C (mmol/L)	2.58±0.81	2.57±0.74	0.087	0.931
HDL-C (mmol/L)	1.12±0.31	1.14±0.35	0.385	0.701
HbA1c (%)	6.56±1.83	6.54±1.85	0.071	0.943
Urea nitrogen (mmol/L)	8.91±2.91	8.86±2.92	0.113	0.910
Creatinine (μmol/L)	108.05±24.89	107.75±27.12	0.074	0.941
Uric acid (μmol/L)	441.23±140.35	439.91±145.25	0.060	0.952
eGFR (ml/(min·1.73m^2))	68.51±19.94	73.75±21.35	1.636	0.103
LVEF (%)	29.12±7.97	35.95±10.05	4.665	<0.001
LVEDD (mm)	63.12±17.41	59.46±16.23	1.457	0.147
LVESD (mm)	48.24±15.43	45.62±14.14	1.192	0.235
LAD (mm)	45.01±13.86	43.46±12.52	0.793	0.428
bFGF (pg/ml)	53.38±18.54	83.32±26.60	7.867	<0.001
NYHA class				
II-III	46 (82.14)	166 (88.30)	1.435	0.231
IV	10 (17.86)	22 (11.70)		

Note: ICM, ischemic cardiomyopathy; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate; bFGF, basic fibroblast growth factor; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LAD, left atrial diameter; NYHA, New York Heart Association Functional Classification.

Table 4. Multivariate COX regression analysis

Items	β	SE	Wald χ^2	*P*	HR	95% CI	
Age	0.142	0.061	5.447	0.020	1.153	1.023	1.299
Diabetes	0.413	0.102	16.429	<0.001	1.512	1.238	1.847
LVEF	1.107	0.312	12.579	<0.001	3.024	1.641	5.574
bFGF	1.485	0.41	13.123	<0.001	4.416	1.977	9.863

Note: SE, standard error; β, coefficient of regression; Wald χ^2, The Wald value; HR, Ratio of risk function values; 95 CI%, 95% confidence interval; bFGF, basic fibroblast growth factor; LVEF, left ventricular ejection fraction.

find biomarkers that can reflect the clinical characteristics and prognosis of ICM.

bFGF has been shown to be an important survival (anti-apoptotic) factor in multiple cell types [16]. The cardioprotective effect of bFGF has been confirmed in both animal models of ischemic oxidative damage and oxidative stress-induced cellular models, and its mechanism of action involves endoplasmic reticulum stress, mitochondrial dysfunction, autophagy, etc. [14, 17, 18].

A total of 244 ICM patients and 244 healthy controls were included in this study. It was found that bFGF was lowly expressed in the serum of ICM patients. Wang et al. [14] showed that bFGF regulated autophagy and ubiquitinated protein accumulation induced by myocardial I/R via activating the PI3K/Akt/mTOR pathway, which is consistent with the trend of this study. Further analysis showed that the low bFGF group had significantly lower LVEF level, older age and higher NYHA class than the high bFGF group. LVEF is the most used objective index to evaluate left ventricular systolic function in ICM patients, and it is also an effective clinical index to measure the prognosis of patients with systolic cardiac insufficiency. That is, patients with low left ventricular ejection function have more severe coronary stenosis, which is a greater threat to the life of patients [19, 20]. NYHA classification is a commonly used evaluation index

of cardiac function in patients with cardiomyopathy [21]. The above results indicate that bFGF may be related to the severity of the disease in patients with ICM and has a certain clinical evaluation and prognostic value.

In this study, LVEF, age, NYHA class and bFGF were analyzed as exposure factors to rule out the relationship between bFGF and prognosis of ICM patients due to the influence from age, LVEF and NYHA class. Univariate results showed that age, hypertension, diabetes, LVEF and bFGF were associated with poor prognosis in patients with ICM. Wasserstrum et al. [22] showed that diabetes was a risk factor of poor prognosis in ICM patients. Hsu et al. [23] proposed that hypertension and diabetes were both risk factors for ischemic stroke, which is consistent with this study. Thereafter, multivariate COX analysis was conducted to eliminate interfering factors, and the results showed that after adjusting for age, diabetes and LVEF, low bFGF was still a risk factor for poor prognosis in patients with ICM. Namely, patients with low bFGF had a higher risk of poor prognosis than those with high bFGF (HR =4.416).

In patients with ICM, due to long-term insufficiency of coronary blood supply, the myocardium is hypoxic, resulting in myocardial fibrosis, ventricular remodeling as well as abnormal LAD and LVEDD, increasing the incidence of arrhythmia, progressive cardiac congestion, eventually leading to heart failure [24, 25]. A study of left ventricular remodeling after ICM showed that bFGF induced angiogenesis and attenuated left ventricular remodeling after surgery [26]. Overexpression of bFGF also increased cardiomyocyte viability after injury in isolated mouse hearts, and delivery of bFGF during reperfusion protected the heart from I/R-induced oxidative damage and cell death [14]. In addition, in rat myocardial I/R model, bFGF activated the PI3K/AKT signaling pathway and improved myocardial I/R reperfusion injury [27, 28]. Therefore, it is speculated that in patients with ICM, bFGF may also activate the PI3K/AKT signaling pathway, reduce myocardial cell apoptosis, increase micro vessel density and repair myocardial injury. However, the specific mechanism remains to be studied.

Limitations of the study

The number of cases in this study is small, and dynamic monitoring of data is lacking. The sample size will be expanded in the later stage, and real-time dynamic monitoring of patients will be carried out. Also, the specific mechanism of bFGF in ICM will be further investigated in future experiments.

In conclusion, bFGF is lowly expressed in the serum of ICM patients, and those with low bFGF have a higher risk of poor prognosis, so serum bFGF levels have a certain value in the prognostic assessment of ICM patients. It is expected to further clarify the application value of serum bFGF in judging the condition of ICM patients, and provide an effective theoretical basis for the treatment of ICM.

Disclosure of conflict of interest

None.

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